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Chemical and Biological Information Technology
($C^{hem}B^{io}IT$)
A Science and Technology Roadmap

Drafted by the COBRA roadmap team
John S. McCaskill, Martyn Amos & Steen Rasmussen
with key contributions from the (30 person strong)
ChemBioIT Panel of Experts
and the
Online Survey on ChemBioIT
http://www.cobra-project.eu/

"Life is a self-sustained chemical system capable of undergoing Darwinian evolution."
G.F. Joyce, 1994

In stark contrast with current computer technology, biological cells compute in construction using molecular and spatial information, in order to delimit, organize, power, sustain, repair, move, communicate, reproduce, protect and evolve themselves robustly from simple and scarce material and energy resources in their complex environments.

Mastery and adaptation of this programmable self-production capability with novel chemicals, information, architectures, environments and objectives will lay the basis for the sustainable, biocompatible and personalized intelligent device construction and sustainable engineering of the future. This major goal requires a dedicated roadmap of activities spanning from synthetic chemistry and synthetic biology to physical self-assembly and embedded evolving artifacts and systems, involving information processing and production at multiple scales.

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Table of Contents

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Further experts are required to continue to develop the draft roadmap, especially from industry, - please apply to the authors if you wish to participate in this ongoing process.

EXECUTIVE SUMMARY

Still in its infancy as a human technology, Chemical and Biological IT (C^hemB^ioIT) is a prerequisite for a sustainable world that integrates ongoing distributed information-rich fabrication with the chemical and biological systems that surround and comprise us, and could become the major focus of computing inside the next twenty years. Using molecular and spatially embedded information to modulate and direct the myriad processes of chemical and biological fabrication down to the molecular scale will challenge computer science and radically expand the total volume of information and communication traffic in human society and the environment. Every week in the scientific literature discoveries of C^hemB^ioIT implementations, architectures integrating material production with information processing, and applications thereof are appearing. The literature also documents the rapid advance of our theoretical understanding of the potential of self-organization and evolution in deployed material processing systems. With roots in Computer Science[1], Artificial Life and Biomimetic Systems, Synthetic and Systems Chemistry and Biology, DNA & Membrane Computing, Nanotechnology and Biotechnology, Evolution Theory and Algorithms, Lab on a Chip Research, Autonomous Systems, Chemical and Biomimetic Robotics, Ubiquitous and Reconfigurable Computing, and Personal and Additive Manufacturing this rapidly evolving field is permeating more and more established disciplines and beginning to be addressed by programs not only in the European Union and its member nations, but also in the United States, Japan and other industrial and developing countries. It will impact all aspects of sustainable society from personalized medicine and diagnostics to custom agriculture, decentralized environment (energy, water and waste) management, the "internet of things" and personal fabrication, to education, communication and entertainment.

C^hemB^ioIT is being pursued *via* a diverse range of experimental approaches in both purely chemical and biological systems from a broad set of scientific disciplines, concentrating on subsets of the fundamental challenges involved. So far, experimental achievements in C^hemB^ioIT are predominantly at the proof-of-principle stage in terms of complexity and their ability to exhibit key biological properties such as autonomous information processing and ongoing or adaptive reconstruction. It will be necessary to develop significantly more complex, controlled and integrated systems before the theoretical potential of C^hemB^ioIT comes to fruition and the complementarities of programmability and autonomy, of general vs. special-purpose functional systems, of purpose-built and evolvable systems, delimit the landscape of opportunities. It will also be necessary to bridge systems self- organizing at the molecular scale with human scale artifacts and systems, and to bridge the gap between electronic, chemical and biological information processing systems. Although these gaps are considerable in experimental implementations today, they continue to close.

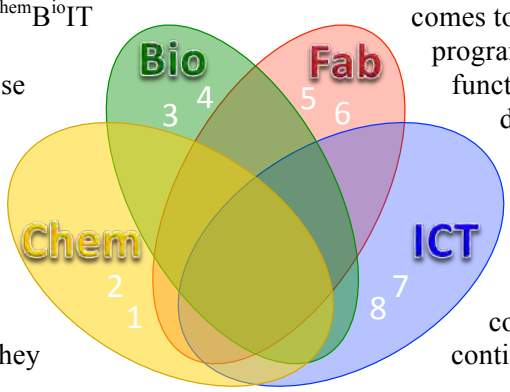

Fig 1. Four contributing disciplines to ChemBioIT.

To facilitate the progress of C^hemB^ioIT research towards a sustainable technology, integrating information and material processing at all scales, two one day workshops were organized in Paris and in Orléans at Conferences on Artificial Life (2011) and Unconventional Computing (2012) and an Online Survey of the area conducted, to provide an initial delineation and roadmap from which a panel of experts could be distilled. A further workshop at the Ruhr Unviersität Bochum (2013) and subsequent consultations completed the identification of the technical panel (as listed on p4 of this document) and the structure and focus of the roadmap.

The overarching distilled target objective for the field and this roadmap is:

[1] Notably with computer science founding father John von Neumann's work on universal construction machines.

Integration of production and information processing down to the molecular scale: i.e. to develop a portfolio of emerging $C^{hem}B^{io}F^{ab}I^{nfo}$ Technologies by 2024 that allow humanly configured but locally (e.g. genetically) encoded, autonomous control of computed ongoing fabrication in macroscopic artifacts, with precision down to molecular scales. The technologies should be sufficiently generic to serve as a solution toolkit for a diverse range of societal and technical challenges.

Typical examples of such technical challenges include self-repair, adaptive material devices, human interfacing, and generic construction information encoding. Typical societal applications might be to smart diagnostics, artificial tissues, water purification, renewable energy harvesting, resource recovery and waste management, and personal fabrication of smart artifacts. This objective, while only one of many possible objectives in $C^{hem}B^{io}IT$ is paradigmatic, recognized by a large fraction of the community, and should serve as a focus for establishing core technologies and capabilities that will be useful in the entire field. The intent of this roadmap is to set a path leading to the desired $C^{hem}B^{io}IT$ portfolio by 2024 by providing some direction for the field with specific six- and twelve-year technical goals. 2024 is 10 years from the proposed publication and completion of this roadmap.

While remaining within the domain of basic science, the five-year (2019) goal would project $C^{hem}B^{io}IT$ far enough in terms of linking autonomous programmable molecular fabrication with smart macroscopic artifacts that the potential for further scalability could be reliably assessed. The ten-year (2024) goal would extend $C^{hem}B^{io}IT$ into the adaptive/evolvable regime, involving systems with construction processes that are determined adaptively by the problems at hand as part of the autonomous computation and not pre-specified. These high-level goals are ambitious but attainable as a collective effort with cooperative interactions between different experimental approaches and theory.

Within these overall goals, different scientific approaches to $C^{hem}B^{io}IT$ will play a variety of roles: it is expected that one or more approaches will emerge that will actually attain these goals. Other approaches may not—but will instead play other vitally important roles, such as offering better scalability potential in the post-2024 era or exploring different ways to implement molecular information directed material construction, which will be essential to the desired development of the field as a whole. At the molecular end, two major subfields can be distinguished, one embracing synthetic biology with GMOs and the other fully chemically synthetic but making use of biological principles. Considerable evolution of and hybridization between approaches has already taken place and we expect this to be strengthened and fostered by the roadmap and necessary to final success.

In common with many S&T roadmaps, *"*a second function of the roadmap is to allow informed decisions about future directions to be made by tracking progress and elucidating interrelationships between approaches, which will assist researchers to develop synergistic solutions to obstacles within any one approach. To this end, the roadmap presents a simple graphical representation using a common set of criteria and metrics to capture the promise and characterize progress towards the high-level goals within each approach. The detailed- view will incorporate summaries of the state-of-play within each approach, attempting to capture its role in the overall development of the field. A summary provides some recommendations for moving toward the desired goals."[2]

The $C^{hem}B^{io}I^{nfo}F^{ab}$ Technology Framework that we envision in this roadmap will open up fascinating, powerful new computational construction and material processing capabilities: for collecting and communicating information about the nanoworld; allowing complex devices to be constructed economically and sustainably; and for investigating alternative programmable fabrication architectures. $C^{hem}B^{io}IT$ systems of unprecedented complexity will be created and controlled, potentially leading to greater fundamental understanding of how biological organisms emerge from a

[2] A Quantum Information Science and Technology Roadmap: http://qist.lanl.gov

physicochemical world, which is no longer only of historical interest to the origin of life but for the future of technology. We can foresee that these $C^{hem}B^{io}$IT capabilities will lead into an era of "$C^{hem}B^{io}$IT devices" such as human health monitoring systems, and autonomous custom coating depositors. We anticipate that there will be considerable synergy with nanotechnology and biotechnology, especially synthetic biology. The social dimension of this initiative should not be neglected, since this is a technology with the potential to fundamentally transform the nature of human artifacts and the role of human information processing in our daily lives. While all of this is a tremendous challenge, it also is a path that will lead to unprecedented advances in both fundamental scientific understanding and sustainable new technologies. We invite you to join us in adding structure and cohesion to this road mapping initiative.

Part I Introduction to the ChemBioIT Roadmap

Overview of ChemBioIT

Over the past few years, technological advances in chemistry, molecular biology, functional materials and engineering have brought biological and chemical information processing within our reach. The ability to build, design and grow ICT systems that can exploit these processes will lead to revolutionary advances in the future. The fundamental challenges facing C^hem B^io IT revolve around the evolution, construction and control of collections of individual elements, such as evolved and functional molecular complexes up to self-assembled microstructures, from protocells to artificial cells, and from synthetically engineered bacteria to neural cells. These components will be capable of "intelligent" and designer-independent functioning, and be able to respond via self-assembly and/or self-regulation. In order to harness these systems, we need to be able to engineer and control chemical reaction and molecular self-assembly at the micro-level, as well as to understand and control macroscopic and population-level behavior. This initiative is based on our increasing understanding of complex chemistry, of the extraordinary natural engineering processes by which living cells operate, as well as fundamental insights into the dynamics of large numbers of interacting agents in complex systems theory. It also depends on astounding current progress in interfacial systems that connect such chemical and biological systems to current computer control technology, such as microfluidic lab-on-a-chip actuator and sensor technology up to electronic chemical cells. We can already approach the construction of an artificial construction matrix for C^hem B^io IT using pioneering implementations of this approach.

Chemical and biological systems are already being harnessed for radically new forms of *computation* and nano- and micro scale *construction*.[3] Unlike technical systems, natural systems are inherently self-organizing, self- repairing, resilient, distributed and adaptive. The underlying characteristic that is critical for this roadmap is their information-encoded bottom-up self-production. This not only goes hand in hand with cost-effectiveness, robustness and sustainability, but also allows new forms of inbuilt optimization and evolvability. Chemical and cellular systems can be interfaced with traditional, silicon-based substrates, but increasing the level of encoded information control in chemical systems and the radical reprogrammability in cellular systems are important steps towards fully self-producing technical systems. The growth and integration of emerging research areas such as supramolecular and systems chemistry, synthetic and systems biology (incl. cellular computing), artificial cells (incl. protocells), molecular information processing (incl. DNA machines), lab-on-a-chip (incl. MEMS and microfluidics), robotics (incl. chemical and micro-robotics), advanced functional materials, nanotechnology and artificial intelligence have lead to biological and chemical information technologies becoming one of the most vibrant and important emerging research domains in recent years.

ChemBioIT seeks to focus the unique potential of extending the biological encoding of information relevant to construction and function to a broader platform in synthetic chemistry, synthetic biology, functional materials and technical systems with novel architectures. C^hem B^io IT is an *enabling technology*, with wide ranging application areas for current information and communication technologies (ICT) and beyond. The long term

[3] **Amos, M.**, Dittrich, P., McCaskill, J.S. & Rasmussen, S. (2011) Biological and chemical information technologies. *Procedia Computer Science* **7**, p.p. 56-60, doi:10.1016/j.procs.2011.12.019.

potential for creating more life-like and intelligent computational, information processing and production processes will open up applications in most sectors of our society. Possible midterm application areas for technologies emerging from this work include engineered intelligent diagnostics and drug delivery systems, artificial tissues, nanotechnology for energy and environmental applications, adaptive bioelectronics and molecular synthesis.

Traditional ICT relies on human-engineered solutions implemented on a silicon-based substrate. Although powerful in terms of raw processing capabilities, modern computers lack the adaptability, robustness and flexibility of natural systems. A main reason for this lies in the fact that they are not constructed or evolved as embedded systems directly in the natural context or their field of deployment. Even the simplest organisms are capable of reconfiguring their internal architectures in response to combinations of external signals and internal programming; a process that is inherently *bio-chemical* in nature. Furthermore, bio-chemical systems continuously produce their own material building blocks. The field of C^hem B^io IT seeks to harness the capabilities of natural and chemical systems. Rather than simply *deriving* inspiration from living systems, C^hem B^io IT researchers seek to *directly use or construct* these systems for the purposes of co-engineering computation and production.

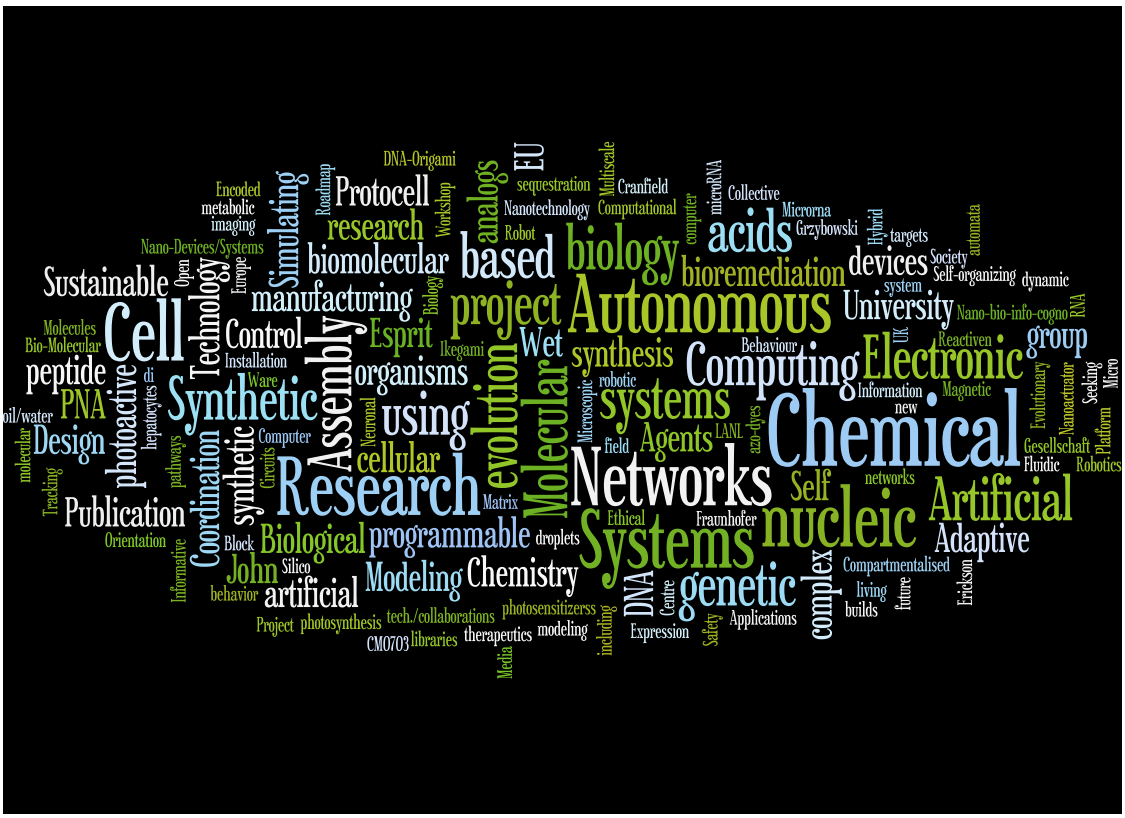

Fig. 1 Word cloud assembled from 70 identified C^hem B^io IT projects. The word cloud gives a visual impression of important recurring concepts in C^hem B^io IT, without revealing underlying structure to the field. Assembled via public tool at http://www.wordle.net.

Simple synthetic self-replicating chemical systems have been researched for almost 30 years now and making use of biochemical enzymes produced by protein translation, more powerful biomolecular self-replicating systems have been extended (e.g. PCR) far from their cellular origin and context, so that C^hem B^io IT is in possession of a powerful arsenal of

construction tools. At the same time synthetic biology is pushing back the envelope of traditional genetic engineering to tackle whole genomic modifications to move cell functionality significantly closer to technical applications. While the vision of von Neumann's second universal construction machine is still elusive for chemistry as a whole, there are growing subdomains of informational molecule chemistry, notably but not exclusively those surrounding DNA, in which with a combination of computational and manipulative competence we are gaining programmable construction capabilities. Our ability to integrate different chemistries involving metabolic catalysts, replicable molecules and amphiphiles for compartmentation is opening up novel pathways to construct artificial and proto-cells with radically new chemistries and properties. Our ability to integrate different functions into populations of cells is opening up novel pathways to orchestrate cell populations for computational and construction purposes. Between these two extremes are a plethora of interesting chemical and subcellular functionalities awaiting exploitation, once the means for programming their integration has been established: for example artificial synapses or photosensitive processors.

It is proposed that C^hem B^io IT in this roadmap will focus on achieving the overarching objective listed in the executive summary:

> ***Integration of production and information processing down to the molecular scale:*** i.e. to develop a portfolio of emerging C^hem B^io I^nfo F^ab Technologies by 2024 that allow humanly configured but locally (e.g. genetically) encoded, autonomous control of **computed ongoing fabrication** in macroscopic artifacts, with precision down to molecular scales. The technologies should be sufficiently generic to serve as a solution toolkit for a diverse range of societal and technical challenges.

This will require the parallel development of embedded molecular and cellular computing with informed molecular, cellular and macroscale construction. The objective is both sufficiently focused for a road mapping activity and sufficiently broad to capture the focus of key researchers in the field. We see it as the decisive challenge for a new era of sustainable technology with the core advantages of living systems and adequate controllability. The key tradeoff between autonomy and control will be one of the issues dealt with in the roadmap.

Vision for ChemBioIT unifying computation and construction

Information processing in biological systems is intimately linked with programming ongoing construction and reconstruction processes. The results of biological computations are revealed primarily in intricate constructions, and on longer timescales in adaptations and systematic environmental modifications. Even in the human brain, there is enormous ongoing constructive activity regulating neural connections and memory. The C^hem B^io IT community maintains that modern technology can and should deal with the integration of programmed construction of complex embedded systems with their deployment: for sustainability, for further advances, for personal customization, for personal security, for societal benefit. Although information technology has long embraced the biological trick of digitally encoded information directing complex construction processes, it currently does so in distant centralized large factories: using huge ultra-mass-production foundries in ultra-clean remote locations. This process, driven by the economic pressure of Moore's law associated with the rapid expansion of information technology, has reached its economic limit. However, now as information technology engages more strongly with embedded systems at microscopic scales, the serious limitations of this approach for enabling society to take full benefit of information control are becoming clear.

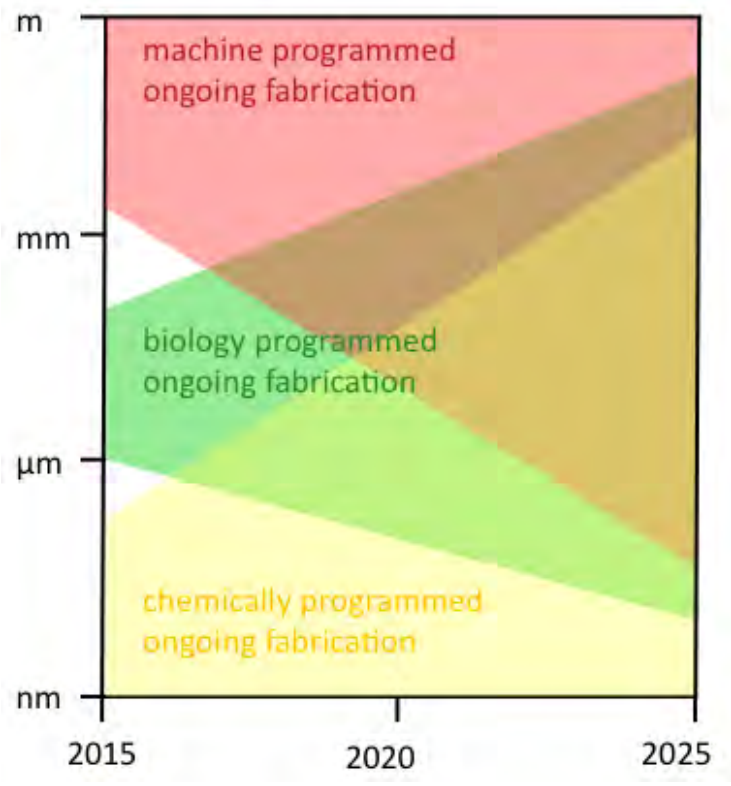

Fig. 2 Scale roadmap of size for integrated ongoing technology fabrication.

The use of human programmed information processing to direct complex fabrication processes (that allow on-site individual customization, self-repair and adaptive change) is currently limited in scale, compared with the much broader ranges of already achieved integration for factory machine fabrication, natural biological systems and chemical industry; all of which cover the full scale of structures from nm to m.

Our ability to program biological systems to produce intricate technology spanning different scales is very limited still compared with the achievements of natural evolution. Although our brains perform impressive information processing tasks, achievements in engineering information processing systems using biological substrates are still elementary in comparison. However, impressive achievements in areas such DNA Computing in the programming of chemical synthesis and DNA nanomachines, and in synthetic biology in the area of genetic circuits, demonstrate the promise of combining information processing paradigms with evolution for the constructive control of microscopic systems. Spatial self-organization and evolution are two equally important players in allowing these two new technologies to be applied to new problems at larger scales. The integration of chemical experimentation in lab-on-a-chip and smart particle technologies, together with the miniaturization of constructive robotics through additive manufacturing (e.g. 3D functional printers) provides the third pair of technologies enabling an integration of ongoing fabrication with deployment, making use of digital information.

An increasingly large community of scientists and engineers are now working in the focal point of this development (see Fig. 1), and the time is ripe for a first stab at a science and technology roadmap that can help integrate these developments. While no single technology is expected to overcome the challenges associated with ongoing fine-grained fabrication, we expect to see the different technologies grow more and more together, each taking on processes and methodologies characteristics of the other until it will be unclear whether manufacturing and chemistry have become more biological or biology more technological.

The role of information technology in all of this is twofold. On the one hand information technology has pioneered the digital information encoding revolution, built like biology on replicable and algorithmically processable strings of information. On the other hand, computer hardware technology has pushed the envelope of detailed manufacturing of macroscopic objects down to the nanometer scale of resolution. Computer science, also in its bioinformatic understanding of biological systems is beginning to assimilate novel

architectures and hardware processing concepts, extending beyond traditional hardware production and reconfigurable hardware. At the same time, the simulation of physical and chemical systems and of complex engineering artifacts has proceeded to the point where design and operation choices in the real time operation of fabricating systems can be made based on detailed situation-relevant simulation. Simulation is already being incorporated to enhance the power of evolution in the design of experimental systems.

The ability to copy and modify complex objects is by no means something to be taken for granted. Chemists have had to work extremely hard to begin to approach this functionality even in simple systems, biology had to wait for it for millions of years in a vast spatially diverse reactor on (so far as we know yet) just one of a very large variety of planetary environments, technologists have had to retreat to clean rooms using ultra-pure materials such as silicon. Von Neumann's analysis of self-reproducing automata takes the extreme position of serially programmed digital manipulation of matter, whereas natural systems exploit self-assembly, kinetic self-organization and evolution to manage complex synthesis without centralized fine-grained control. Robots are increasingly embracing physical embodiment to take advantage of natural information processing to complement digital programming. Synthetic biologists are having to work hard to achieve some measure of engineering modularity in the genetic programming of cell function. It is the synthesis of these areas that holds the promise of gaining control over ongoing detailed fabrication.

Purpose and structure of roadmap

The purpose of this roadmap is to provide a starting point for an integrated approach to the central challenge of C^hem B^io IT – integrating ongoing construction and computation in programmable material systems. It is a science and technology roadmap and does not address particular products or market decisions. The area is of absolute strategic significance as a transformative future emerging technology in its own right, able potentially to radically transform the entire basis of human technology, and like the radical transformation proposed for example in Quantum Computing, requires at this early stage of development a focus on main research threads rather than products.

Six main experimental topics (or areas) define the main thrusts towards the overall roadmap goal in the next ten years, and are complemented by two further theoretical threads involving simulation and computation of construction processes. These eight topics were further subdivided into subtopics representing particular research approaches to the roadmap common goal. We have structured the roadmap to incorporate as clearly as possible the diverse contributions of an extended panel of experts on these subtopics. Their input, structured in a common way through a submission form (see Appendix 1), has been collated and sorted to address the major roadmap themes. The next part (II) of this roadmap introduces these eightfold core technologies for C^hem B^io IT, along with two overarching areas dealt with in less detail: energy and social and environmental sustainability. The essential idea, contribution to the roadmap central goal and the main achievements (with development status) to date form the bulk of the contribution, together with additional comments by panellists.

In Part III we turn to a detailed presentation of the future of these core technologies in the next 10 years. The analysis is divided up into a projection of the present to the 5-year and 10-year situation, with a detailed perspective on dependencies and accompanying breakthroughs and contributions to other fields. The ten metrics , introduced in the following section, were also evaluated by the panel for each subtopic and for the these three phases of development.

In Part IV we present three case studies of current and recently completed projects that unite different core technologies to make progress towards the roadmap goal. These projects, financed by the EU, are Bactocom, MATCHIT and MICREagents.

In Part V, we perform an analysis of the scientific and societal impact, especially towards sustainability, of the roadmap, again compiling responses from the panel of experts in a topic by topic approach.

The roadmap is complemented by a set of references to reviews in the areas of the core technologies and appendices including summary tables for the main compiled results.

Metrics for assessing progress and subtopics towards the overall goal of the roadmap

Two types of metrics will be used to evaluate community progress along the roadmap towards the complex goal of integrating computation with construction:

(i) objectives measures: quantitative and semi-quantitative measures on progress of implementations en route to this overarching goal

(ii) developmental measures: assessing the maturity, transferability and reliability of technologies and experimental approaches

The objective measures contain fundamental measures of C^hem B^io IT performance, which contrast with living systems primarily in their programmability and with current ICT systems in all but the SSE directions. (see Fig. 3) The axes in opposite directions are to some extent complementary, it is hard to go far out from the center in opposing directions simultaneously. A number of the axes have quantitative measures. Others are given a succession of discrete qualitative stages as indicators of progress. These metrics were reviewed by the panel before being used in the detailed roadmaps with the detailed key presented in Part III. We can overlay the rubber band metrics (e.g. blue line figure) for various core technologies to assess the different contributions of the various approaches to advancing the field towards the overall goals. The metrics also allow some statistical assessments of progress towards the overarching roadmap goal to be made.

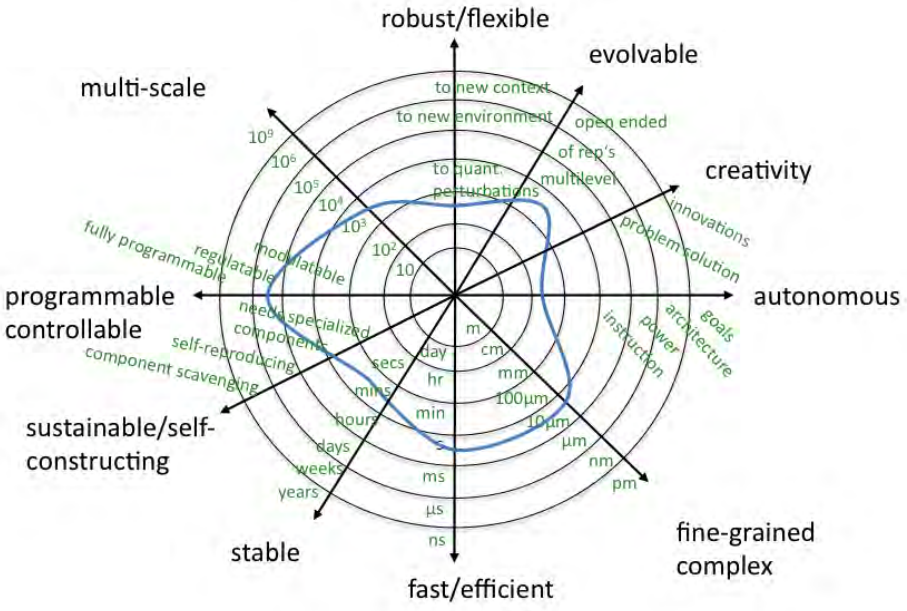

Fig. 3 Some ChemBioIT metrics with an example of a scenario plotted on the circular metric map. The metrics are quantitative or qualitative with distinct categories separated by rings. Some metrics oppose one another and are difficult to fulfill simultaneously. Where possible, these are placed on opposing sides of such a

diagram. Scenarios that produce large areas on such a plot are desirable for ChemBioIT.

The developmental status measures, in contrast, assess the maturity of the technologies, independently of their progress towards the final C^hem B^io IT goals:

a) an approach amenable to modular integration and automation
b) an approach robustly transferrable between labs
c) an approach firmly established scientifically
d) an approach with some experimental evidence as to viability
e) an approach verified by simulation and quantitative estimates
f) a hypothetical approach, no known implementation so far.

Other metrics could be considered, including production costs, socioeconomic costs, environmental footprint, etc, but we shall concentrate on the metrics above in the S&T roadmap.

Further examples of characterizations of the area of ChemBioIT are shown in Figs 4,5. The first focuses on the different levels of complex systems at various scales, while the second uses a different representation of a Venn diagram involving the four sets Chem-Bio-Fab-ICT to place various projects and initiatives as moving towards the complete intersection of these four strands.

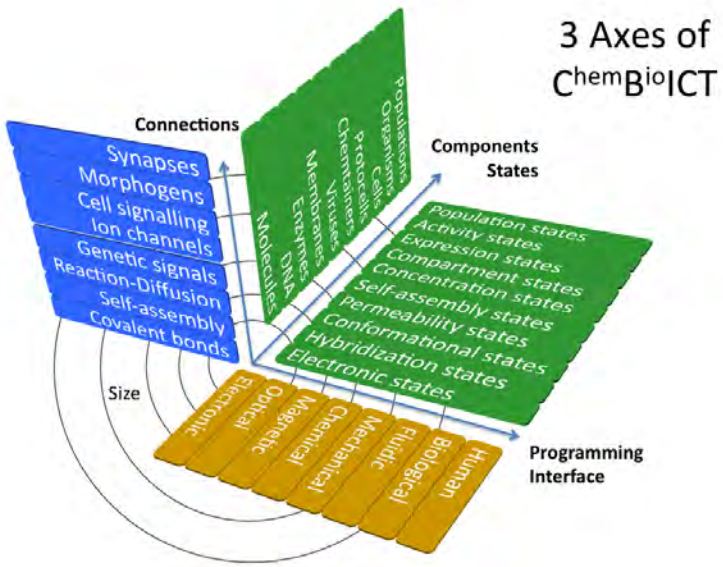

Fig 4. Three axes of ChemBioIT. Illustration of one of the many possible classification schemes in which the nature of C^hem B^io IT is outlined in spanning from nano to macroscopic scales with different types of components, connections, and programming interfaces.

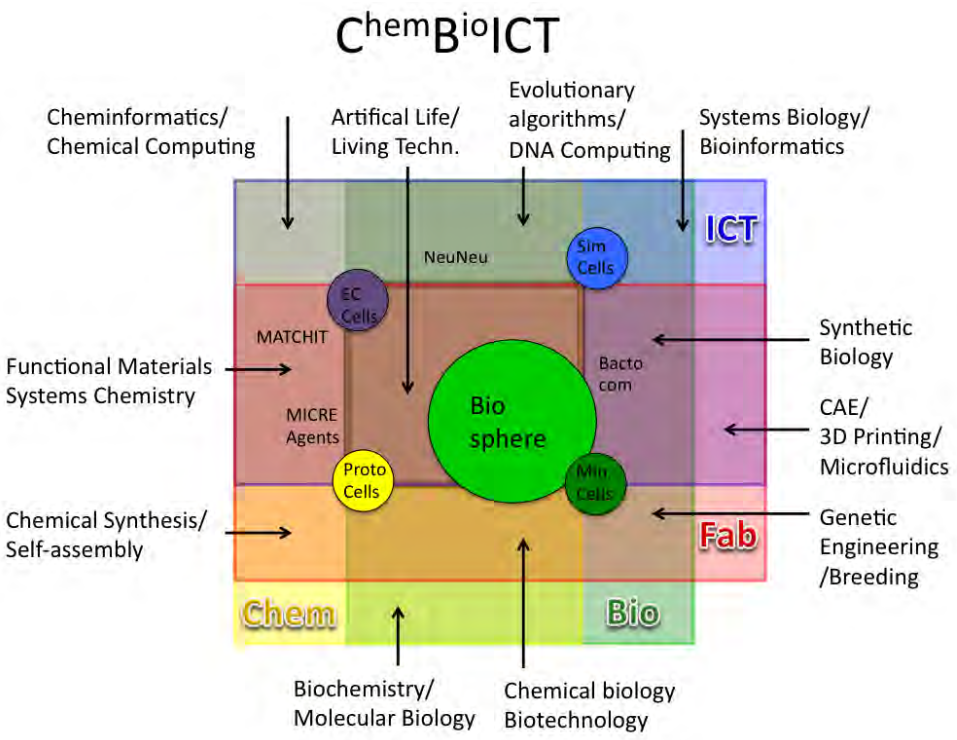

Fig. 5 Venn diagram of C^hem B^io F^ab ICT The 4 set Venn diagram shows both the focus of the initiative towards the common overlap of Chem, Bio, Fab and ICT, and the placement of some currently recognized initiatives and projects along with the biosphere.

Part II Core Science and Technology Areas for C^hem B^io IT

We have identified the following core technologies that will contribute separately and in concert to achieving the overall goal of autonomous fine-grained multi-scale fabrication.

1. MOLECULAR COMPUTING & TEMPLATE CHEMISTRY
1a. Systems Chemistry, Supramolecular and Synthetic Chemistry
1b. DNA computing and DNA machines
1c. Inorganic biology and genetic alternatives to nucleic acids
1d. Artificial chemistries and formalisms for molecular construction and IT

2. SPATIAL SELF-ORGANIZATION & SELF-ASSEMBLY
2a. Reaction Diffusion Systems and Chemical Pattern Formation
2b. Multiphase Chemistry involving self-assembled mesoscale structures
2c. Surface and interfacial chemical systems: including multilayer fabrication
2d. Iterative chemical processing systems with integrated separation and cleanup
2e. Computational and theoretical bounds for self-organization and -assembly

3. CELLULAR AND CELL-LIKE COMPUTATION AND PRODUCTION SYSTEMS
3a. Cellular Synthetic Biology using radical GMOs
3b. Cellular computation and GRNs involving cell communication
3c. Neural computation in artificial networks
3d. Artificial tissue engineering using structured chemical/material scaffold
3e. Information encoding in cellular systems

4. EVOLUTIONARY PROCESSING
4a. Genetic information encoding principles for ongoing construction
4b. *In vitro* molecular evolution, combinatorial chemistry
4c. Combinatorial functional materials (including polymers)
4d. Generative and developmental systems: for integration of production and construction
4e. Evolutionary Design of Experiments
4f. From reconfigurable to self-constructing and self-repairing systems

5. HYBRID MEMS, MICROFLUIDIC & ELECTRONIC EMBEDDED C^hem B^io IT
5a. Microfluidics, LOC and other hybrid chemical/physical technologies
5b. Fabricated micro-and nanoparticles interacting with C^hem B^io IT systems
5c. Electrokinetic and electrochemical systems
5d. Autonomous chemical sensor and actuator networks & intelligent microparticles
5e. Hybrid systems involving cells
5f. Information processing principles in hybrid systems

6. AUTONOMOUS ROBOTIC CONSTRUCTION
6a. Chemical robotics, Autonomous Experimentation and Swarm Chemistry
6b. Additive manufacturing, 3D functional printing, steganography & related fab
6c. Multiscale and hybrid microrobotic systems interacting with chemical construction
6d. Evolutionary robotics involving functional material modification
6e. Embodiment and chemical information encoding in robotic construction systems

7. SIMULATION
7a. Simulation of C^hem B^io IT processes and subsystems
7b. Simulation integrated design and programming for C^hem B^io IT
7c. Simulation integrated evolution for C^hem B^io IT

8. COMBINATION OF COMPUTATION WITH CONSTRUCTION
8a. Information encoding and communication of information associated with construction
8b. Connecting natural computations (molecular, membrane, cellular etc)
8c. Programmability and programming autonomous systems
8d. Architectures for combined computation and construction

These topics are aligned symmetrically with respect to the overall structure of the C^hem B^io IT area as shown in the following figure:

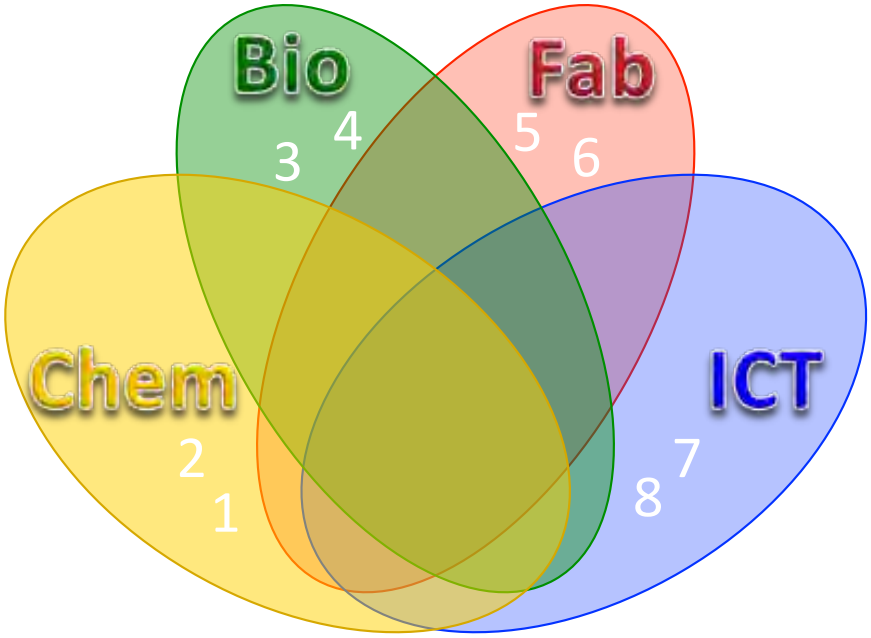

Fig. 2.1 Roadmap Venn diagram of disciplines Chem-Bio-Fab-ICT with location of the main topics or areas 1-8 to be analyzed in the roadmap.

Additional overarching topics that will be discussed but in less detail are:

9. ENERGETICS FOR INFORMED CONSTRUCTION
9a. Light driven mechanisms (e.g. dye solar films/cells and Si components)
9b. Chemical battery and fuel cell electronics (e.g. enzymatic sugar power) electronics
9c. Capacitive coupling between powered electronics and microparticle chemistry
9d. Miscellaneous power sources incl. magnetic, vibrational, others

10. ECOLOGICAL & SOCIAL ASPECTS
10a. Sustainable energy and resource systems: incl. “cradle to cradle”, iterative chemistry & recycling
10b. Personal fabrication and internet supported fabrication systems
10c. Human C^hem B^io IT interfaces
10d. Social and ethical recommendations and guidelines for C^hem B^io IT

The panel experts were requested to complete a template form (see Appendix 1) asking twelve questions for each of the subtopics in areas 1-8 above, and requesting metric tables for 10 progress metrics to be filled out: for now, in 5 years and in ten years. Some of the subtopics were addressed by two or more panelists, the others by one. The results were compiled and collated in a database. We have divided the presentation of the findings into several sections of this report. Here we first compile the main features of each approach: the main idea, its relevance to the roadmap, main achievements so far, and analysis of strengths, unknowns and weaknesses (SUW). For topics 7 and 8 we then conclude this section with the input of all subtopics on the role of simulation and theory and with a short discussion of the other overarching themes of energy, society and sustainability. In Part III we then present the results pertaining to the future, and there present the compiled metric data from each of the subtopics. In Part V, we discuss the impacts of the roadmap using the input from Q10.

Fig. 2.2 Core technologies, fields, areas and subareas. Top: arrangement. Right: legend.

The roadmap deals with the integration of the four fields of Chemistry (and Physics), Biology, Automated Fabrication and Information Technology towards C^hemB^ioFabIT . Each of these four fields is represented with two areas in the roadmap.

SA	Short Name	Subtopic of ChemBioICT Roadmap
1a	SysChem	Systems Chemistry, Supramolecular and Synthetic Chemistry
1b	DNAComp	DNA computing and DNA machines
1c	InorgBio	Inorganic biology and genetic alternatives to nucleic acids
1d	ArtChem	Artificial chemistries and formalisms for molecular construction and IT
2a	ReacDiff	Reaction Diffusion Computing and Chemical Pattern Formation
2b	Multiphase	Multiphase chemistry involving self-assembled macroscopic structures
2c	Interfaces	Surface and interfacial chemical systems: including multilayer fab
2d	IterChem	Iterative chemical processing systems with integrated separation and cleanup
2e	ThSO&SA	Computational and theoretical bounds for self-organization and -assembly
3a	SynthBiol	Cellular Synthetic Biology using radical GMOs
3b	GRNCell	Cellular computation and Genetic Regulatory Networks involving cell communication
3c	ArtNeural	Neural computation in artificial networks
3d	TissEng	Artificial tissue engineering using structured chemical/material scaffolds
3e	CellInfEnc	Information encoding in cellular systems
4a	GenCode	Genetic information encoding principles for ongoing construction
4b	IVMolEvol	In vitro molecular evolution, combinatorial chemistry
4c	CombFnMat	Combinatorial functional materials (including polymers)
4d	DevelSys	Generative and developmental systems: for integration of production and construction
4e	EvDesExp	Evolutionary Design of Experiments
4f	Selfrepair	From reconfigurable to self-constructing and self-repairing systems
5a	LOC&hybrid	Microfluidics, LOC and other hybrid chemical/physical technologies
5b	µ&NPs	Fabricated micro-and nanoparticles interacting with ChemBioIT systems
5c	Elec-kin/chem	Electrokinetic and electrochemical systems
5d	AutoSensAct	Autonomous chemical sensor and actuator networks down to cellular size and intelligent microparticles.
5e	HybCellFab	Hybrid systems involving cells
5f	HybInfProc	Information processing principles in hybrid systems
6a	ChemRobot	Chemical robotics, Autonomous Experimentation and Swarm Chemistry
6b	AddManuf	Additive manufacturing, 3D functional printing, steganography & related fab
6c	MultiscaleRob	Multiscale and hybrid robotic systems interacting with chemical construction
6d	EvoRobotics	Evolutionary robotics, including functional material modification
6e	EmbodyRob	Embodiment and chemical information encoding in robotic construction systems
7a	SimSubSys	Simulation of ChemBioIT processes and subsystems
7b	SimDesProg	Simulation integrated design and programming for ChemBioIT
7c	SimIntEvol	Simulation integrated evolution for ChemBioIT
8a	ITConstruct	Information encoding and communication of information associated with construction
8b	NaturalComp	Connecting natural computations (molecular, membrane, cellular etc)
8c	ProgAutonom	Programmability and programming autonomous systems
8d	ArchComCon	Architectures and optimization for combined computation and construction

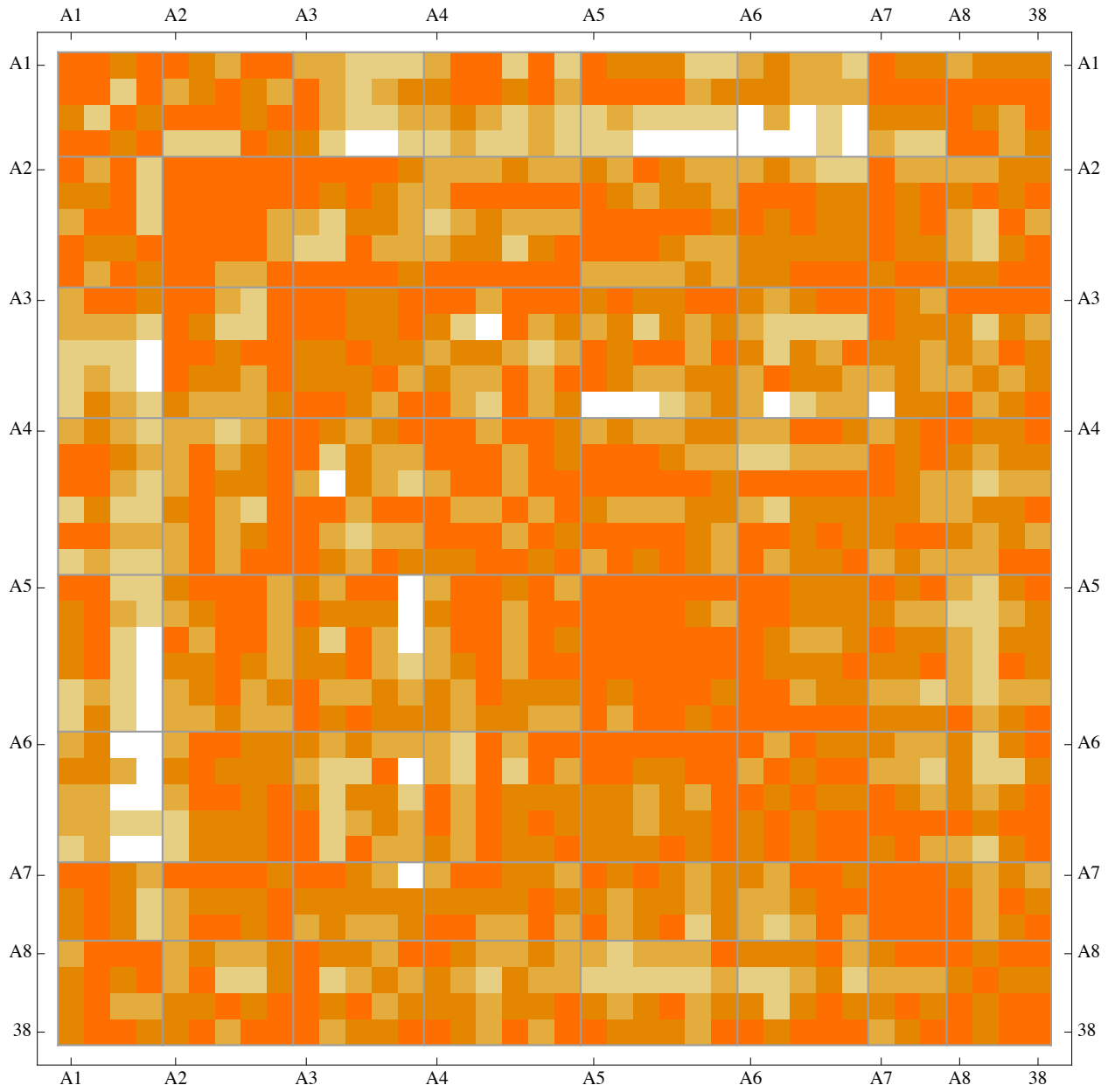

Fig. 2.3 Connections between different subareas in the core technologies of the roadmap. The 38 subtopics in 8 main areas (Area A1-8) above are correlated with one another using five colors (white to orange) with following scale: 0 no known connection 1 connections mainly unexplored 2 significant connections not yet well explored 3 many connections 4 very strong connections. The grey blocks delimit the extent of the main areas 1-8.

Fig. 2.3 explores the connections between the different subtopics in the core technologies as in Fig 2.2. The connection strengths were entered symmetrically in a 38x38 table after digestion of the material input from panelists in the roadmap and with the background of long experience in the area of C^hem B^io IT. They include major potential rather than just already completed connections between the subtopics. The overall result is a very dense and strong network of connections illustrating the fundamental coherence of the roadmap as an area in its own right. Connections within the main areas are somewhat stronger than between areas. Experimental connections between with theory, simulation and computing (Areas 7-8) are consistently strong.

1. MOLECULAR COMPUTING & TEMPLATE CHEMISTRY

The first area of the roadmap involves synthetic chemistry in connection with informational molecules as functional nanosystems. Three levels of doing this can be discerned a) with organic molecules with or without enzymes b) with molecules derived from DNA and c) with very different inorganic chemical substrates. The first three subtopics address these three approaches, with the first two topics having significant common ground. For example, DNA has been also been used to generate enzyme-free synthetic systems in Systems Chemistry. The final subtopic concerns abstract formalisms and simulations for exploring the interaction of information processing with chemical construction such as Artificial Chemistries.

1a. Systems Chemistry, Supramolecular and Synthetic Chemistry

The main target is to use molecular information to direct autonomous synthesis that replicates this information via supramolecular complexes and the systems' kinetics. Already, in the absence of other information mechanisms (e.g. biochemical enzymes), simple chemical information in various small organic molecules can be replicated synthetically.

1b. DNA computing and DNA machines

The main target is to use DNA to direct assembly of complex structures and the operation of molecular machines. The considerable sequence programmability makes progress towards autonomous fabrication in this area significant, including directing the assembly of other nanoscale and even microscale objects.

1c. Inorganic biology and genetic alternatives to nucleic acids

The ability to build complex combinatorial structures in for example polyoxometalates and replicate structural variations thereof opens interesting possibilities to develop a self-informed inorganic autonomous fabrication that can already span spatial scales (e.g. in tube structures).

1d. Artificial chemistries and formalisms for molecular construction and IT

Research on algorithms and architectures for organizing molecular construction as an information process single out particular chemical mechanisms and properties (e.g. chemical organizations, sensitivity analysis) that highlight important targets for experimental work on building molecular systems that unit construction and information processing.

The main conclusions of this area for the roadmap are that while the Systems Chemistry community is addressing more fundamental issues such as mechanisms of enzyme free replication, the origin of homochiral chemical synthesis and the kinetics of cooperative chemical systems, the DNA Computing/Machines community is making significant progress towards overall roadmap goals on a broad front from a more engineering perspective. DNA is already being used in signal processing, amplification and functional modes, and through the Origami approach has been made to interact functionally with microscopic structures such as nanopores, and in the self-assembly of microscopic objects such as beads and vesicles. Inorganic biology is an exciting new area which is just emerging with proof of principle experiments. The theoretical backdrop to the area involves multiple layers of detail in molecular modeling and is complemented in part by Artificial Chemistry and Molecular Evolution modeling of combinatorial sets of reactions. The area needs a strong interaction with Area 2 to proceed further up the organizational scale towards multiscale roadmap goals. It will benefit from a stronger engagement with evolutionary principles (Area 4) to foster general purpose design and with hybrid micro- and nanosystems (Area 5) to increase the level of experimental integration (see also Case study III in Part IV).

2. SPATIAL SELF-ORGANIZATION & SELF-ASSEMBLY

Whereas the first area focused on chemical synthesis, the second area addresses the scaling up of molecular properties to chemical collectives including information processing potential. This can occur firstly through an interplay of physical transport with chemical reactions as in reaction diffusion systems, leading to various pattern forming self-organizing kinetic processes. It can also occur in multiphase systems via specific molecular recognition and self-assembly or involve layer-by-layer processing at macroscopic interfaces. A key goal of collective chemical processing is to establish iterative processing for chemical collectives, returning product mixtures to clean starting states. These four approaches are complemented by a fifth subtopic on the theory of self-organization and self-assembly, required to frame limits and opportunities for future research.

2a. Reaction Diffusion Systems and Chemical Pattern Formation

Reaction diffusion systems were an early contender for autonomous structure formation in chemistry (BZ reaction and earlier) and biology. Their importance for complex autonomous fabrication is being enhanced by deployment in microfluidic and multiphase systems and their coupling with genetic information.

2b. Multiphase Chemistry involving self-assembled mesoscale structures

Membranes, emulsions, nanoparticles, droplets and other multiphase container systems including morphological computation with and self-assembly of such structures provide a suite of techniques for bridging molecular to microscale autonomous fabrication including approaches involving self-replicating protocells.

2c. Surface and interfacial chemical systems: including multilayer fabrication

Layer by layer deposition of structures for example has long been posited as an alternative genetic mechanism for information transfer and is being exploited in the fabrication of complex functional surfaces, including under electrochemical control.

2d. Iterative chemical processing systems with integrated separation and cleanup

An autonomous version of synthetic chemical reaction pathways requires the integration of separation processes to purify next reactants from complex product mixes. Lab on a chip integration is providing local mechanisms to approach this with increasing process autonomy, but the separation processes still need to be directed by molecular information.

2e. Computational and theoretical bounds for self-organization and -assembly

In formulating such processes, it is important to draw on theoretical understanding of any necessary tradeoffs for example between construction speed and fidelity, between adaptability and self-repair properties and reliability of function.

The main conclusions of this section are that multiphase self-organization in chemical containers and interfacial chemistry in conjunction with both self-organized and manufactured micro-surfaces will need to complement reaction-diffusion systems to challenge the sophistication of cellular self-organization towards the roadmap goals. Ongoing work is showing increasing sophistication of information processing, but more work will be necessary to integrate the dynamic control of containment with the control of chemical reactions and transport. New opportunities are being opened up with nanoscale and microscale structuring (see Area 5), but leave a part of the system as a rigid environment which at present can at best be modified by chemical reactions and not rewritten. Micro- and nanosystems should however allow increasing development of modular standard environments that provide programmable structure to the chemical systems and enhance functionality. Investment in iterative processing and distributed chemical cleanup and concentration of synthetic products will be necessary for ongoing chemical fabrication to be integrated to complete the roadmap. This area is benefiting strongly from intuition developed in studying cellular systems (Section 3) and work addressing evolution (cf Area 4) has only rarely exhibited any of the exciting potential for cooperation available in spatially structured systems. Although reaction diffusion systems have even been employed for robot controlling (Area 6), multiscale integration has not yet reached to higher level functionality.

3. CELLULAR AND CELL-LIKE COMPUTATION AND PRODUCTION SYSTEMS

This area of the roadmap concerns the use of living cells (or cell-like chemical systems) for the purposes of computation and/or production. Although most subtopics involve the manipulation of chemical and/or biological material, all require mathematical modeling and/or simulation of both intra- and inter-cellular processes. The first two subtopics are closely linked, with single-cell synthetic biology now being scaled up to consider the engineering of microbial consortia. Neural computation, on the other hand, attempts to model the brain at the level of individual neurons, and to emulate neural processing using chemical systems. Tissue engineering attempts to mimic physical structures, and to evolve/design new human designed/desired structures. Of particular interest is the integration of stem cells into artificial scaffolds, and how these (and other engineered influences) might be used to guide development in an artificial structure. The final topic offers a common thread, since the development of conceptual models of how processes operate inside cells are fundamental to our understanding of the nature and limitations of "computation" in living material.

3a. Cellular Synthetic Biology using radical GMOs

Top down synthetic biology at the cellular level transcends traditional genetic engineering in orchestrating complex novel functionality into organisms from multiple concerted genetic alterations (not isolated mutations or insertions). Typical targets are to modify bacteria as efficient fuel cells or for environmental remediation. It is increasingly clear that making major changes to the genomes of existing cells usually runs into major compatibility problems resulting form the lack of modularity of intracellular processes. Bottom up artificial cell assembly is more challenging and less advanced, but can in the long term presumably sidestep the modularity issues for the top down approach.

3b. Cellular computation and genetic regulatory networks involving cell communication

One solution proposed by Solé and others is to distribute changes across multiple cells (retaining viability and simple added function) and use communicating processes involving multiple cells to achieve complex functionality. The modulation of genetic regulatory networks can then be made more manageable towards achieving complex objectives with cell populations. It is yet unclear how well this can be exploited for complex spatial fabrication processes.

3c. Neural computation in artificial networks

Neural signal processing can be emulated without cells using sustained reaction-diffusion systems with multiphase and microfluidic systems. Such signal processing may also be of value in controlling complex chemical construction processes.

3d. Artificial tissue engineering using structured chemical/material scaffolds

The growth of artificial tissues in (partially programmable) chemically reacting dynamic scaffolds may provide a further interaction between fully biological and semi-autonomous, chemical construction processes.

3e. Information encoding in cellular systems

Apart from the experimental thrusts in this topic, progress towards C^hem B^io IT construction systems can also be made by theoretical computer science investigations of powerful sets of basic operations, information encodings and information flows that efficiently mediate construction and computation in cellular systems.

The main roadmap conclusions for this area are that synthetic biology/engineered consortia and tissue engineering offer a clear route towards progress towards the *production* goals. "Molecular scale" operation is inherent to these areas, as synthetic "devices" are proteins, plasmids, etc. "Production" potential in single cell synthetic biology is less clear, although many existing applications (eg. drug precursors) do have this as a fundamental aim. Multi-cellular synthetic biology and tissue engineering seem to offer a more realistic route towards production-based applications; moreover, these systems will be adaptive and self-repairing in nature. If the aimed-for goal lies more towards the development of *autonomous* systems, then progress will be required in neural computation. All of these areas will require advances in both our understanding of fundamental biophysical processes, and our ability to adequately represent, model and predict them.

4. EVOLUTIONARY PROCESSING

Evolutionary processing is necessary to deal with the search for good chemical solutions in the space of a large combinatorial variety of alternative structures. The distributed and locally autonomous

mechanisms of evolutionary search based on local proliferation and selection mechanisms need to be complemented by processes allowing programming constraints to be introduced effectively. While evolution research has made significant progress in the optimization of molecular structures via sequence, the use of evolution to solve complex functional problems at the systems chemical or supramolecular levels is still limited, although the evolutionary design of experiments is promising, and must be expanded systematically if the evolution area is to help attain the overarching roadmap goal. Evolutionary processing is an area that is being combined with the other 5 experimental thrusts and with simulation and computation to launch a broad-based procedural attack on the overarching roadmap objective.

4a. Genetic information encoding principles for ongoing construction

The choice of representations for structural and functional information in systems that integrate construction and information processing is critical. There is common consensus that the genomes of organism not only contain information about the current instantiation that they encode, but also structural information ensuring the evolvability of this encoding. "Representing more than the information needed to produce a single individual, the genotype is a layered repository of many generations of evolutionary innovation, and is shaped by two requirements: to be fit in the short term, and to be evolvable over the long term through its influence on the production of variation."[4] Other issues involve the evolution of genetic coding, the evolution of evolvability and the sharing and division of information between organisms.

4b. In vitro molecular evolution, combinatorial chemistry

In vitro molecular evolution can be seen as an iterative extension of combinatorial chemistry with ongoing selection. Fabrication embracing it requires a quasi-genetic description of variants at least in terms of reproducible construction procedures, with an efficient encoding of the search space, and can be used to overcome uncertainties in viable construction protocols and performance properties.

4c. Combinatorial functional materials (including polymers)

The colligative properties of advanced functional materials can be tailored by compositional or structural details that are increasingly acquiring a combinatorial complexity. Like membranes and surface coatings, functional materials including magnetic, piezoelectric, porous, and thermoplastic materials are being structured with ever increasing information content and can be then used to control construction processes in increasingly sophisticated fine-grained forms.

4d. Generative and developmental systems: for integration of production and construction

The formal study of evo-devo systems suggests new instantiations for combining the power of development with evolution. The strong examples from well-studied cases of cellular differentiation from single cells to organisms, including slime mold, drosophila, zebra fish etc, provide a wealth of detailed information and principles about the orchestration of morphogenesis that can also be employed in more technical contexts.

4e. Evolutionary Design of Experiments

The extension of genetic information from structural encoding to fabrication protocol information allows the evolution of experimental protocols when coupled to an evaluation procedure. This provides an extension of evolution beyond biological DNA encoding.

4f. From reconfigurable to self-constructing and self-repairing systems

Reconfigurable hardware stands in contrast to programming (software) or parameterization of systems. The boundary between these approaches is however continuous. An external controller usually controls reconfigurable systems. If the controller also becomes part of the system and the system is able to build parts on its own then the term self-construction is used.

Reconfiguration is useful in combinatorial construction, since it may require less information to build complex structures by starting from existing (usually modular) structures. Systems with this ability are able to repair themselves, if they have a notion of target structure.

[4] Quote: Genetic and Evolutionary Computation Conference 2014 . Track: Generative and Developmental Systems (GDS) 2014. http://www.mepalmer.net/gds2014/

5. HYBRID MEMS, MICROFLUIDIC & ELECTRONIC EMBEDDED ChemBioIT

Hybrid micro- and nanosystems will help integrate and automate experimentation. Whereas much work has been expended on the lab on a chip approach, this needs to be complemented by a number of other areas: smart micro- and nanoparticles, more fine-grained and symmetric functional integration of electronic and chemical processing layers, autonomous networks of sensors and actuators bridging different scales, hybrid systems with cells, and the reconfigurable architecture paradigm. The main conclusion of the roadmap is that this area is vital to establish programmable integrated interfaces to self-organizing subsystems in the other areas. It enjoys great vitality currently and is poised to assist reaching the overarching roadmap goal, especially if the integration of system fabrication with operation is pursued. The main weakness of the area is not being able to do synthesis from scratch of all components in the deployed system, and finding ways to add functionality to generic resource building blocks that integrate electronic or other control mechanisms will help move this area towards the roadmap goal.

5a. Microfluidics, LOC and other hybrid chemical/physical technologies

As chemical information processing systems, microfluidics and LOCs are most advanced in the area of diagnostics, with systems currently involving tens of thousands of active elements (such as valves) and massively parallel programmed operation. Fabrication processes typically provide limited quantities, which is reasonable for rare or amplifiable products such as DNA, but generally limiting. Processes allowing self-construction or self-repair are still rare and of limited complexity. Nonetheless major progress is expected in the coming years.

5b. Fabricated micro-and nanoparticles interacting with ChemBioIT systems

Another large future area of activity in C^hem B^io IT involves using programmably constructed micro- and nanoparticles as a component in directing the functional behavior of chemical and biological systems.

5c. Electrokinetic and electrochemical systems

"From ion channel nanopores to electronic chemical systems" Direct electronic control of chemical processes has been explored in a number of contexts ranging from neural systems and chemical membrane sensors to electronic DNA chips and molecule, nanoparticle and cellular manipulation systems. Coupling micro- and nanoscale- electric fields with complex molecular structures allows an effective modulation of chemical processes either for diagnosis or construction.

5d. Autonomous chemical sensor and actuator networks

Currently still at the scale of 100s of micrometers, autonomous sensor networks promise to revolutionize a whole range of human and environmental monitoring tasks. If the communication and power problems can be solved efficiently, such networks could also revolutionize distributed fabrication by providing online feedback to direct local fabrication processes.

5e. Hybrid systems involving cells

Multicellular tissue construction also involves feedback from locally communicating sensors and actuators. The manipulation of cellular systems in LOC integration is also driven by diagnostics, both at the single cell and artificial tissue level. Hybrid cellular systems include silicon coupled neuronal, retinal and olfactory systems and their construction is expected to become increasingly iterative, symmetric and programmable in the coming decade.

5f. Information processing principles in hybrid systems

Joint local construction and information processing requires many issues in information management to be resolved and research in IT is required to find optimal mechanisms of information encoding for such systems. For example, the translation of information from one representation to another, so that it can be copied and modified in one representation and decoded and deployed in another is a central issue. In living organisms, this kind of problem is epitomized by the translation apparatus employing the genetic code to link replicable molecules with non-replicable functional proteins.

6. AUTONOMOUS ROBOTIC CONSTRUCTION

This area of the roadmap concerns the construction of robots (functional devices capable of (semi-) autonomous operation of specific tasks), and associated foundational enabling technologies (such as additive manufacturing and 3D printing). These robots may be based on chemical systems, hybrid

systems, or evolutionary systems involving material modification. Underpinning all of these areas is the need to consider how information might be encoded in such robotic systems, and how embodied processing might be best harnessed.

6a. Chemical robotics, Autonomous Experimentation and Swarm Chemistry
Chemical robots control the uptake, reactions and release of chemicals in complex environments and may be capable of autonomous actions, collective processing and communication with one another and an external IT system. Currently at the level of simple operations like drug release it is possible that they can be developed further to orchestrate complex constructions autonomously, either in defined spatial relationships or swarms.

6b. Additive manufacturing, 3D functional printing, steganography & related fab
The steady increase in flexibility, speed and resolution of 3D printing and other additive manufacturing technologies is allowing them to address increasingly complex fabrication tasks involving chemical and cellular systems. The 3D printing of complex cellular structures embedded in scaffolds or nutrient structures will soon be reality. Construction progress down to the molecular level requires an integration of autonomous self-assembling processes with larger scale external control.

6c. Multiscale and hybrid robotic systems interacting with chemical construction
Hierarchies of robots at different scales, each controlling the next layer of autonomy, could be employed to create efficient control information flow in multi-scale fabrication processes. Such hierarchical robot systems are still in their infancy. Hybrid robots interacting with chemical or biological systems have been explored.

6d. Evolutionary robotics involving functional material modification
This involves physical embodiments of robotic self-construction reaching down to the material components – building functional devices from non-functional materials.

6e. Embodiment and chemical information encoding in robotic construction systems
The use of physical and chemical information to direct or codirect the process of construction of/by autonomous robotic systems may provide significant gains in terms of avoiding complex digital computations and interface conversions, taking advantage of the inherent computational capabilities of the embodiment. Taking advantage of such principles in a mixed signal processing context, with both chemical and electronic information and exploring principles for effective decompositions is one of the topics here.

The main roadmap conclusions for this area are that the most likely route for short- to medium-term success will lie in taking a *hybrid* approach to autonomous robotics, whereby chemical systems are combined with more traditional electronic and material substrates. However, while this will significantly change our view of robotics, it will still require significant advances in terms of how such systems might be "programmed" (or even "evolved"). Underpinning this is the need to better understand the fundamental nature of computation in such analogue systems; whilst hybrid systems offer major benefits, with potential for mixed signal processing in both chemical and electronic media, the ability to adequately *control* and *power* such systems when scaled up still presents a significant challenge.

7. SIMULATION

In this section, the role of simulation is analysed as a push initiative in its own right. The demands and appeals to simulation, theory and computation for the experimental thrusts 1-6 are collated in a separate section following section 8. Simulation is regarded as playing an increasingly important and essential role in achieving roadmap objectives at a variety of levels: for understanding and optimizing component processes and subsystems, to support whole system design and programming, and as an integrated part of model based feedback in evolving complex C^hem B^io IT systems in connection with Area 4. The combination of simulation with programming languages describing system content and integrated boundary conditions (e.g. micro- and nanosystems geometry) allows programmable systems to be simulated in increasing sophistication.

7a. Simulation of C^hem B^io IT processes and subsystems

Simulation relevant to fabrication needs to be done at several resolutions with very small systems being investigated with quantum-chemical properties, small systems via molecular dynamics, intermediate systems with coarse-grained particle dynamics (e.g. DPD, SPH) and large systems with container-based simulations or via stochastic or deterministic differential equations. Incorporating information processing into simulated models is straightforward as long as these models are particle-based. Systems biology simulations up to whole cell function are now approaching the complexity if not yet predictive power required for multiscale autonomous fabrication.

7b. Simulation integrated design and programming for C^hem B^io IT

ChemBioIT fabrication typically involves a hierarchy of complex dynamical systems. The design and programming of such systems requires integrated simulation that can only involve idealized modular subsystems due to computational bottlenecks. Systems must also be architected to allow efficient and reproducible customization and programming for desired properties.

7c. Simulation integrated evolution for C^hem B^io IT

The integration of complex system simulations into evolutionary processes will allow a more effective usage of limited test bandwidth (restricted to residual uncertainties). This is expected to become increasingly important in the iterative design and optimization of complex semi-autonomous fabrication processes spanning the molecular to microscales.

The roadmap contributions here and the feedback on Simulation, Theory and Computation following Area 8, both point to an increasing and vital role for simulation in achieving the roadmap goals. Attention will have to be paid beyond multilevel simulation methodologies to interfacing simulation with modular programming environments, the integration of simulation as a component process in real running C^hem B^io IT systems and to the autonomous identification of emergent quantities and higher level descriptions of phenomena. There are acute computation time issues still facing stochastic simulation, or any description of physical systems that embraces potential novelty arising from massively parallel detailed interactions that are abstracted away in more economical higher level approaches. Further research in massively parallel simulation systems and programmable embedded simulations would therefore also complement simulation based on sophisticated hierarchies of abstraction.

8. COMBINATION OF COMPUTING WITH CONSTRUCTION

This area of the roadmap concerns the development of frameworks for information processing (at different scales, and in very different domains) that will be required for construction and production of molecular-scale objects and devices. The fundamental underpinning first topic concerns how information can be encoded and transmitted in a diverse range of systems; we then consider how "networks" might be connected across scales, how such systems might therefore be "programmed", how *ad hoc* systems might be generalized into useful computation/construction architectures, and how such architectures might, in the future, be best optimized for adaptability, self-modification, etc.

8a. Information encoding and communication of information associated with construction

Specific examples of these issues have been identified in many of the topics, but here central questions arising on all platforms can be dealt with in theory and simulation and communicated between the different implementation platforms.

8b. Connecting natural computations (molecular, membrane, cellular etc)

The multi-scale linkup of locally programmed construction requires local information processing at multiple scales, and so the connection of DNA computing, membrane computing, cellular computing and reaction-diffusion computing for example will be important to orchestrate this local programmable control on the different levels.

8c. Programmability and programming autonomous systems

Strictly a contradiction, because autonomous systems are self-controlled, programming these systems in the simplest case means specifying certain constraints or conditions. These may be external (e.g. environmental patterns) or internal (e.g. genetic sequences) to the system. At the highest level, programming is replaced by convincing the autonomous system to respect the external controller's communicated needs e.g. via rewards.

8d. Architectures for combined computation and construction

The formal and practical investigation of novel architectures combining computation and construction, and going beyond the current systems in reconfigurable computing, will pay dividends for advancing the roadmap as a whole.

8e. Optimizing computation for construction

This topics deals with optimality and efficiency of computation as required to direct construction. Different criteria relate to overheads in intermediate information storage, conversion, communication, to robustness and managing information at different length scales etc. Other aspects relate to optimization with respect to future introspection and self- repair, to adaptability, to external controllability and so on.

The main roadmap conclusions for this area echo, in some ways, those of area 6 (autonomous robot construction), in that hybrid systems may offer a powerful route forward, with unconventional devices serving as special-purpose "co-processors" combined with traditional devices. There exist a significant number of powerful material frameworks and associated formalisms. However, there is a distinct need for a framework in which to design, perform and analyze "mixed media" computations, as most studies to date have only been performed on a single substrate, existing theory is severely lacking, and the computational challenge involved in simulating such systems will require significant advances.

DETAILED CONTRIBUTIONS OF CORE TECHNOLOGIES TO THE ROADMAP

See also Futures and Impact sections, Parts III and V below, for further contributions.

1a. Systems Chemistry, Supramolecular and Synthetic Chemistry

Günter von Kiedrowski
Andreas Herrmann

Basis of the Approach

Standard chemistry leads to the creation of structures. Structures are networks of nuclei connected by electrons. Reactions are also networks of molecules connected by transformation of electron structures. What we need to learn is to teach these networks more life-like features by being able to synthesise issues like feedback, control, information processing, logical switching in a modular sense. So the field of systems chemistry is about networks. Making and using atoms as building blocks to make networks of reactions. If we understand life as a prototype, then of course we have the trichotomy of genetic, metabolic and containment information and we need to try to integrate the components into larger arrays. Systems chemistry is related to the issue of emergence : a property that is arising from interactions. However the challenge is to teach and control these networks in the same way as organic chemists do synthesis : the stage of development is still in its infancy despite the huge body of work on catalysis : e.g. phase contact/micellar catalysis. Going a step further – toward self-constructing, self-repairing, self-modifying systems, evolutionary systems, and systems that respond adaptively to changing environments – is still difficult. A benchmark goal is the protocell. Chirality is an important issue: the origin of homochirality is critical here for evolvability. Although Szostak suggests that 5 years will suffice, one must be sceptical that progress will be so rapid. The chemical industry does not have transferable synthesis routes, programmable in the same way that biology is: when it does, progress will be rapid. This should also be more environmentally benign than the approach today.

In the field of supramolecular and synthetic chemistry, it will be of particular importance to develop chemical reactions or catalytic processes that can be integrated into biological systems. This challenge can be mastered by bioorthogonal reactions and by extending their still limited variety. Furthermore, one can think of developing nucleic acid and protein or peptide catalysts that facilitate non-natural transformations. This expansion of reaction scope might be realized with pristine nucleic acid or protein scaffolds but might also benefit from artificial cofactors. In this way, metabolic processes can be extended, which is especially attractive for secondary metabolites that represent important drugs or pharmaceutical intermediates. In the context of metabolism, supramolecular systems should be developed that allow interfacing with ICT systems. Since the input and output of silicon-based ICT hardware can be easily realized by magnetic or optical signals, (supra)molecular chemical structures need to be developed that interact with proteins and nucleic acids in response to such stimuli. Such structures can either be organic molecule-based switches or photo-active proteins and nucleic acids that allow for optical control on the metabolic or genetic level. Such switchable entities are not only important for interfacing the biological world with the ICT domain but are valuable tools both in and as a bridge to systems biology. Another important task for synthetic chemistry in the field of ICT and biology is the replacement of natural catalytic systems by purely synthetic ones. Although Nature has evolved an intriguing plethora of protein catalysts, enzymes suffer when put in a non-natural environment. The shelf-life is short, they easily degrade or denature if not stored under appropriate conditions. In contrast, synthetic chemists have evolved a large variety of catalysts that are very robust and do not suffer regarding stability issues. Such systems might replace enzymes for interfacing with electronic systems because they can withstand the demanding conditions such as are found at electrodes or electrode surfaces. Moreover, they are excellent reporter systems for diagnostic assays that can produce specific color or fluorescence signals.

Contribution to Central Overall Goal

This is an alternative to the Drexlerian vision of nano tech organised machinery, based on a rigid diamond-like architecture. Systems chemistry will contribute by using a less rigid, more "plastic" or loose structure. We need to develop a set of strategies which couple a solid architecture with architectures that use information to process plastic structures: there systems chemistry can contribute. For example, if we think about the brain, it is not only electrical, but it is continuously rebuilding itself morphologically, but it is not a fixed set of neurons. Chemistry that can deliver plastic changes in structure will need to be further researched in the area of chemistry.

Main Accomplishments

1a	Main Achievement	Year	By	DS[5]
1.	Self-replicating molecules	1986	v. Kiedrowski	c
2.	Chiral symmetry breaking	1994	Soai	c
3.	Partial integration of subsystems towards protocell	2008-10	J. Szostak, L. Luigi, v. Kiedrowski,	c
4.	Models of plasticity wrt to polymerization	2011-13	Wolf, Willner	d
5.	Metabolic networks	2005?	S. Benner	c

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

1a	Strengths	Unknowns	Weaknesses
1.	Plasticity, adaptability, changeability needs interfacial systems chemistry : not possible with Si machining	The structure of water and interfacial chemistry	Weakness is that of chemistry: a piece of novel chemistry requires long work to take next step
2.	Enabling technology for the roadmap	Attaining atomically detailed structures beyond the 5 nm scale	Lack of modularity of chemistry : each new molecule is different, with certain unpredictable properties
3.	Systematic scientific development		Chemical space harbours its own surprises (lack of programmability), although much can be done with serious simulation.

1b. DNA computing and DNA machines

Friedrich Simmel
Martyn Amos

Basis of the Approach

The subarea (today) aims at the realization of molecular information processing capabilities and molecular machines based on nucleic acids, and the integration of these within autonomous molecular robotic and fabrication systems. Nucleic acids are used as the molecular substrate in this area (most often DNA, but also RNA and sometimes a few enzymes) as their sequence directly determines (via base-paring) their interactions. Thus it is relatively straightforward to design molecules with certain shapes and mechanical properties and link them together into networks of interacting entities. A fundamental idea is to use the biophysical properties of molecules such as DNA (but also RNA) to somehow encode "computations". These may be thought of as a series of controlled transitions through a number of states, which is defined both by the internal "programming" of the system and the input it receives. Thus a more recent term established for this field is "molecular programming". MP also envisions the development of software tools that allow one to "program" molecular structures, devices, and reactions on a symbolic level, and "compile" them down to a molecular level. The information-encoding nature of DNA (RNA) seems to be well suited for such an approach. Early work on DNA computing focussed on the solution of "traditional" computational problems, the motivation being that the massive inherent parallelism of operations on DNA, combined with its vast potential for storage miniaturisation, meant that we could attack problems that defeated traditional silicon-

[5] DS = Development Status Metric with following meanings
a) an approach amenable to modular integration and automation
b) an approach robustly transferrable between labs
c) an approach firmly established scientifically
d) an approach with some experimental evidence as to viability
e) an approach verified by simulation and quantitative estimates
f) a hypothetical approach, no known implementation so far.

based machines. However, this ambition was never really underpinned by serious theory, and it quickly became clear that this route would result in a dead-end. However, the growth of so-called "DNA origami", molecular programming/automata and controlled self-assembly has led to a "second generation" of realistic DNA computing applications that work in well-defined environments.

Contribution to Central Overall Goal

Up to a certain degree, this is exactly the goal of this field and what in part already has been achieved. Molecular structures and also dynamic reaction circuits can be designed on an abstract level, and then transferred into DNA/RNA sequences, which allows their hardware implementation. Production and information processing in nucleic acids is strongly connected. What is currently not yet possible is the realization of autonomously running processes that can be programmed/varied "on the fly". This will require permanently running, out-of-equilibrium dynamical systems with defined interactions with their environment and internal control circuits/programs - essentially cell-scale/cell-like reaction systems. This is something that is actively pursued by some researchers in the field (but which is also at the border to protocell/artificial cell research etc.). From a more practical perspective, control over molecular-scale interactions via "programmed" responses to external stimuli will facilitate a next generation of material production, drug delivery and diagnostics.

Main Accomplishments

1b	Main Achievement	Year	By	DS
1.	Combinatorial problem solution	1994	Adleman	
2.	Molecular automaton	2004	Benenson	b
3.	Software packages	2003	Pierce lab	
4.	DNA self-assembly & origami	2006	Rothemund	
5.	DNA nanomachines	2010	Stojanovic, Winfree, Yan	
6.	Strand displacement	2011	Yurke, Qian	
7.	DNA computing/molecular programming	2011	Lulu Qian & Erik Winfree	
8.	DNA origami in living organism	2014	Amir	d

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

1b	Strengths	Unknowns	Weaknesses
1.	DNA origami i) works relatively well, ii) it is amenable to automation/computational design, iii) has inspired many researchers Essentially, one can achieve almost arbitrary shapes, and diverse dynamics with DNA or DNA devices, but not arbitrary "function".	The usage/development of synthetic DNA analogues may be required in the future or some sort of "chemical translation".	The drawback is that DNA/RNA may not be the best molecule from a "materials" point of view, Chemical functionalization is still difficult, and not everything can be done that might be desirable. Also the aqueous/salty environment is not ideal for many applications.
2.	Demonstrable control over nano-scale self-assembly. DNA Nanomachines have an impressive array of achievements ranging from stepped movement to fabrication control and even self-replication.	"Killer applications" Scalability to large structures, and complex processes.	Another issue is "scale". It is currently not clear how one would generate large quantities of DNA devices, or very large structures, or operate DNA computing circuits very fast and without leakage/crosstalk (i.e., precision).
3.	Impressive computational performance with "seesaw gates" and strand displacement. Modular systems combining DNA processing with DNA synthesis. Proof of principle of integration with living cells/organisms. Integration with microfluidics.	Potential health/ethical/environmental implications	Still relatively few "real world" applications. Continued emphasis (in some quarters) on trying to solve computationally hard problems. Relative lack of automation

Additional Comments

Software packages: Extremely important for the field certainly was the development of software packages for design and analysis, most notably NUPACK by the Pierce lab (2003-now), the caDNAno software for origami design by Douglas (2009-now), and a finite element program for the analysis of mechanical properties of origami structures (Bathe 2011). There are also others, but these are the most widely used. NUPACK (in contrast to mfold or the Vienna package) also allows for multistrand analysis and design. Some people have just recently begun to model DNA nanosystems on an atomic/molecular level (in particular the coarse-grained oxDNA model by Doye, Louis, etc, 2012, and an MM/MD study by Aksimentiev, 2013). For dynamic DNA circuits, one can also utilize common systems biology software. Classifies diversely as a-e in terms of the developmental metrics.

Strengths, unknowns and weaknesses:
The main strengths of DNA-based information processing and DNA machines are their rational, sequence-based design and construction, which can be implemented on a (electronic) computer. Molecular properties are very well known and structures and interactions can be analyzed/predicted much better than for almost any other molecular system. Furthermore, DNA sequences can be synthesized by automated synthesis, and thus a "real" molecular implementation of a computational design is readily achievable.
Strength 1. Even though this does not directly count as DNA computing/DNA machines, some of the developments here had an influence on the subarea. The most important accomplishments of the past years were the development of the DNA origami technique by Rothemund, 2006, and in 3D by Shih, 2009. A related technique is the single-stranded tile assembly by Peng Yin (2010,2011) . In principle, all of these are variations of traditional Seeman/Winfree-type assembly, but the focus is (so far) on molecular objects rather than lattices/crystals. What is remarkable about DNA origami is that it i) works relatively well, ii) it is amenable to automation/ computational design, iii) has inspired many researchers and attracted them to the field, which resulted in increased activity in that area. A lot could be said about DNA nanostructures and potential applications here, but that would lead into a different area (most of the time, there is no information-processing, dynamical, self-organizing aspect). Classifies as a) - e)
Strength 2. There has been a lot of work on DNA-based nanomachines of diverse types in the past decade (a review is found, e.g., in Krishnan & Simmel, Angew. Chem., 2011). Most of these are relatively simple molecular switches, which are not particularly interesting in the context of the subarea. Among the more important recent achievements were: - DNA walkers that walk over longer (origami-based) tracks - DNA "spiders" by Stojanovic, Winfree, Yan 2010, and several walker types by Turberfield 2011-2012. - a DNA-based assembly line for "programmable" assembly of nanoparticles (Seeman, 2010). - switchable containers (such as the origami box by Gothelf, Kjems 2009) - there have also been interesting developments in the context of "programmable fabrication": DNA directed synthesis (previously developed by David R. Liu at Harvard in the 2000s) was also realized on DNA origami structures (Seeman, Gothelf, Turberfield, 2011-now) and even combined with molecular walkers (D. R. Liu, 2012). - first attempts to make "self-replicating" systems based on DNA nanostructures (Chaikin, Seeman 2011). Classifies as c) & d)
Strength 3. The greatest achievement in DNA computing in the past few years was certainly the development of a simple concept for DNA circuitry called "DNA seesaw gates" by Lulu Qian & Erik Winfree in 2011 that could be used to realize the largest DNA-based molecular computing networks so far (including a network for square root computation using 130 DNA strands (!) and the implementation of neural network computing). Apart from seesaw gates, in general so-called "DNA strand displacement" (DSD) circuits have become the new DNA computing paradigm. They typically use disruption of simple secondary structures (like duplexes, hairpins) for the "activation" of specific sequences, and thus allow building up molecular networks. Major achievements were logical evaluation of miRNA patterns (Seelig, 2006), molecular feedback/amplifying networks (Zhang, 2007, and Yin & Pierce, 2008), conditional single-base change detection (Zhang, Seelig, 2013) and programmable chemical controllers (Cardelli, Phillips, Soloveichik, Seelig, 2013) Another development were small biochemical networks with only a few enzymes, most notably the "DNA toolbox" by Yannick Rondelez 2011-now, and "genelet circuits" by Jongmin Kim and Erik Winfree (2006-now). It is not particularly good style, but in this context one probably also has to mention our utilization of genelet circuits for the control of DNA nanodevices and production of RNA molecules (2011), and their encapsulation in cell-sized compartments (2014). Classifies as a), c) & d)

Contribution to Energetics and Sustainability. Progress in subarea 1b would maybe also help in topics 9,10. Energetics for informed instruction: the contribution to this aspect is not obvious, but of course production by self-assembly and within cell-scale compartments potentially is very energy-efficient. Energy input is of course required for the starting materials. In the case of "synthetic biological" implementations (within bacteria or eukaryotes), the energy will be provided through the metabolism of the host organism. Artificial cells will require development of their own energy sources, which might also be some sort of light-driven chemical reaction. There are no clear contributions to 10b-10c.

1c. Inorganic biology and genetic alternatives to nucleic acids

Lee Cronin
Steen Rasmussen

Basis of the Approach

The key idea is the exploration of how stochastic chemical processes lead to the establishment of the minimal machinery of evolution i.e. an evolution first concept at the origin of life, and also for use in artificial life approaches to allow emergence of maximal function with minimum bit-content but allowing for physiochemical programming via self-assembly. The Glasgow group (L. Cronin) has assembled an unparalleled range of automatic chemical robots including flow systems, micro / milli / liquid handling robots capable of random chemistry, stochastic processing, emergence of function followed by maintenance of function. The use of algorithmic programming of chemistry as a search engine to truncate the state-space and also evaluate possible new self-organising and assembling architectures with dissipative dynamics is a key goal underway.

Biology is in general thought of as being composed of organic materials although many key processes (e.g. the metabolism) contains inorganic components. However biological elements and processes may be assigned functions even in the event of substituting organic by inorganic materials. Imitating biology, by components that have similar or identical patterns in terms of functionality, but have organic constituents replaced with synthetic inorganic equivalents, may e.g. provide us with the power to control and manipulate states and processes otherwise inaccessible in living system or even make new artificial living constructs. The ability to build complex combinatorial structures, for example based on polyoxometalates, and replicate structural variations thereof opens interesting possibilities to develop a self-informed inorganic autonomous fabrication that can already span spatial scales (e.g. in tube structures).

Contribution to Central Overall Goal

Research in inorganic biology is a multidisciplinary endeavour placing chemistry and ICT centre stage, allowing the programming of chemistry and exploring new substrates as heterotic computing layers, as well as device / architecture fabrication on the nanoscale right up to the macroscale for control of complex chemical systems.
Inorganic biology contributes a promising connection between ICT and ChemBio as an extension of information (or other) components to be composed of inorganic materials as well. This provides more design opportunities and maybe even novel ways to integrate semiconductors (and conductors) within ChemBio components.

Main Accomplishments (Cronin)

1c	Main Achievement	Year	By	DS
1.	Self-assembling inorganic molecules in seconds from a state space $>10^{120}$	2010	Cronin	d
2.	Inorganic replicator systems	2014	Cronin (in press)	d
3.	Flow system search engine	2012	Cronin (Nature Chemistry)	c
4.	Algorithmic programming of chemical systems	2014	Cronin (Nature Communications, Nature Chemistry)	c

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

1c	Strengths	Unknowns	Weaknesses
1.	The special strength of this is that it potentially defines a new route to view evolution outside of biology placing emphasis on functional complexity with minimum 'templated' bit content.	The idea of using non-organic polymers for evolutionary molecular dynamics is both risky and innovative.	

1d. Artificial chemistries and formalisms for molecular construction and IT

Peter Stadler
Peter Dittrich

Basis of the Approach

Development of a formal framework to understand chemistry as a constructive system. Current approaches include algebraic systems as well as -- presumably more promising - [graph] rewriting systems to model chemical transformations. Artificial Chemistries aim at providing an "effective theory" of [mostly organic] chemistry. At present there are few practical applications to chemical engineering/farbication, although progress in the direction of devising "one-pot reactions" as alternative strategies to chemical synthesis do not seem far away.

Different formal approaches are available for describing and designing molecular computing systems. Reaction kinetic models like chemical differential equations are used to describe systems with a small number of species and different (often continuous) concentration levels, like for chemical neurons (Hjelmfelt/Weinberger/Ross 1991). For a combinatorially large number of species algebraic approaches like term rewriting systems are applied (Berry/Boudol 1989; Paun 2000). As a typical approach in artificial chemistries, the set of molecular species is defined implicitly by a grammar, allowing to handle large even infinitely sized reaction networks. Various techniques from computer science are employed, like finite state machines for describing conformational computing (Zauner/Conrad 1998); or graph theory, Petri networks (Petri 1980), and constrained-based methods for the algebraic analysis of reaction networks. Three approaches for the design of molecular computing systems can be distinguished: (a) Manual design of particular chemical algorithms; (b) Automatic design by optimization, e.g., using evolutionary algorithms; (c) Generative design by using a framework for "compiling" high level descriptions (e.g., sticker model, DNA origami, stack automaton) to the chemical level. Traditional models of of computer science like Turing machines and Boolean networks are also chemically implemented, making a huge body of computational theory available; however at the expense of efficiency, since the chemical medium is highly constrained and its inherent computational properties not exploited. From the study of combinatorially complex chemical systems through artificial chemistries also novel theoretical concepts and tools have been developed, like autocatalytic set theory or the theory of chemical organizations (Dittrich/Speroni d.F. 2007) targeting the qualitative dynamics (i.e. the arrival of novel species over time) of chemical computing.

Contribution to Central Overall Goal

This subtopic provides a theoretical framework and practical computational tools to understand large interacting chemical reaction systems and their internal organization. This is a purely theoretical approach to-date, however.
The theoretical and computational methods mentioned above contribute to the theoretical foundation of BioChemICT. In particular they target the combinatorial nature of chemical systems and the inherent problem of linking algebraic descriptions like rules to dynamical behavior and the actual computation carried out. As pointed out by Zauner, this link is essential for the design and programming of molecular computers.

Main Accomplishments

1d	Main Achievement	Year	By	DS
1.	Abstraction of essential processes like pattern formation and self-replication in the early days of computer science	1953	Turing, von Neumann	f
2.	Theory of chemical organization	2010	Dittrich group	b
3.	Graph based simulation system	2013	Merkle	c
4.	The idea that molecules can compute and molecular computational machines	1970s	M. Conrad and R. Laing	f
5.	Developing abstract formal calculi capturing features of chemistry	1989	e.g. Berry/Boudol	f
6.	Artificial chemistries allowing to simulate large combinatorial systems (e.g., Kauffman 1986, Fontana/Buss 1994) and to develop novel theoretical	1994-2007	Kauffman 1986, Fontana/Buss, Dittrich/Speroni	e

	concepts like chemical organizations (Fontana/Buss 1994; Dittrich/Speroni d.F. 2007).			
7.	Development of more realistic rule-based descriptions of chemical systems (e.g., BNGL, Kapa, graph-chemistry) with the potential of automatic course-graining, e.g., through abstract interpretation	1986,1994,2007	J. Feret/ V. Danos (last part)	e

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

1d	Strengths	Unknowns	Weaknesses
1.	The theoretical foundations are relying on structural and formal sciences, like reaction network theory and formal languages, which makes the approach applicable to very different systems at various scales, i.e. from single molecules, over molecular complexes, compartments, cells, organisms, and hybrid bio-electronical systems.	Unclear at present how much chemical realism can be achieved	Provides [at present] qualitative results/predictions only Efficiency (chemistry is slow compared to electronics)
2.	Concise formal framework, mathematically well defined. Robustness is achieved due to a decentralized dynamics and emergent control.	A unifying theory dealing with the combinatorial nature of molecular computing is still missing.	Universality (in the sense of Turing) is often lacking.
3.	The system can be inherently be creative, if combinatorial molecules like polymers are used.		Manual programmability (since difficult to foresee the result of a micro-rule)

2a. Reaction Diffusion Computing and Chemical Pattern Formation

Jerzy Gorecki
John McCaskill

Basis of the Approach

The interest in reaction diffusion computing with excitable chemical medium was motivated by qualitative similarities between the properties of excitable media and nerve cells. If one considers a spatially distributed excitable medium then such medium behaves like we expect the nerve cells do. A small medium perturbation that does not exceed the threshold value and rapidly disappears. Therefore, the medium shows no activity that can be related to information processing. Perturbations, that exceed the threshold can generate excitations observed as high concentrations of selected reagents. If a perturbation is local and diffusion of reagents is allowed, then pulses of excitation formed by peaks of concentrations can propagate through the medium. In chemical information processing media, as well as in biological systems, information can be coded in the presence of excitations or in their trains. Therefore, we can believe that relatively cheap experiments on information processing with excitable chemical medium like Belousov-Zhabotinsky reaction can help to understand strategies of biological information processing, that, if studied in-vivo are much more expensive and require specialized laboratories. In reaction-diffusion computing information is processed in regions of medium where pulses from different sources arrive and interact. Previous studies have shown that the geometrical structure of the medium is equally important as the chemical kinetics, because it can force required interactions. A structure of active elements, suitable for information processing can be built of droplets containing nonlinear chemical medium inside. For Belousov-Zhabotinsky reaction such droplets (BZ-droplets) are mechanically stable if they are covered by a lipid layer. Structures of droplets with controllable chemical properties can be generated with microfluidic reactors, therefore one can hope that future chemical "computers" can be manufactured as the result self-organization at carefully selected nonequilibrium conditions.

The central idea of linking reaction diffusion systems with computational morphogenesis dates back to the seminal paper of Alan Turing on "Chemical Morphogenesis", establishing reaction-diffusion systems (RD) as a potential alternative platform for universal construction to the cellular and kinetic automata models of von Neumann. Reaction-diffusion systems combine local transport by diffusion with chemical reactions to propagate information and construct patterns in the form of concentration profiles. Usually, additional processes, such as concentration-induced phase-changes, are required to fix temporal concentration patterns to allow them as a substrate for increasingly complex pattern formation. It appears most likely that RD will be employed in conjunction with other approaches, as in biology, to achieve complex genetically-directed construction by locally autonomous processes. McCaskill pioneered the investigation of RD which can evolve on laboratory timescales using microfluidic structures to constrain the dynamics, demonstrating that evolvable RD might be a candidate for information directed construction. Reaction diffusion systems have been used extensively in both chemistry and biology to describe pattern forming systems. Initially met with skepticism by molecular biologists (cf. Meinhardt), reaction diffusion systems are now agreed to play a significant role in development, at least since the experimental demonstration of Turing structures (de Kepper) in chemical systems. Investigations of computations using RD are now common (e.g. Gorecki, Zauner), often in conjunction with micro channel networks. Reaction-diffusion systems are employed to enhance the resolution of pattern transfer in conventional lithography and in various other pattern-forming processes. Epstein has pioneered the investigation of droplet-segregated media for pattern formation, as taken up by M. Heymann, Zauner and others. Progress in modular in vitro genetic amplification systems (e.g. Montagne) make significant further progress in this area in the near future likely.

Contribution to Central Overall Goal

Reaction diffusion computing nicely fits into the main goal of ChemBioIT activity. On the one hand the results obtained within reaction diffusion computing can contribute to the other core technologies on ChemBioIT shortlist; on the other hand the progress in reaction diffusion computing depends on the results obtained in the other fields. A few examples: (i) New fabrication techniques like microfluidics are commonly used to generate BZ-droplets. (ii) Electrical fields are potential tools for droplet manipulation in multiple droplet structures. (iii) Evolutionary processing, and especially the genetic programming seem to be well suited to find the optimum programing algorithms for reaction-diffusion computers.

The main impact of reaction-diffusion systems is in linking reaction kinetic properties of molecules to spatial pattern formation in a continuous phase, allowing specific structures to be formed at well-defined locations to build higher order complexity. No "wires" are required, with directional information emerging as a dynamical property of interacting concentration waves through the nonlinearity of chemical kinetic dependence on concentration under mass-action. Since the resolution and directional control of such pure RD processes are limited, it is most likely that RD systems will contribute to the overall goal of the roadmap as a component structuring process in conjunction with other methods, especially induced phase-transitions and evolutionary approaches. Such systems can also be used in conjunction with processes like chemotaxis to enrich the repertoire of programmable dynamical structures achievable.

Main Accomplishments

2a	Main Achievement	Year	By	DS
1.	Optical control of nonlinear chemical medium	1989	Kuhnert,Agladze,Krinsky	b
	Chemical morphogenesis	1953	Turing	f
2.	Concepts of information processing in compartmentalized excitable chemical media	1995	Showalter,Steinbock,Toth, Yoshikawa	d
	Evolving RD systems	1991-3	Hogeweg, McCaskill	d
3.	Belousov-Zhabotinsky reaction in droplets separated by organic phase with lipids or surfactants	2000	Epstein, Vanag	c
	Turing patterns experimental	1994	de Kepper	c
4.	Application of microfluidic devices in reaction-diffusion computing	2005	Epstein, Herminghaus	c
	RD computation	1995	Showalter,Yoshikawa, Gorecki	d
5.	Strategies of teaching for a medium composed of active droplets	2012	Dittrich, Gruenert, Gizynski, Gorecki	e

	Evolving RD in multiphase systems	2008	McCaskill, Packard, Bedau, Rasmussen	d

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

2a	Strengths	Unknowns	Weaknesses
1.	RD is a general mechanism used ubiquitously in biology. Good information processing applications of reaction-diffusion medium are highly parallel. They are an inspiration for algorithms running on classical computers.	What are the miniaturization limits of reaction-diffusion information processing? Can one have reliable information processing with hundreds of molecules? Are there efficient programming methodologies in the light of non-linear interactions?	Diffusion is a local process and thus provides interactions with nearest neighbors. For complex operations long distance interactions between active centers are required. Time and space scales are limited by molecular diffusion.
2.	Self-organization phenomena can be used to assembly processing devices from droplets containing active medium. RD systems allow combination with signal amplification for general computation.	How to optimize information coding and relate it with chemical kinetics? How to best combine with more permanent multi-phase structure formation in artificial systems. Stability of complex structures to external perturbations.	RD computing with a typical nonlinear chemical medium is slow. For practical applications we need a faster (smaller?) medium. Isotropy in space means that information is broadcast in all directions.
3.	It is relatively easy to make 3D structures of active elements (e.g. droplets). Allows combination with genetic molecules to allow evolution.	What is the optimum applications of reaction-diffusion medium for information processing? Can we build universal computer with reaction diffusion medium without Boolean coding and logic gates?	There is no on/off switch in reaction diffusion computer. At the moment it operates up to the moment all reagents are consumed.

Additional Comments

At the moment it is not a problem to self-assemble 2D or 3D structures of interacting droplets. However it seems difficult to control information inflow and outflow. Moreover, reactions in a droplet system start immediately after all reagents are mixed. I do not know how to stop medium activity and restart it when required.

Simulations are very important because potential realizations of reaction-diffusion computers can be verified in-silico before experiments. But in my opinion it is more important if results of simulations do not agree with theory because it indicates that we do not understand the physical processes determining the time evolution of considered computing medium.

2b. Multiphase chemistry involving self-assembled macroscopic structures

Steen Rasmussen

Basis of the Approach

Self-assembly is usually referred to as an entropy driven process (down hill in terms of free energy) of higher order molecular structures in water or some other solvent. Multiphase chemistry may occur at and around the interfaces created by self-assembled structures: Membranes, emulsions, droplets, microtubules, XNA structures, actin filaments and other multiphase (filament, container or active) systems. Further, self-assembly can occur at ICT active surfaces or can even occur between small ICT components. Morphological design and computation with and self-assembly of such structures provide a suite of techniques for bridging molecular to micro scale autonomous functionalities including motility, protection and fabrication including approaches involving artificial self-replicating protocells as well as subcomponents of modern living cells. Various systems may exhibit different characteristics under different conditions and time frames and the possible interplay and interchange between micro components. Their stability, interchangeability, re-organization and functional significances are extensively studied in the scientific

community.

Membranes, emulsions, nanoparticles, DNA-scaffolds, actine motors, microtubules, droplets and other multiphase container systems including morphological (and DNA) computation with and self-assembly of such structures provide a suite of techniques for bridging molecular to micro scale autonomous fabrication including approaches involving self-replicating protocells, although protocells also includes active metabolic elements. Various systems may exhibit different characteristics under different conditions and time frames and the possible interplay and interchange between micro components. Their stability, interchangeability, re-organization and functional significances could be discussed. An important connection to ICT is e.g. through DNA to chips at programmable addresses (e.g. through electrodes), which can address containers decorated with complementary DNA, which again can address other DNA decorated containers. Two DNA linked containers can fuse and mix content resulting in chemical reactions and thus the production of new materials. Recursive, programmable: computer control of electrodes, chemical control of DNA addressing, and membrane control of container mixing - action of this nature has a huge potential in nanoscale material production. Metabolic processes can occur across membranes or at membrane/droplet surfaces.

Contribution to Central Overall Goal

This area supports critical scientific investigations for a successful coupling between biochemistry, supramolecular chemistry and ICT. It is a critical element in the C^hem B^io IT Roadmap. As in biology, where multiphase systems limit the domain of reaction-diffusion, and provide a substrate for a wealth of large scale phenomena (e.g. blood vessels), chemical construciton and information processing only really come into full play when the molecular level is complemented with multiphase physical systems.

Main Accomplishments

2b	Main Achievement	Year	By	DS
1.	Passive aggregates (e.g. membranes, droplets, microemulsions). Self-replicating micelles and vesicles	<1990 1989	many groups P. Luisi, P. Walde	a d
2.	Active components (e.g. microtubules, actin, etc)	<2000	many groups	b
3.	Membrane computing	<2010	Paun, + many groups	c
4.	ChemBio-ICT component self-assembled new functions	2008-2015	e.g. projects: ECCell, MATCHIT, MICREAgents	d
5.	autonomous self-replicating protocells	current	e.g. groups of Szostak, Rasmussen, Cronin, Chen ...	e

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

2b	Strengths	Unknowns	Weaknesses
1.	Bottom up approach. DNA computing & membrane computing can be implemented directly based on self-assembly.	No direct engineering approach seems available to create desired higher level functionalities	Very difficult to impose direct control - only indirect control possible via environment Labor intensive - costly
2.	Flexibility and scalability. Directed self-assembly is down-hill theomodynamically ($\Delta G < 0$).	An emergent - or self-organized - engineering approach is necessary	Usually the systems(chemistry) becomes messy very quickly once more components are mixed
3.	Specificity (ability to target) We can make molecular programmed nanoscale to mesoscale structures/ functionalities.	Unknown how to predict general self-assembled mesoscale structures	Difficult - often impossible - to design top down -need to design bottom up. Trial and error method often necessary in design - lack of theory

2c. Surface and interfacial chemical systems: including multilayer fab

Nicolas Plumeré
Itamar Willner

Basis of the Approach

Directed 3D Self-assembly of molecular building blocks to form patterned multilayers of interconnected functionalities. Signal-triggered monolayer controlling interfacial electron transfer, hydrophilic/ hydrophobic properties, and specific recognition properties will find important functions in controlling reactivity at surfaces. Triggering inputs could be electrical, optical, pH or chemical stimuli. Pre-programming of the monolayer/thin film modifying layer by molecular imprinting protocols, and chemical "memory" structural/functional elements might lead to highly reactive and selective interfaces.

Contribution to Central Overall Goal

Self-assembly guided by the molecular building block design combined to external stimuli (optical, electrochemical, chemical ...) for complexes structure fabrication with nanometric precision. State of development: an approach with some experimental evidence as to viability. Self assembly of individual building blocks each bearing multiple functionalities for activation via external stimuli. Specific combination of local electrochemical, and local optical triggers confers to each molecular building block a specific code and thus a high information content in the 3D layer.Writing and reading processes will be performed: i) in the 3D layers directly: confocal optical methods and 3D networks of individually addressable electrodes would be developed for local activation of the individual building blocks in the 3D layers. ii) after unfolding the 3D layer in nanochains of the molecular building block (as in EVINCE Project).

Main Accomplishments

2c	Main Achievement	Year	By	DS
1.	Programmed pattern generator	2005	Basu	c
2.	Synchronised genetic clocks	2010	Danino	c
3.	Edge detector	2009	Tabor	c
4.	Circuit evaluation	2011	Regot	c
5.	DNA messaging	2012	Ortiz	c

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

2c	Strengths	Unknowns	Weaknesses
1.	Production of chemically well defined building blocks	Precise structure of the self assembled layers	Reproducibility of the self assembly process
2.	Construction of complex assemblies in a single or few steps	Mechanism of multiple parallel and orthogonal process in 3D layers	Impact of stochastic gene expression
3.	Possibility to introduce multiple and invidually adressable functions via specific stimuli	Ability of engineered consortia to maintain long-term homeostasis	Difficult to eliminate cross-talk between components

2d. Iterative chemical processing systems with integrated separation and cleanup

Uwe Tangen
Steen Rasmussen

Basis of the Approach

An autonomous version of synthetic chemical reaction pathways requires the integration of separation processes to purify next reactants from complex product mixes. Lab on a chip integration is providing local mechanisms to approach this with increasing process autonomy, but the separation processes still need to be directed by molecular information. Can there be a classification of reactants and products from similar and dissimilar processes that can aim to draw up an equation for different combinations and get more precise results with more accurate approximation? More on-a-chip separation methods and increased equipment accuracy as well as simulation may lead to better control of these chemical processing systems if each reaction is looked into from multiple perspectives.

Contribution to Central Overall Goal

ICT at the molecular level requires amplification, cleanup, mix and split at least. A detailed control at the molecular level seems to be infeasible and thus requiring at least partial autonomous processing. In that sense this approach is central to the common roadmap goal.
Critical part of ChemBio-ICT integration, where ICT mainly acts as an external programmable matrix that enhances the detailed process control, separation and cleanup.

Main Accomplishments

2d	Main Achievement	Year	By	DS
1.	Separation compatible with reaction	2013	Tangen et al.	d
2.	Isothermal amplification compatible with separation	2014	Von Kiedrowski, Plasson, McCaskill	d
3.	Iterative amplification	2013	Minero, McCaskill	f
4.	Integrate iterative amplification and cleanup	2013	Wagler, McCaskill	f

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

2d	Strengths	Unknowns	Weaknesses
1.	controlled environment	interaction and crosstalk between parts of the system	difficult interfacing to outside world
2.	relatively easy to be integrated in small form factors	contamination of surfaces	Loss of material without amplification

2e. Computational and theoretical bounds for self-organization and -assembly

Steen Rasmussen

Basis of the Approach

We don't yet have a theory for self-organizing and self-assembling processes, which are usually connected to molecular construction processes, and there is no direct connection between these processes and the ability of a system to perform computations. By nature both self-organizing and self-assembly processes are bottom up without any centralized control, the first developing local order driven by an external flow of free energy, the former developing local order although entropy driven and down-hill in free energy. The nuts and bolts of physical computation are also partly bottom up and governed by local interactions, but programmability of computational processes are usually top down and a direct top-down programmability of self-organization and self-assembly is not available. In formulating such processes, it is important to draw on theoretical understanding of any necessary tradeoffs for example between simplicity and accuracy and between the possible levels of description. Also, which questions to address about these systems? Are we investigating e.g. construction speed versus fidelity, is it between adaptability and self-repair properties, between energy consumption and energy conservation, or reliability of higher level functions? How far can these boundaries be pushed and what are the negative implications of the same? What is the limit to which such artificially constructed systems actually retain their originality and more importantly mimic the real systems? Working backwards, can prioritization of outcome and reliability be determined, and then formulation of processes be worked out around this?

Contribution to Central Overall Goal

Critical to the ChemBio-ICT roadmap as it involves how material construction and computation is connected

Main Accomplishments

2e	Main Achievement	Year	By	DS

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

2e	Strengths	Unknowns	Weaknesses

3a. Cellular Synthetic Biology using radical GMOs

Angel Goñi-Moreno
Martyn Amos

Basis of the Approach

Synthetic biology concerns the application of engineering principles to the rational redesign of living (cellular) systems for the purposes of obtaining useful (human-defined) behaviour. This might include the production/delivery of drugs, bioengineering, environmental monitoring/remediation, sensing, etc. The field has rapidly developed over the past 15 years, from initial conceptual studies to a major area of interest with significant funding support, international conferences and journals, etc. "Synthetic biology is still in its early stages of development. If we stick with the comparison to the microchip industry and consider that the first transistor was developed in 1947, then we are now at about 1960." (Silver, et al., 2014).

Top down synthetic biology at the cellular level transcends traditional genetic engineering in orchestrating complex novel functionality (which most importantly involves rational design and engineering principles) into organisms from multiple concerted genetic alterations (not isolated mutations or insertions but also use of big synthetic elements). Typical targets are to modify bacteria as efficient fuel cells or for environmental remediation by changing their way of processing information. It is increasingly clear that making major changes to the ('genomes') genetic material of existing cells usually runs into major compatibility problems resulting form the lack of modularity and orthogonality of intracellular processes. Bottom up artificial cell assembly is more challenging and less advanced, but can in the long term presumably sidestep the modularity issues for the top down approach. the synthethis of novel parts designed to avoid cross-talks (while keeping standard activity) tackles the aforementioned issue inside cells.

Contribution to Central Overall Goal

This approach may cover the whole roadmap definition from the start to the end (in a specific domain) rather than contributing to it in a single step/stage of it. The "down to the molecular scale" bit is quite clear, as we use genetic technology for our devices (promoters, plasmids, proteins, ...) thus molecular scale. The overall goal also mentions "information processing" as the aim of the devices, and that is exactly the goal when creating genetic circuits: to alter/modify the flows of information through the engineered molecular machinery. The "production" side of the roadmap goal is not that clear to me. If it means to construct physically the device instead of simulating/modelling it, that is also the goal of synthetic biology: alter/modify cells (GMOs) by placing inside the produced synthetic circuit. This approach travels in parallel with others along the roadmap. Genetic encoding is fundamentally inherent to synthetic biology. Many existing applications are production-based in nature (eg. drug precursors), and several studies examine autonomous construction of spatially-resolved structures.

Main Accomplishments

3a	Main Achievement	Year	By	DS
1.	Minimal cell	1999	Hutchison	c
2.	The repressilator	2000	Michael Elowitz	b
3.	Engineered gene circuits	2002	James J. Collins	b
4.	Registries of parts	2003	MIT/others	a
5.	Multicellular pattern formation	2005	Ron Weiss	b
6.	MAGE	2009	Wang	a
7.	Distributed Logic Gates	2011	Ricard Sole	b
8.	CRISPR	2013	Gaj	b
9.	Amplifying Genetic Logic Gates	2013	Drew Endy	b
10.	Synthetic yeast chromosome	2014	Boeke	d

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

3a	Strengths	Unknowns	Weaknesses
1.	Brings together scientists from many disciplines in a strong and vibrant community	What about ethics? As the discipline evolves, the ethics issues will emerge. Future	Fashion-victim discipline. What is science? and what is not? (i.e. iGEM)

		public response to potentially controversial developments.	Relative lack of "real world" applications
2.	Brings standards to biology, thus turns it into a "technical science" Integration of "design thinking" into biology.	Fundamental understanding of gene circuit operation. Standards arise. But, who is to say which standard is more standard than which?	"Fast" development impedes "good" development (i.e. publish FAST, a LOT and NOW). As a basic science (hard to build apps now) the funding cuts is killing entire research systems.
3.	Endless source for biotech applications. Needs have driven significant technological developments (assembly, analysis, etc.).	Definition of what synthetic biology actually IS! Is this a boom? Or a here-to-stay approach? Introducing Syn Bio in univeristy degrees may help to regulate it.	Difficulty of mammalian synthetic biology. Lack of fundamental biological understanding

3b. Cellular computation and Genetic Regulatory Networks involving cell communication

Martyn Amos

Basis of the Approach

Synthetic biology is an emerging research field, in which engineering principles are applied to natural, living systems. A major goal of synthetic biology is to harness the inherent "biological nanotechnology" of living cells for the purposes of computation, production, or diagnosis. As the field evolves, it is gradually developing from a single-cell approach (akin to using standalone computers) to a distributed, population-based approach (akin to using networks of connected machines). We anticipate this eventually representing the "third wave" of synthetic biology (the first two waves being the emergence of modules and systems respectively, with the latter still yet to peak). It is clear that the internal environment of the cell places a natural upper bound on the complexity of engineered modules that can be introduced via synthetic biology techniques. Attention has therefore turned to engineering solutions that go beyond single cells, and consider microbial consortia. These are made up of multiple populations of microbes, that interact to give rise to behaviour that can be much more complex than the sum of the parts. Brenner, et al. (2008) list the benefits of using such mixed populations in synthetic biology: (1) The ability to perform complex tasks that are impossible for individual strains; (2) Robustness to environmental perturbation; (3) The ability to use communication to facilitate a division of labour; (4) Biological insight that can be derived from engineering consortia.

Contribution to Central Overall Goal

As Khalil & Collins (2010) highlight, "there is an emerging branch of synthetic biology that seeks to program coordinated behaviour in populations of cells, which could lead to the fabrication of novel biomaterials for a variety of applications. The engineering of synthetic multicellular systems is typically achieved with cell-cell communication and associated intracellular signal processing modules... Weiss and colleagues have done pioneering work in building biomolecular signal processing architectures that are able to filter communication signals originating from 'sender' cells. These systems, which can be programmed to form intricate multicellular patterns from a solid-phase cellular lawn, would aid the development of fabrication-free scaffolds for tissue engineering." This latter application is just one suggestion for how engineered microbial consortia may be used, and other potential applications include biosensing and large-scale, engineered, distributed cellular "decision making".

Main Accomplishments

3b	Main Achievement	Year	By	DS
1.	Programmed pattern generator	2005	Basu	c
2.	Synchronised genetic clocks	2010	Danino	c
3.	Edge detector	2009	Tabor	c
4.	Circuit evaluation	2011	Regot	c
5.	DNA messaging	2012	Ortiz	c

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

3b	Strengths	Unknowns	Weaknesses
1.	Ability to decouple modules (encapsulation and reuse)	Degree to which mammalian cells can be engineered in populations	Narrow bandwidth of most existing communication schemes
2.	Flexibility and scalability (different messages, with different content types)	Inter- and intra-kingdom consortia engineering? Possibilities and capabilities?	Impact of stochastic gene expression
3.	Specificity (ability to target messages at certain cells in a mixed population)	Ability of engineered consortia to maintain long-term homeostasis	Difficult to eliminate cross-talk between components

3c. Neural computation in artificial networks

Chrisantha Fernando
Phil Husbands

Basis of the Approach

Neural signal processing can be emulated without the need for cells (or neuron like processors) using sustained reaction-diffusion systems with multiphase and microfluidic systems. Such signal processing may also be of value in controlling complex chemical construction processes. A related and important area is the role of diffusing chemical signalling within neural networks. In this case the neurons are present and the chemical signalling acts in concert with electrical signalling between the nerve cells. Diffusing chemicals are released from the body of nerve cells and can act over relatively large volumes affecting many other nerve cells simultaneously without being electrically connected to them (so called volume signalling). The action of such chemical signals is usually modulatory, adding several dimensions of complexity and processing power to the operation of neural networks. Reaction-diffusion systems have been demonstrated, in simulation and in reality, to be capable of generating sensorimotor behaviour in mobile agents (simple robots) without the need for additional processing. This includes behaviours requiring memory. Volume signalling has been demonstrated in neural preparations and detailed simulation models have been built of the process. (Simulations of) artificial neural networks incorporating volume signalling have been demonstrated to be highly evolvable and to make highly efficient (minimal resources) controllers of robots engaged in senosrimotor behaviours.
The essential principle in conventional neural computaiton is to model the brain at the neuronal level. Connectionist approaches are now being extended by recent developments in deep learning. Spiking networks are being understood in terms of plasticity rules such as STDP, ITDP, IP, etc... Symbolic connectionism tries to integrate the physical symbol systems approach with distributed neuronally plausible operations.

Contribution to Central Overall Goal

This area contributes to several key areas of the roadmap, but chiefly cellular and cell-like computation and spatial self-organisation. A better understanding and control of these processes will be central to realising the common roadmap goal in future autonomous systems. The massive investment into neural networks by Google/Facebook etc... emphasises the practical importance of brain-inspired computation in the real-world. For a review of the accomplishments in the area, please see any standard textbook in the field[6].

Main Accomplishments

3c	Main Achievement	Year	By	DS
1.	R-D systems for minimally cognitive tasks	2010	Husbands	e
2.	R-D systems for robot control	2003	Adamatzky	d
3.	cellular hardware implementation of R-D type dyamics	1999	P. Arena	c

[6] e.g. (i) http://www.inference.phy.cam.ac.uk/itprnn/book.pdf
(ii) http://www.amazon.com/Pattern-Recognition-Learning-Information-Statistics/dp/0387310738/ref=pd_bxgy_b_img_y

4.	efficiency of volume sigbnalling for robot control	1998	Husbands	d
5.	establishment of importance of chemical signalling in neural modulation in natural systems	2004	Marder	c

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

3c	Strengths	Unknowns	Weaknesses
1.	evolvable	scalability	how to exploit higher dimensional systems
2.	potential for highly reconfigurable systems	practical processing speeds realisable	programmability
3.	simultaneous processing on several different spatial and temporal scales.	long-term stability	development of more complex architectures

3d. Artificial tissue engineering using structured chemical/material scaffolds; Additive manufacturing, 3D functional printing, steganography and related fab

Andreas Schober

Basis of the Approach

I focus in the following on the application of the two core technology 3d in combination with 6b. Main idea: By combining methods and materials from different fields with consideration of all geometric scales involved in a biological system: In principle it should be possible on the one hand to mimic functional biological structures and on the other hand to construct and to evolve human designed or inspired devices. The latter can lead to the development of real new biotechnical devices or on a level of research to a remodeling and design of experimental setups which can answer and examine scientific biological questions analog to setups in physics or chemistry (see our review ELS, Schober et al. 2013). The upcoming stem cell paradigm might lead to a breakthrough, but even taking this alone there are restrictions: the time needed for construction of such tissues (look how long humans need to become a fully equipped organism), the connections between blood capillaries of embroid bodies and blood capillaries implanted in bodies in the medical application etc. In this way it appears that a combination of engineering principles like scaffolds, guidance of cell adhesion and migration and the combination with stem cell approaches could solve the problems of artificial organoids/tissues modeling. But in all approaches the main unsolved question in the design of tissue like structures is the vascularization. Most of the experts in this field (tissue engineering-, stem cell-,scaffold experts) identify this problem as the key problem for getting tissue like 3D multicell type cultures living and functional as in biological organism. Because of the limitations even of stem cell derived embroid bodies the vascularization issue becomes a key problem in keeping bigger cell cultures alive. Within this problem 3D organ printing experts get a step closer to the solution. So a spin-off of Forgacs group Organovo claims already to make "Microvascular Networks" within the printed liver tissues. Nevertheless as Lewis et al. 2014 pointed out, the ink must be biocompatible, the patterned cells must not be damaged,the resulting vascular system must be perfusable and then the whole 3D living structure should remain viable. Far away from designing real tissues arbitrarily from scratch, the way to real function will only be poorly reached by one method, but the combination of above mentioned methods will overcome the problems.

Contribution to Central Overall Goal

Nevertheless the approaches and fusion of methods should lead to a construction method which should allow in a consecutive row of steps to design artificial biological tissues. The idea in the context of the roadmap is that given the basic vascular structures and the right cell types releasing the right signal molecules to each other would allow the biological material to switch on the correct genetic and epigenetic programs for adaptation and evolution of the correct tissue like structure (similar to repair mechanism of t biological samples). The idea to involve all geometric scales in the construction of a biological system has been advanced by Bhatias group and by ours and is embedded in the overall goal of the fine-grained multi-scale fabrication of the road map. If one could transfer the methods of micro and nanotechnologies to the design of tissues, the problem would be solved. The reasons for that are: You need abrasive and additive methods for real organic and anorganic 3D structures. This is partially solved. If it can be transferred to the living material then the problem would solved.

Main Accomplishments

3d	Main Achievement	Year	By	DS
1.	organ printing	2003	Mironov	b
2.	step towards vascularisation	2012	Bhatia	d
3.	stem cells reprogramming	2008	Yamamaka	b
4.	Clinical transplantation of a tissue-engineered airway	2008	Macchiarini	a
5.	Laser processing of advanced biomaterials	2005	Chichkov	b
6.	Fusion of methods	2013	Schober	c

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

3d	Strengths	Unknowns	Weaknesses
1.	Creating artificial living systems is having great scope for the future biotechnology, system biology, pharmaceuticals and tissue engineering.	Molecules which guide and switch cells in a reproducible way under the control of the human constructor	Still the lack of biocompatibility of polymer material
2.	The cellular manipulation through the above mentioned approach is the only feasibility for achieving such a complexity.	Maintainance of tissue function made by artificial means	Universal scaffold and material for controlling multi cell culture
3.	Steps towards a tool box in designing 3D hybrid structures and first clinical trials		Limitation of primary human cell culture

3e. Information encoding in cellular systems

Luca Cardelli

Basis of the Approach

Cellular machinery uses computational mechanisms and principles of operation that are unfamiliar to mainstream hardware and software engineering: stochastic, highly concurrent, highly reliable, hybrid (digital-analog), compartmentalized organizations. Part of the challenge of understanding and (re-)engineering biological systems is to develop conceptual models of how activities are coordinated and carried out in cellular systems. These span fundamental theoretical questions of what is computable by various physical mechanisms available to molecular biology, and what design principles (algorithms) can be used to achieve desired effects and functionality. Suitable theories of what is computable and how by, for example, ordinary chemical reactions, protein interactions, and membrane interactions, are actively being pursued. We are still very far from a general understanding of how cells compute and process information (and materials), either in the genome, in the proteome, or in the organization of cellular compartments.

Contribution to Central Overall Goal

Fundamental understanding of molecular mechanisms related to information processing.

Main Accomplishments

3e	Main Achievement	Year	By	DS

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

3e	Strengths	Unknowns	Weaknesses
1.	Mathematically sound.	Applicability/feasibility.	Sometimes far from experimental realization.

4a. Genetic information encoding principles for ongoing construction

Peter Wills

Basis of the Approach

The evolution of general physical mechanisms which define a class of entities, conditions or events can serve as a basis for discrimination between alternative (members of the class) and thereby be used for constructive computation (physical processes controlled by information recognition). Genetic coding is the natural paradigm of an operative system of this sort.

Contribution to Central Overall Goal

The roadmap requires the computational control of local constructive processes. This will require a process of evolution during which solutions are found in a combinatorial jungle. General mechanisms of information transfer which can operate at increasing levels of information processing density will allow the search space to be explored and solutions to be honed with ever finer precision.

Main Accomplishments

4a	Main Achievement	Year	By	DS
1.	Coding self-organisation	1993	P.R. Wills	e
2.	Evolution of genetic representation	2001	Füchslin/McCaskill	e
3.	Stepwise improvement of coding	2004	Wills	e

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

4a	Strengths	Unknowns	Weaknesses
1.	Biological paradigm is understood	Whether effective emulation of biology is possible	Biological example is very chemically restrictive and may not be easily transferable
2.	Proteins are demonstrably able to cover a huge catalytic space	Whether strictly collinear information processing is a advantage	How to set up the possibility of increasing functional complexity is not well understood
3.		Not obvious what to choose as "general mechanisms"	

4b. In vitro molecular evolution, combinatorial chemistry

John McCaskill

Basis of the Approach

In vitro molecular evolution aims to evolve molecules and molecular systems outside of cells, making use of chemical or biochemical (involving biologically translated protein enzymes) amplification, intrinsic or directed mutation and either inbuilt selection via proliferation rates or survival or directed evolution using specially designed molecular selection steps such as binding and separation (e.g. SELEX or chromatographic separation or selective destruction). Combinatorial chemistry differs in its mechanism of creating, by directed synthesis pathways involving stepwise multiple outcomes, rather than by amplification with mutational errors. The essential idea is to gain chemical control of the production and testing of new molecular variants for a given purpose, as opposed to rational chemical synthesis of specific targets. Since the founding work of Sol Spiegelman in the 1960s, the field has reached a significant level of sophistication, shared between experimental exploration of fundamental scientific issues of the nature of molecular evolution and the origin of life and more engineering issues of usage to generate increasingly complex systems. The availability of general DNA amplification protocols such as PCR, and isothermal amplification system such as SDA, have enabled widespread application of in vitro molecular evolution.

Contribution to Central Overall Goal

As a vehicle for achieving the roadmap goal, it is likely to play a component role, being combined with rational design of subsystems to optimise processes, rather than to be successful as an entire evolutionary process in generating multi scale self-organising systems of significant complexity in the near future.

Main Accomplishments

4b	Main Achievement	Year	By	DS

1.	Evolution in vitro	1967	Sol Spiegelmann	c
2.	Quasispecies	1971	Manfred Eigen	c
3.	Selex : directed evolution	1990	L. Gold, A. Ellington	b
4.	Cooperative evolution	1997	Ellinger, Ehricht and McCaskill	d
5.	Recipe encoded genes	2000	S. Brenner, Affymetrix	c

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

4b	Strengths	Unknowns	Weaknesses
1.	Ability to evolve solutions without detailed chemical knowledge of desired structure	Optimal encoding of information for evolutionary search	Distributed processes are subject to parasitic instability
2.	Ability to be implemented in hours on laboratory timescales without cellular complications	Ability to constrain solutions for simplicity and modularity	Potential sensitivity to uncontrolled environmental conditions
3.	Generalizable to higher level (e.g. encoded) evolutionary processes	Population size and generation time limits for effective evolution	Difficult to accurately predict or program in advance

4c. Combinatorial functional materials (including polymers)

Andreas Herrmann

Basis of the Approach

The first examples of automated preparation and screening of material libraries from the 1970's were dealing with inorganic materials and the exploration of superconducting alloy systems. Only in the 1990's combinatorial approaches to investigate the many properties of soft synthetic polymer materials like molecular weight, polydispersity, viscosity, hardness or stiffness were pursued. The main reason for that was that high-throughput screening methods were missing. Since then the fabrication of combinatorial material libraries of polymeric systems has become a standard tool to explore material property space ranging from screening for fluorescent features over molecular weights to block copolymer morphologies.

Besides constructing libraries from different polymer components, synthetic efforts have been explored to control the sequence of monomers along a single polymer chain to achieve soft matter functional materials. The synthesis of block copolymers containing different monomer blocks is easily achieved by controlled radical polymerization mechanisms. Nowadays even single monomers can be incorporated into a polymeric chain almost reaching the precision of natural biomacromolecules like proteins or nucleic acids. Another way to fabricate functional polymeric structure bridging the synthetic world of chemists with the biological world is hybrid materials like combinations of DNA with synthetic polymers called DNA block copolymers.

Apart from synthetic polymer systems, the evolution of complex functionalities was so far mainly limited to protein and nucleic acid structures. In the future, this repertoire of structures will be extended to modified natural building blocks up to systems that are completely unrelated to amino acids and nucleotides. To achieve this, enzymes need to be engineered to accept modified non-natural building blocks. Moreover, fabrication and replication schemes for polymers are required that allow perfect sequence control along a non-natural polymer backbone. Since many growth reactions are not compatible with aqueous environments replication schemes in non-aqueous environments are of particular interest. Even more important than new replication schemes for synthetic polymer structures are screening and directed evolution methods to evolve desired material properties. While screening for bond formation or cleavage is relatively simple the detection of material properties is much harder especially when it comes to high throughput assays. The origin of that is twofold. On the one hand, material properties are usually not a single molecule feature but originate from the interaction of many molecules together and are even dependent on the size of the ensemble, the history of the sample and the processing. The second factor that complicates generation of new material properties by directed evolution is that certain material features need to be coupled to a replicative advantage. This is especially challenging when dealing with mechanical, optical or electronic properties.

Contribution to Central Overall Goal

Synthetic functional materials based on synthetic and biological macromolecules are very important to realize applications of integrated information containing chemical systems. They are very important to bridge length scales of several orders of magnitude because they can be organized in a hierarchical way. For the timeline of the roadmap it is predicted that especially hybrid systems might be of particular importance since some functionalities realized in synthetic systems are still very hard to realize with natural biopolymers like electronic charge transport. Therefore, the hybrid systems might also play a pivotal role in interfacing biological with Si-based device structures.

Main Accomplishments

4c	Main Achievement	Year	By	DS
1.	Screening of superconducting alloys	1970	J. J. Hanak	c
2.	Screening of fluorescent properties of conjugated polymers	2002	P. H. Dixneuf	b
3.	Screening molecular weights of PE from catalyst library	2000	A. Herrmann	c
4.	Screening block copolymer morphologies	2001	A. Karim	b
5.	Synthesis of block copolymers by controlled radical polymerization	1997	K. Matyjaszewski	b
6.	Incorporation of single monomer in polymer chain	2012	J. F. Lutz	c
7.	Fabrication of DNA block copolymers	2006	A. Herrmann	c
8.	Enzymatic amplification of highly functionalized DNA	2004	M. Famulok	c

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

4c	Strengths	Unknowns	Weaknesses
1.	Combinatorial material libraries from polymers are relatively easy to synthesize and automation has progressed in recent years.	How far can the synthetic robots be integrated into computational systems	Size of libraries of synthetic macromolecules is small compared to sequence space in biopolymers.
2.	Solid phase synthesis of unnatural sequence specific polymers allows perfect sequence control	Screening for functionality	Small molecular weights and limited backbone structures
3.	Synthetic biopolymer hybrids add significant functionality to informational biomolcular systems allowing their interfacing with devices.	General procedure of how to bridge the microscopic and macroscopic world unknown.	Replicability is limited compared to DNA and proteins.

4d. Generative and developmental systems: for integration of production and construction

Peter Dittrich

Basis of the Approach

The main idea of the study of generative and developmental systems is to bring together biological and technical knowledge about evolution and development (evo-devo) to design and implement novel (computing) devices with a specific structure and functionality. Evo-devo deals with representations of genotype and phenotype, genotype-phenotype mapping, variation operators, fitness functions, metrics, etc. The strong examples from well-studied cases of cellular differentiation from single cells to organisms, including slime mold, drosophila, zebra fish etc, provide a wealth of detailed information and principles about the orchestration of morphogenesis that can also be employed in more technical contexts. While engineered biological evo-devo systems do not exist yet, evo-devo has been instantiated in various virtual environments (e.g. biomorphs, Dawkins 1986), in electronics (e.g., Embryonics, D. Mange et al.), robotics (cf. "developmental robotics"), or abstract environments like computer programs (C. Ferreira 2001). State-of-the art evo-devo systems in virtual 3D-environments can handle multi-creature populations evolving in the same environment; commercial applications are found especially in the entertainment industry (e.g. virtual actors). Also evo-devo at a cellular level is approached in-silico (e.g., cf. Eggenberger). In genetic programing (GP), various generative representations are available; experimental studies have shown that

adding development to program evolution can significantly improve performance in GP (C. Ferreira 2001). The progress in evolvable hardware (EHW) is similar to that in developmental GP; developmental evolution of circuits in reconfigurable hardware can be performed. EHW provides the fastest currently available way for evaluating an objective function in-materio, i.e. by a physical process. In the area of (autonomous) robots, evo-devo processes are run in simulation and the resulting structures are build in reality (e.g. Pollack), this includes recent progress in evolving soft robots (e.g. Lipson). A designed physical system with a fully embodied evo-devo process does apparently not exist yet.

Contribution to Central Overall Goal

Evo-devo can be used as the actual information driven construction processes, potentially down to the molecular scale. On the other hand, evo-devo could be an approach for the design, adaptation, and self-repair of macroscopic C^hem B^io IT artifacts.

Main Accomplishments

4d	Main Achievement	Year	By	DS
1.	Mechanisms of morphogenesis (no evo)	1952	A. Turing	e
2.	Evo-devo simulation	1986	R. Dawkins	c
3.	Virtual evo-devo in realstic 3D virtual physical world	1991	K. Sims	d
4.	Evo-devo of function (electronics and computer programs)	2000	D. Mange /C. Ferreira	d
5.	Physical instantiation of virtually evolved artefacts by evo-devo	2000	J. Pollack / H. Lipson	d

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

4d	Strengths	Unknowns	Weaknesses
1.	Can automatically generate structure and function of an artefact, given an objective function	There is no formal evo-devo theory suitable for using in an evo-devo design process	Expensive (in terms of computation and time needed)
2.	Is creative, suprising resulting designs possible		Only simple functional structures (at the order of 10 logical elements) can be evolved.
3.	Adaptive; can be used as an adaptation mechanism after structural perturbation		Requires still a lot of manual fine tuning (e.g. of objective function and parameters)

Additional Comments

Written with the help of Gabi Escuela. The above is a quite subjective view.

4e. Evolutionary Design of Experiments

Irene Poli
Norman Packard

Basis of the Approach

The complex systems found in the realm of ChemBioIT are, by their very nature, impossible to solve, i.e. it is impossible to derive the systems with desired properties from first principles. This fact gives rise to an evolutionary experimental approach to design, where experimental probes explore large spaces of possible experiments, typically with many experiments operating in parallel, generation after generation. The design of each successive generation of experiments is best accomplished by building a succession of models to predict good experiments for the following generation. The parameters that specify the experiment become the 'genome' of the evolutionary process, and may be quite general in nature, including chemical structures, chemical protocols, and fabrication protocols. The resulting evolutionary algorithm has a fitness function that is rooted in experimental reality, and as become known as the Evolutionary Design of Experiments (EDoE).
Evolutionary design of experiments may be contrasted with the traditional data-mining approaches commonly used for 'Big Data', which arise here because in chemical and biological experimentation we

frequently observe an increasing number of really imposing datasets; imposing in size, for the huge number of measurements provided by technological advances; in dimensions, for the very large number of variables that investigators wish to consider in developing their research; and in complexity, for the high level of connectivity among attributes in these large dimensional datasets. These increases in the size, dimensionality and complexity of datasets pose a challenging methodological/inferential problem: how can we extract the relevant information from these huge datasets, and how can we interpret the meanings of this information, even to the point of discovering new entities or functionalities? More generally, how can we turn these massive datasets into scientific and technological progress? Attempts to deal with these issues are a hot topic in current research, often referred to under the rubric of Big Data. Researchers have succeeded in developing many advanced statistical methods, data mining procedures and visualization techniques to deal with the Big Data problem. However, the problem is still an open problem with no fully satisfactory solutions even under strong assumptions on the formal structure of the problem.
The evolutionary design of experiments addresses this problem from a different perspective: rather than produce ever-faster datasets and then seek to extract and interpret the relevant data buried within them, this approach aims to produce very small informative datasets, i.e. data that are constrained by construction to contain the most relevant information for the problem under study.
The essential idea of this approach is to generate efficiently and then process just the information relevant to the problem under study. The approach is based on population experimental design and is constructed as combination of evolutionary computation procedures (e.g. evolutionary strategies, genetic algorithms, ant colonies optimizations, particle swarm optimization) and inferential statistical models (e.g. Bayesian probabilistic networks, stochastic neural networks, regression models). The state of development of this approach is satisfactory and in progress, with several experimental evidences of being able to generate very small informative datasets, which provide accurate and reliable information, using a very limited amount of resources, avoiding unnecessary a priori cuts of information and reducing possible ethically inappropriate experimentation.
Use of evolutionary design of experiments goes hand in hand with development of high throughput experimental infrastructure. Many examples of high throughput infrastructure have been commoditized, such as liquid handling robots. Microfluidic high throughput infrastructure is just on the cusp of becoming widely available.
Evolutionary design of experiments takes a large step in the direction of automation of the scientific discovery process. It provides a principled approach to experimental execution; it currently plays no role in formation of hypotheses that drive experiments.

Contribution to Central Overall Goal

Engineering of ChemBioIT systems is difficult because of our inability to derive or compute characteristics of these systems from first principles. This forces us to rely less on top-down engineering approaches, and increasingly on bottom-up approaches to reach engineering goals. Experimental exploration using evolutionary design of experiments is a principled bottom-up approach that has proven its efficacy in several contexts.

Evolutionary design of experiments is quite general; the approach has been used from the molecular level to architecture of buildings and urban design. It naturally spans the three domains that make up ChemBioIT, Chemistry, Biology, and Information Technology.

Main Accomplishments

4e	Main Achievement	Year	By	DS
1.	Algorithm formulation	2007	Poli, Packard, et.al.	e
2.	Vesicle optimization	2010	Hanczyc, Poli, Packard et. al.	d
3.	Protein expression protocol	2011	Caschera, Hanczyc, et. al.	b
4.	Protein design	2012	DeLucrezia, Poli, et. al.	d
5.	Molecule design	2014	Borrotti, Poli, et. al.	d

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

4e	Strengths	Unknowns	Weaknesses
1.	Generally applicable to a wide	Time scale: to surmount	Challenge of including a priori

	range of experimental contexts.	engineering challenges, how much evolutionary time will be needed?	knowledge in the evolutionary algorithm
2.	Scales well with technological increases in high throughput infrastructure and computational bandwidth.		Genetic encoding of spatial structure is difficult (e.g. for small molecule design, 3D printed structures).

Additional Comments

Regarding Expected Breakthrough 1: Currently much of data acquisition is often realized without any statistical design, and experimentation is frequently conducted by investigating one variable at a time with as many trials as possible, assuming that "more data is always better", thus generating the Big Data problem. Also, doing experiments or simulations investigating only one or a few variables at a time can be misleading, since it ignores variable interaction effects, and this can produce erroneous interpretation of the experimental results. The evolutionary design will also change the common practice of addressing high dimensionality by a priori cutting or ignoring sets of variables, with such decisions often taken on inappropriate grounds.

4f. From reconfigurable to self-constructing and self-repairing systems

Uwe Tangen

Basis of the Approach

Reconfigurable hardware stands in contrast to programming (software) or parametrization of systems. The boundary between these approaches is however continuous. An external controller usually controls reconfigurable systems. If the controller also becomes part of the system and the system is able to build parts on its own then the term self-construction is used. Reconfiguration is useful in combinatorial construction, since it may require less information to build complex structures by starting from existing (usually modular) structures. Systems with this ability are able to repair themselves, if they have the notion of target structure.

Contribution to Central Overall Goal

Reconfigurable hardware is an intermediate test-bed for testing algorithms on an electronic medium which are supposed to be implemented in ChemBio-hardware . This approach helps to close the gap between a high level theoretical description or simulation of an algorithm and the direct implementation in chemBio-hardware.

Main Accomplishments

4f	Main Achievement	Year	By	DS
1.	Analog evolution in digital hardware	1996	Adrian Thompson	b
2.	Embryonics	1996	Daniel Mange	c
3.	Multiplexer-based cells	1998	Daniel Mange	c
4.	Computing with attractors	1988	B. A. Huberman	e
5.	Evolutionary fault repair in space applications	2001	Vigander	e

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

4f	Strengths	Unknowns	Weaknesses
1.	Can be used to test algorithms before they are implemented in the target hardware	is it possible to drastically reduce the power consumption of these devices?	Reconfigurable hardware has its own life, long learning curve required.
2.	Safe playing, all the side-reactions in the target hardware can be neglected.	what is creativity?	As a very abstract emulation machine it can not cope with all the dirty details of the target hardware.
3.	Allows a much better observability than in real hardware		Observability, still possible, is already limited.

5a. Microfluidics, LOC and other hybrid chemical/physical technologies

Cyril Delattre
Patrick Wagler

Basis of the Approach

As chemical information processing systems, microfluidics and LOCs are most advanced in the area of diagnostics, with systems currently involving tens of thousands of active elements (such as valves) and massively parallel programmed operation. Fabrication processes typically provide limited quantities, which is reasonable for rare or amplifiable products such as DNA, but generally limiting. Processes allowing self-construction or self-repair are still rare and of limited complexity. Nonetheless major progress is expected in the coming years. Current fabrication of microfluidics and LOCs is serial and mainly surface based, with image transfer and writing protocols and including deposition techniques as spin coating, sputtering or Chemical Vapour Deposition to modify surfaces. MEMS technologies are wide ranging with many different techniques and methodologies to sequentially pattern different thin film layers that ultimately form three-dimensional functional systems. All technologies conform to the following basic steps: a. deposition, b. patterning, and c. etching or lift-off. Rather complex protocols involving many photomasks and layers of structural processing work routinely after suitable testing and optimization.

One such LOC technology involves electrowetting. Electrostatic forces are used to control the interface (triple contact line) between a liquid and a solid, and to increase the apparent wettability of the solid surface. This phenomenon is called electrowetting for this very reason. The only really needed condition is to have a liquid in which charges can be accumulated under the effect of an electric field. This approach works best if : (i) A dielectric material is present (ii) The surface is already hydrophobic with low contact angle hysteresis (reversibility) (iii) The droplet is immersed in a filler fluid (non miscible with liquid of interest) This approach is also widely used for optical applications : (iv) Lenses : Changing the contact angle leads to a change in focal distance of a liquid lens(v) Displays : Spreading a colored droplet under the effect of the electric field leads to a colored pixel that can be turned on and off. Electrowetting has been developed really far for Lab on Chip and optical applications, with products available on the market. In parallel, multiple companies have products near market or in early stage.

Overview of Products development state in the area of electrowetting:
Companies and Applications
A. Industrial products available:

1. Varioptic/ Parrot	Lenses for industry
2. Advanced Liquid Logic	Lab on Chip for human diagnostics and sample preparation for genomics

B. Product in development - Near market:

1. Liquavista / Samsung	Flexible displays
2. Optilux	Lenses for portable devices (e.g. cell phones)

C. Product in development - Early state:

1. InStep Nanopower	Energy harvesting in shoes
2. Kapplex	Lab On Chip
3. Gamma Dynamics,	Displays

Contribution to Central Overall Goal

One of the possible routes to enhanced information construction is to achieve a self-assembling mask technology for pattern transfer, so that this would present a hybrid between current and the future self-assembling technology. Furthermore, various initiatives have already started to port microfluidics to a more portable and disposable technology, using techniques such as ink jet printing, with prominent work by the

Whitesides group[7]. Another pioneering approach is based on the development of complete LOCs solutions based on thin and flexible films (Lab-on-a-Foil) e.g. [8]. Both mechanical and chemical or biological effects can be used to control fabrication processes, and it would be of significant advantage to be able to actively modulate the fabrication process based on electrical or optical signals stemming from the electronic components being assembled. With self-assembly based on differential wettability, electrowetting is an option. Electrodes interfering with electrophoretically modulated self-assembly are another option. Much work has already been done on the use of digitally produced electric fields (low voltage) to control the local concentration and aggregation of substances in microfluidic environments.[9]

Electrowetting opens up a digital approach for microfluidics (Digital Microfluidics) allowing the manipulation of a single volume of liquid on a matrix of electrodes through an applied electrical potential. This means that a binary approach can be used just like in computing with transport area (buses), storage area (memory) for example. A 1 position corresponds to an activated electrode carrying a droplet, while a 0 position is a unactivated electrode without a droplet. This innovative way of performing fluid handling is (i) highly programmable through the use of dedicated software, (ii) highly flexible and adaptive (for example if every initial reagents of a library are entered initially, any combination of 2 reagents through combinatorial approach can be done) and can address a high level of complexity. Moreover, using this approach an electrical signal could directly lead to a chemical or a biological reaction. This seems to be one very good way to translate "electricity" into "chemistry" or "biology". Finally, the approach is quite generic and for example not dependent on the material used as based substrate (demonstrations were done with silicon, glass, PCB, flexible PCB, polymer, thin glass, steel, aluminum, copper).

Main Accomplishments

5a	Main Achievement	Year	By	DS
1.	Microfluidic large scale integration (LSI)	2002	Quake	a
2.	Continuous-Flow PCR on a Chip	1998	de Mello, Manz	c
3.	Foldable Printed Circuit Boards on Paper Substrates	2010	Whitesides	c
4.	"Lab-on-a-Foil"	2010	Zengerle	b
5.	Digital electric fields controlling LOC systems	2006	McCaskill, Tangen, Wagler	b
	Electrowetting on Dielectric (EWOD) Technology			
1a.	First paper by B. Berge on EWOD principle	1993	B. Berge	c-d
2a.	Demonstration of Digital Microfluidics and unit operations (UCLA, Duke, CEA) both in open and closed configuration (water/air or water/oil)	1999-2000	UCLA, Duke, CEA	c
3a.	Understanding the phenomena and expanding the range of applications (immunoassays, PCR, enzymatic reactions, cell culture, sample preparation, magnetic beads manipulation, all-terrain droplet manipulation,...)	2000-2009	U. Toronto	b
4a.	Display based on Electrowetting (Liquavista) / Hermetically sealed and ready-to-use lab-on- chip based on EW for PCR	2010	Liquavista, CEA	b
5a.	Lab-on-Chip based on EW (PCB technology to be cost effective) available through NUGEN + Clinical study on NBS in the US	2011	Adv. Liquid Logic	a-b

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

[7] G. M. Whitesides et.al. "Foldable Printed Circuit Boards on Paper Substrates" Adv. Funct. Mater. (2010) 20, 28.

[8] R. Zengerle, et.al. "Lab-on-a-Foil: microfluidics on thin and flexible films." Lab on a Chip (2010) 10(11), 1365.

[9] Wagler, P. F., Tangen, U., Maeke, T., & McCaskill, J. S. (2012). "Field programmable chemistry: Integrated chemical and electronic processing of informational molecules towards electronic chemical cells." *Biosystems*, 1–16. doi:10.1016/j.biosystems.2012.01.005

5a	Strengths	Unknowns	Weaknesses
1.	Parallel processing Digital approach - just like computing	Reproducibility Still requires liquid to be entered by one way or another onto the device	Reliability Highly sensitive to materials handling
2.	Large scale integration capability High resolution capability Access to very small volumes	Positioning accuracy Access to very small volumes: no real physical limitations have been observed but there might be some	Surface fouling
3.	EWOD: Feedback is possible through impedance measurement	Cost scaling with integration	Manipulation of any solvent for chemical reactions

5b. Fabricated micro-and nanoparticles interacting with ChemBioIT systems

John McCaskill

Basis of the Approach

Micro- and nanoparticles (NPs) provide a modular synthetic target, at a mesoscopic level well above the molecular level of conventional inorganic and organic synthesis, which can be used to program the properties of microscopic systems in solution and interact with other ChemBioIT systems. Collective properties of such particles belong to the area of colloid science, including sophisticated self-assembly, although in the larger size range above a micrometer they are termed suspensions. Programming includes not only specific control of size, but decisively of surface coating (including ionisation and hence charge control in solution) in addition to shell structure, porosity and other physical properties. Various quantum effects in the electronic density of states as a function of particle size (number of atoms) have permitted metallic NPs to be fine tuned as optical sensors (quantum dots). The programmable control of particle interactions has been very effective at the NP scale, allowing complex assemblies of particles in 2D and 3D to be constructed. McCaskill et al (EVINCE, 2013) have proposed investigating chains of NPs and their folded structures as a suitable target for mesoscale programmable synthesis. Microscale particles have been combined with other properties such as super paramagnetism to allow their widespread biochemical use in programmed separations of surface bound biopolymers. Gel-based micro particles have been employed in chemical synthesis, as a substrate for combinatorial synthesis, with the possibility of encoding synthesis recipes in co-encapsulated DNA (for selection and subsequent identification, Affymetrix). Such particles have been extended to program uptake and release of molecules, for example through temperature or pH dependent phase changes or electromagnetic wave response, the former finding widespread application in programmed drug release, and warranting the term "chemical robotics". With Janus particles, internal directional structuring of NPs to allow directional specific association has begun.

Contribution to Central Overall Goal

Generally, micro- and NP chemistry and physics is now well poised to form a platform for programmable ongoing synthesis, although very few efforts integrate ongoing particle production with their use. An exception is perhaps the use of alginate and reversible block copolymer gels to make micro particles in droplet microfluidic systems. The fact that NPs are effective in separations and cleanup, and in packaging chemical release implies that they are definitely relevant to a fully chemical realisation of the overarching roadmap goal, once their synthesis is made compatible with the milieu in which they should function. At the very least NPs should play an important role in delivering chemicals to and sensing chemicals in the other framework approaches to achieving the roadmap goal.

Main Accomplishments

5b	Main Achievement	Year	By	DS
1.	Use of DNA-encoded beads in protein evolution	1992	Brenner S., Affymetrix	b
2.	Magnetic beads	1976+	John Ugelstad	a
3.	Colloidal quantum dots	1982+	Louis Brus	a
4.	Janus NPs allowing programmable NP colloids	1985,1988+	Woo Lee, C. Casagrande	d
5.	Dynamical self-assembly, reversible release NPs	2002	Grzybowski,	b

			Whitesides	

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

5b	Strengths	Unknowns	Weaknesses
1.	Allows modular separation of particle synthesis/properties from collective deployment	NPs with on-board electronic logic exploiting quantum principles possible in principle	Compatibility of conditions for synthesis and deployment
2.	Wide range of properties and coatings possible and programmable	Surface interaction effects in solution require further characterisation	Ability to program detailed internal structure currently limited : beyond Janus particles
3.	Bridging molecular and microscopic scales	Extension of biopolymers to quasi-bio-NPs with rich combinatorial repertoire of functions	Still not good toolsets for parallel control and manipulation of NPs (cf AFM)

5c. Electrokinetic and electrochemical systems

John McCaskill

Basis of the Approach

The central idea is that interfacing electronic and chemical systems is a direct and natural way to abstract the best of electronic information processing with human interfaces and chemical information processing with direct control of construction : with direct impact on the overall roadmap objective of achieving programmable construction. Direct electronic control of chemical processes has been explored in a number of contexts ranging from neural systems and chemical membrane sensors to electronic DNA chips and molecular, nanoparticle and cellular manipulation systems. Coupling micro- and nanoscale- electric fields with complex molecular structures allows an effective modulation of chemical processes both for diagnosis and construction. Electrochemical reactions can be initiated by micro electrodes to gain direct electronic control over chemical processes, albeit this control is complicated by complex surface effects. Nonlinear electrokinetic phenomena allow energy transduction in batteries and super capacitors, selective sorting of molecules and particles, autonomous locomotion of particles and the control of constructive processes via transport. Such effects have been examined in the ECCell project, directed towards electronic chemical cells, by McCaskill and collaborators. Electronic integration now allows micro scale particles with on board CMOS electronics controlling electronic actuation and sensing to be constructed, and another project is exploring their use in directing chemical construction, MICREAgents. The ability of nano structures to attain dimensions below the Debye screening length has meant that electrostatic and electrokinetic interactions can have a strong influence on molecular transport and electronic signals detected from this transport. For example in the field of nanopores, molecular sensitivity in Coulter counting has been achieved. The combination of electronic nanopores with nanoparticle polymer synthesis has been the subject of a recent proposal, EVINCE, coordinated by McCaskill. Zhirnov et.al. have analysed theoretically what would be required to produce a 10µm sized nanomorphic cell, capable of autonomous power and reconstruction.

Contribution to Central Overall Goal

This subarea can contribute to the common roadmap goal in two ways. Firstly as a hybrid interface system, involving a non-self-constructing electronic part, for programming chemical systems towards ongoing construction (with chemical feedback information). Secondly, with the advent of autonomous microscopic electronic particles that can sequester power from their environment or from globally applied electric fields (bipolar power), such smart particles can be included in an overall chemical construction system that is able to reconstruct itself. A reservoir of naked smart particles can be customised by the system and incorporated in the construction system. The existence of nanopore molecular detection makes it clear that the integration of electronics and electrokinetic processing can achieve single molecule sensitivity and high throughput.

Main Accomplishments

5c	Main Achievement	Year	By	DS
1.	Electronic DNA immobilization	1997	Heller, Herlne	a

2.	Nonlinear electrokinetics	2004	Bazant	e
3.	Single molecule sensitive nanopores for DNA sequencing	2009	Bayley	c
4.	Electronic chemical cells	2011	McCaskill et.al.	d
5.	Microscale electronic chemical autonomous agents	2013	McCaskill et.al.	d

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

5c	Strengths	Unknowns	Weaknesses
1.	Direct interface between programmable electronics and chemistry	Attaining sufficient specificity of reaction control with voltage (need coatings)	Involves some hard to reproduce hardware parts
2.	Scalable down to nano electrodes and nano pores and up to cms	Avoiding side reactions and electrode interaction side effects such as leakage	Complexities of surface and electrokinetic effects at molecular level
3.	Rich array of electrokinetic and reaction phenomena, including locomotion	Upgrading low voltages of autonomous power with potentials for reactions	Needs to be combined with self-assembly and kinetic chemical self-organisation

5d. Autonomous chemical sensor and actuator networks down to cellular size and intelligent microparticles.

John McCaskill
Itamar Willner

Basis of the Approach

The essential idea of this approach is to bring together the information storage and processing capabilities of high density electronics with the material construction and molecular information processing capabilities of chemistry in autonomous artifacts at the same space scale as cells. In order to complete this objective, the electronics must become autonomously powered or be able to absorb power from its environment at the 10µm space scale, and it must have two way (actuator, sensor) interfaces to the chemical system it is immersed in. The chemistry must be sensitive to the electronic actuation and self-organize to complete the artificial cell. Such HECCs may have an electronically active docking surface on their exterior, which will allow them to communicate electrically with one another or an electronic docking surface that is powered by and connected to an electronic computer. In the future, as energy resource scavenging become more effective, they may allow RFID like wireless or optical communication. The cellular structures could for example then be instructed to self-assemble into antennae to support this process.

Autonomous chemical sensors or actuator networks may be fabricated by the assembly of stimuli-triggered polymers undergoing gel-to-solid phase transitions. By the incorporation of conductive materials (e.g., nanoparticles, graphene, carbon nanotubes) insulating to conductive transitions of the networks may be envisaged. Thermal, chemical, electrical and pH may trigger the phase transitions and stimulate accompanying volume changes and switchable electrical properties.

Contribution to Central Overall Goal

This approach contributes in two fundamental ways to the overall roadmap goal. Firstly, it will provide a more programmable path to self-constructing chemical systems. Although the blank electronic substrate will not by 2024 be able to be produced by the hybrid electronic chemical cells (HECCs), it can be mass produced and then assimilated in a self-reproducing process and reprogrammed by the HECCs. Secondly, it will provide an ideal interface to human information exchange with the novel self-reconstructing material.

Main Accomplishments

5d	Main Achievement	Year	By	DS
1.	Coupled active CMOS chips with natural neural cells were pioneered by Peter Fromherz as a hybrid system on an electronic dock.	1991	Peter Fromherz	c
2.	A MEMS support system for future artificial cells was first developed in the PACE project (initiated by McCaskill,	2004-2008	PACE Project (coord. McCaskill, 15 groups)	d

	Packard, Rasmussen and Bedau). Since then there has been considerable MEMS lab on a chip activity to support artificial cells – mostly along the liposome direction, e.g. vesicle guns.			
3.	Electrochemically activated DNAzyme sensors	2009-12	I. Willner	c
4.	Electronic artificial chemical cells were first researched by McCaskill's team and colleagues from other institutions in the ECCell project. There the concept of an electronic genome was developed, and electrochemically directed replication and compartmentation processes were established. The active electronic component was remote and the microelectrodes all interconnected on a macroscopic surface.	2008-2012	ECCell Project (coord. McCaskill, 6 groups)	d
5.	Imprinted surface reservoirs for uptake and release of chosen metabolites in sufficient quantities for bulk reaction control.	2010	I. Willner	c
6.	A feasibility theoretical analysis for a nanomorphic cell at the 10μm scale.	2011	Zhirnov and Calvin.	f
7.	Autonomous electronic "lablets" are being developed in the MICREAgents project. There the target is 100μm sized devices integrating electronics and chemistry (see Unconventional Computation article) and website. The distinguishing feature is autonomous control of pairwise lablet-lablet association with chemical and electronic communication that self-assembles an inner chemical space, that can function like the contents of a cell. An electronic docking surface will serve as a communication interface	2012-2015	MICREAgents Project (coord. McCaskill, 10 groups)	e

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

5d	Strengths	Unknowns	Weaknesses
1.	The ability to bootstrap on top of the progress in traditional electronics and MEMS/NEMS (e.g. 3D integration)	There are some problems with the first aspect, because electronics is primarily geared to high frequency operation and parasitic currents are getting larger with increased integration, not smaller	The fact that the electronics substrate is not itself amenable to ready self-construction, although more strongly integrated organic electronics may change this
2.	The ability to harness electronic computers in developing the electronic side of the artificial cell.	Most power sources only deliver low voltage, that needs to be scaled up for electrochemical control.	The complications of gaining control of electrokinetic and electrochemical processes at the microscale and the sensitivity of microelectronics to chemical interference.
3.	No need to do "chip in a lab" heavy-weight interconnections for power, control and communications	New tools for the parallel selective manipulation of labelled smart particles are required. Autonomous locomotion is possible but its efficiency and controllability in complex fluid environments unknown.	

Additional Comments

Autonomous sensor networks at scales down to 200 μm have been developed, with self-assembly to antennae structures and are being miniaturized by Sandia. Various types of foldup cubes based on bimetals with radio communication have been developed, and allow electronic integration with containment control. The MATCHIT project has established DNA addressable chemical containers that may also be useful in this initiative. The Whitesides group and A. Terfort have developed some self-assembling electronic circuitry that helps pioneer the docking process. The zero power initiative is uncovering new techniques for resolving the autonomous power

problem, from solar to ambient power scavenging. Self-motorizing particles based on bimetallic elements demonstrate that one might also achieve locomotion control through this combination.

5e. Hybrid systems involving cells

Andreas Offenhäusser

Basis of the Approach

Convergence of neuroscience and microelectronics offers a promising approach for the creation of neuron-chip hybrids. These systems can provide new insights into neurological mechanisms leading to neuro-based IT approaches and in addition, bidirectional communication between individual neurons and micro-electronics could lead to the development of neuroprosthetics equipped with neuro-electronic hybrids directly coupled to higher brain functions. Despite considerable progress in micro-electronic design, there remain some serious challenges to improve the interface between neurons and chip. In particular, current devices suffer from a low signal-to-noise read- out ratio and lack a one-to-one correspondence between neurons and electrodes.

Contribution to Central Overall Goal

Neuro-electronic or cell-electronic hybrids are able to undergo a functional and anatomical reconfiguration, on the basis of the activity-dependent plasticity and rewiring properties of neurons or the communication between cells, under some control by the experimenter. The ability to build, design and grow ICT systems that can exploit biological and chemical information processing is in the center of the common roadmap.

Main Accomplishments

5e	Main Achievement	Year	By	DS
1.	Bidirectional signal transfer	1991,5	Fromherz	c
2.	Closed loop signal processing	2002	Fromherz	d
3.	Multisite recordings and stimulations	2013	Hierlemann	c
4.	Brain computing interface	2008	Pittsburg	b
5.	open loop BCI	2000	Nicolelis	d

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

5e	Strengths	Unknowns	Weaknesses
1.	Progress in Neuroscience	Control over cellular function	Weak signal transfer
2.	Progress in Micro- & Nanotechnology	Maintain longterm neuro-electronic communication	Reliability of neuronal systems
3.			Design of neuronal signal processing

5f. Information processing principles in hybrid systems

Konrad Szacilowski

Basis of the Approach

The main idea behind current research is the application of various molecular and biochemical systems for advanced information processing. That main, still not achieved goal would be integration of various molecular logic/molecular electronics systems within one hardware platform and use of these hybrid systems for advanced infornation processing. As sensing elements will be naturally embedded constituents, one possible application would be advanced molecular-scale medical diagnostics. While most of the work in the field is done using the digital paradigm (Boolean logic as the main indormation processing scheme), other approaches, including reservoir and membrane computing should be also explored. Some preliminary steps, including memristive polymer-based systems mimicking the natural processes on simple organisms have been already demonstrated.

Contribution to Central Overall Goal

The current research adresses single tasks (e.g. synthesis of materials, construction and testing of devices) but no research on integration of these devices into complex systems has been performed. Single elements

of molecular, biological and neural devices have reached almost the level b (they are easily transferable) but in most cases they are not ready for integration.

Main Accomplishments

5f	Main Achievement	Year	By	DS
1.	first molecular logic gate	1993	AP de Silva	b
2.	advanced molecular scale Boolean devices	2000	AP de Silva	b
3.	16-bit chemical processor	2004	K Szacilowski	c
4.	polymeric memristors/synaptic systems		E Erokhin	c

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

5f	Strengths	Unknowns	Weaknesses
1.	molecular-level miniaturization of devices	interfacing with other devices may be difficult	low stability and reliability, molecular-scale cross talk between devices
2.	simple fabrication (synthesis instead of assembly)	reproducibility of synthesis/assembly	low speed
3.	possible interfacing with neural systems on molecular level	selectivity towards data encoded as chemical/molecular signals	rapid degradation of complex molecular systems, neurotoxicity of molecualr/polymeric interface

6a. Chemical robotics, Autonomous Experimentation and Swarm Chemistry

Frantisek Stepanek

Basis of the Approach

The idea of chemical robots is based on creating robots (i.e., man-made functional devices capable of performing specific tasks autonomously or semi-autonomously) that are based on chemical rather than mechatronic principles both in terms of material composition (e.g. soft matter such as polymers, lipid vesicles, nano- and micro-particle assemblies, etc.) and in terms of functionality. While a "classical" mechatronic robot may carry out tasks such as lifting or moving various objects, the main purpose of a chemical robot is to change the local chemical composition of its environment by absorbing, chemically processing and/or releasing molecules. This may include diagnostic function (chemical sensing, biomedical imaging, etc.), processing and accumulation function (e.g. harvesting of diluted chemical feedstocks, neutralising toxic spills, etc.), or delivery function (e.g. drug delivery, hormonal or neurotransmitter regulation, self-healing materials, adaptive coatings, etc.). Where the quantity of molecules absorbed/released by a single robot is not sufficient to cause the desired macroscopic effect, it may be desirable for chemical robots to act in larger groups (swarms) that are capable of acting in a coordinated fashion (e.g. all release their payload at the same time and place), reversible aggregation into multi-cellular objects, and eventually communication and adaptive behaviour.

Contribution to Central Overall Goal

Chemical swarm robots can represent the embodiment of information chem/bio IT processing. Additionally, the tasks carried out by chemical robots, as outlined above, can be regarded as analog computing, much like the various regulatory mechanisms in living systems.

Main Accomplishments

6a	Main Achievement	Year	By	DS
1.	Autonomous movement of gel by chemical oscillations	2007	Maeda et al.	c
2.	Chemical communication between coupled cells	1980s	Marek and Dolnik	c
3.	Fabrication of multi-compartment liposomes (vesosomes)	2011	Ces	c
4.	Remote control of reaction-diffusion processes in chemical robots	2013	Stepanek et al.	c

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

6a	Strengths	Unknowns	Weaknesses
1.	Based on principle proven by	Technical feasibility of	Difficult to achieve the

	evolution -- swarming.	manufacturing scale-up.	programmability offered by electronic devices.
2.	Offers functionality not achievable by silicon-based electronic and mechatronic devices.	Economics of larger-scale application.	Based on chemistry, thus may cause negative public perception.
3.	Large number of application areas (pharmaceuticals, agro, food, consumer goods, cosmetics...)	Treatment of regulatory authorities such as FDA (Food and Drugs Administration).	Unfavourable ratio between payload and capsule material.

6b. Additive manufacturing, 3D functional printing, steganography & related fab

Steen Rasmussen
Andreas Schober
John McCaskill

Basis of the Approach

3D printing or additive manufacturing is any one of a variety of processes of making a three-dimensional object from a 3D model or other electronic data source primarily through additive processes in which successive layers of material are laid down under computer control. A 3D printer is a type of laptop industrial robot. In recent years, 3D printing has been extended to include the printing of functional systems, such as electronic circuits, involving multiple materials; to the printing of chemicals for spatially defined or combinatorially sampled reactions; to the printing of tissues (cf topic 3d and text therein) ; for the printing of whole printers (e.g. RepRap) and using a variety of technologies for printing down to the nanometer scale. Since the printing machinery can be made from printed materials, it is now possible to attempt to close the construction hardware loop in self-construction. Extending this process down to smaller and smaller printers and down to the nanoscale of resolution brings the field in contact with cellular and molecular systems.

Contribution to Central Overall Goal

This is a critical piece of the ChemBio-ICT roadmap, as these top down technologies, based on programmable material manufacturing machines, have the potential to provide a direct link to the bottom up technologies, based on molecular self-assembly, self-organization and living processes.

Main Accomplishments

6b	Main Achievement	Year	By	DS
1.	Stereolithography of photocurable polymers	1984	Chuck Hull	b
2.	Metal sintering technology	1985-7	Deckard and Beamer	a
3.	Plastic extrusion technology	1990,1995	Stratsys, IMB	a
4.	Laser processing of advanced biomaterials	2005	Chichkov	c
5.	3D printing of chemicals into structures	2012	Cronin	c

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

6b	Strengths	Unknowns	Weaknesses
1.	Open-ended design possibilities which can be shared by everybody: democratizing material production	How to combine top-down and bottom up design - huge engineering challenges	Additive manufacturing is difficult to parallelize in contrast to self-assembly and self-organization
2.	Combine bottom up and top down manufacturing of macroscopic hybrid chembio-ICT objects/artifact with the low-level complexity of living systems	Design such that all parts can be recycled (as the parts in biological systems)	Many additive manufacturing techniques are serial, directed by a limited number of heads. As structures become more fine-grained, this must give way to less information-intense programming including self-assembly.
3.	Steps towards a tool box in designing 3D hybrid structures for tissue engineering and first clinical trials	Maintainance of tissue function made by artificial means	Still the lack of biocompatibility of polymer material. Universal scaffold and material for controlling multi cell culture

6c. Multiscale and hybrid robotic systems interacting with chemical construction

Rudolf Füchslin
Serge Kernbach

Basis of the Approach

Looking forward, one can think about several possible developmental lines for robotics, and autonomous systems in general: the further development of mechatronic systems, the growth of bio- and chemo- synthetic systems, the hybridization of robotics, and the appearance of soft systems. Each of these developments has its own challenges, promises and risks. However, independent of what the dominant future technology might be, we face the new problem of the integration of methodologies, paradigms and approaches from different areas of biology, chemistry and material science into classic robotics. This new integration will require a re-structuring of the current research landscape, which will not only essentially change the way we think about robotics, but also extend the scientific and technological boundaries for synthetic systems. Material sciences, bottom up chemistry and genetic engineering are especially relevant for open-ended evolution and unbounded self-development in autonomous systems - which are essential challenges for autonomous systems. From these scenarios, one may consider the hybrid scenario as the most probable way for future autonomous systems. Here we can identify several open research questions, the most important of them: How the current ICT can be combined with bio-chemical developments? This question is also known in other formulations, as e.g. programmability of synthetic systems, or open-ended embodied evolution, and is the key point in a series of other scientific and technological challenges, and to some extent, even in understanding principles of synthetic life. Many research initiatives, e.g. the PACE project, addressed it; this represents a key aspect of the long-term research agenda.
One special branch of hybrid systems is best understood in connection with some form of active delivery system. Chemical kinetics and physical transport processes are coupled such that a) The chemistry drives transport processes in a non - isotropic manner b) Chemical transport processes within/on the length scale of the artifact result in a directed transport (driven actively or passively) over distances much larger than the extension of the artifact. c) Dependent on properties of the actual location, a limited set of functions (e.g. release of content) is triggered autonomously.

Contribution to Central Overall Goal

To indicate a general way for achieving this vision, I shortly overview the state of the art. One of the approaches is the combination of cultured (living) neurons and robots to investigate the dynamical and adaptive properties of neural systems. This work is also related to the understanding of how information is encoded, and processed, within a living neural network. This hybrid technology can be used for neuro-robotic interfaces, different applications of in vitro neural networks, or for bidirectional interaction between the brain and the external environment in both collective and non-collective systems. Several research projects already address the problem of the control of autonomous robots by living neurons (for example the NeuroBit project). Another ICT-related approach in hybrid systems is inspired by artificial chemistry, self-replicating systems, using bio-chemical mechanisms for, for example, cognition as well as by a general field of material science. In several works, this approach is denoted as swarm chemistry. Researchers hope that such systems will give answers to questions related to developmental models, chemical computation, self-assembly, self-replication, and simple chemistry-based ecologies or technological capabilities of creating large-scale functional patterns.

Specializing to the active delivery system context, the hybrid approach is a first step towards bringing non - trivial decision making processes down to length scales which can hardly be attained with conventional means. Furthermore, not only length scales but also the number of agents is crucial. Autonomous agents, as produced by the research groups listed above, can be generated in very large numbers (from thousands to millions or even more). Even if we could control individual agents, we certainly can't control large numbers of them. Here, ChemBioIT enters a realm which goes beyond what is attainable by conventional IT (or let's say control, it is more a technical than a fundamental issue).

Main Accomplishments

6c	Main Achievement	Year	By	DS
1.	Self assembled multivesicles	2012	Hadorn et al.	b

2.	Moving droples based on Marangoni effect	2008	Hanczyc et al	b
3.	Catalytic Nanomotors	2010	Sen et al	
4.	Heart disease on a chip	2014	Kevin Kit Parker	

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

6c	Strengths	Unknowns	Weaknesses
1.	Many agents can be produced in parallel	Range of functions that can be implemented is unknown (though cells prove a fundamentally rich range)	Engineering such systems may require evolution -> reproduction with inheritance has not yet been demonstrated on a general base
2.	Most systems are robust to mechanical damage		There are major concerns with respect to safety. These concerns are not only politcal but shared by insurance companies
3.	Cheap		A real metabolism (means one that takes up simple energy and material sources from the environment is not yet implemented.

Additional Comments

Füchslin's contribution is based on discussions and input of Maik Hadorn, formerly FLiNT SDU, now ETH Zürich.

6d. Evolutionary robotics, including functional material modification

Daniel Richards

Basis of the Approach

The key idea is to use artificial evolution to discover physical structures that have functional high-level behaviors that can address specific design goals (such as efficient locomotion in unknown environments). This subarea is broad and there are (at least) two significant applications for this approach. Firstly, to create autonomous robots that can perform complex tasks within largely unknown or unpredictable environments. Secondly, to exploit advances in digital fabrication technologies and create new types of materials and physical structures that have tailored qualities (such as mechanical properties) and can provide benefits to a wide variety of engineering domains from biomedical applications to design of high-performance aerospace parts.

Contribution to Central Overall Goal

The ability to manipulate physical matter at the molecular scale and discover macroscopic artifacts for engineering applications that have specific "programmable" high-performance properties and useful dynamic behaviors is arguably the holy grail of this subarea. However, work in this area is currently concerned with the design, simulation and optimization of larger (macroscopic) physical structures. This subarea makes three significant contributions towards the roadmap goal. 1) Development of realistic simulations of non-standard materials. 2) Development of scalable optimization algorithms for generating functional physical designs. 3) Development of advanced fabrication technologies (such as multi-material additive manufacturing machines) for fabricating non-standard material compositions.

Main Accomplishments

6d	Main Achievement	Year	By	DS

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

6d	Strengths	Unknowns	Weaknesses
1.	On-going development of powerful optimization algorithms such as CPPN-NEAT		Computationally expensive simulations and reality gap problems
2.	Advanced and emerging fabrication technologies, especially		

	in the area of additive manufacturing		

6e. Embodiment and chemical information encoding in robotic construction systems

Steen Rasmussen

Basis of the Approach

The use of physical and chemical information to direct or co-direct the process of construction of/by autonomous robotic systems may provide significant gains in terms of avoiding complex digital computations and interface conversions, taking advantage of the inherent computational capabilities of the embodiment. Taking advantage of such principles in a mixed signal processing context, with both chemical and electronic information and exploring principles for effective decompositions is one of the topics here. Optimization of chemical, physical, mechanical and electronic information and processes for conservation of energy and resources without compromising on high efficiency could be looked into.

Contribution to Central Overall Goal

Critical connection between ICT and ChemBio and thus central for roadmap

Main Accomplishments

6e	Main Achievement	Year	By	DS
1.	motility in oildroplets	2007	Martin Hanczyc	b
2.	drug delivery vehicles	1990s	many groups	b

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

6e	Strengths	Unknowns	Weaknesses
1.	bringing the robotics concept to the micro and nanoscale.		small scale makes it difficult to program/control functionalities
2.	programmable ChemBio-ICT robots for movement, construction and production		all weakness and problems associated with self-assemby as robots in part are self-assembled

7a. Simulation of ChemBioIT processes and subsystems

John McCaskill

Basis of the Approach

Simulation is an increasingly important complement to experiment and theory in gaining understanding over complex systems relevant to the integration of chemistry and IT in life-like ongoing fabrication. Efforts to integrate the modelling of the interactions of biological "gadgetry" (in the words of Sydney Brenner) with modular and genetically encoded frameworks systematically have reached considerable sophistication, being pursued jointly by the bioinformatics, bioengineering, molecular biology, biochemical kinetics, biophysics and mathematical modelling communities. Integrated frameworks for non-equilibrium statistical mechanics and coarse grained simulation have been developed (e.g. Öttinger) and much attention devoted to multi scale simulation. Simulation relevant to fabrication needs to be done at several resolutions with very small systems being investigated with quantum-chemical properties, small systems via molecular dynamics, intermediate systems with coarse-grained particle dynamics (e.g. DPD, SPH) and larger (but still microscopic) systems with container-based simulations or via stochastic or deterministic differential equations. Incorporating information processing into simulated models is straightforward as long as these models are particle-based. Systems biology simulations up to whole cell and even tissue functionality are now approaching the complexity if not yet predictive power required for multiscale autonomous fabrication. Remaining barriers still persist, including the comparative lack of reliability of predicting the rates of chemical reactions in complex chemical systems, the inefficiency of accurate stochastic simulation dictated by having to keep track of all possible events, the interplay between collective physical phase-transitions and chemical reactions, and the automatic identification of emergent quantities and their reuse in coarse-grained

simulation. So that while such simulation is essential, it cannot replace systematic exploratory experimentation at the current phase of development.

Contribution to Central Overall Goal

Simulation of component processes and subsystems in ChemBioIT can be used in a number of modes to bring us closer to the roadmap overarching goal. Firstly, such simulation improves understanding of the relationships between different physical and chemical phenomena in such subprocesses. Simulation and experimentally well-characterised subprocesses could be used as building blocks to aid research both in system integration and in evolutionary optimisation of particular subsystems to function in a simulated environment. Starting parameters for experimental optimisation, or model systems for ongoing evolutionary optimisation can be gained. Simulated subprocesses allow understanding to be communicated between scientists and engineers via working models of the proposed phenomena, which allows understanding to be shared and combined. There is always a tradeoff between the attention to physical realism and chemical details on the one hand and simulation efficiency and memory use on the other, so that simulation needs to be conducted in a hierarchy of precisions and simplifications in order to reap its maximum benefit towards understanding and combination.

Main Accomplishments

7a	Main Achievement	Year	By	DS
1.	Simulation of quasi species of computed molecular evolution with RNA folding	1985-8	Fontana, McCaskill	c
2.	Simulation of spatial molecular evolution with CAs	1989	Boerljist & Hogeweg	d
3.	Simulation of cellular biochemistry : SBML	2000	CalTech	b
4.	Simulation of genetic self-assembly	2007	Füchslin, Maeke, McCaskill	e
5.	Simulations linking lipid self-organisation and chemical kinetics of protocell life-cycle evolution	2008	McCaskill, Maeke, Serra, Packard, Rasmussen	e

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

7a	Strengths	Unknowns	Weaknesses
1.	Can be universally applied to any process or subsystem, based on current understanding of physics and chemistry	The extent to which simulation can be simplified without loss of predictive power	Certain key processes such as predicting reaction rates are computationally often prohibitively expensive
2.	Strong sets of tools for analysis of modelling consistency with theoretical frameworks	Evolutionary process capitalise on initially rare events, how mach overhead is needed	Methodologies for embedding accurate simulations in larger extended systems are not yet complete
3.	Ability to integrate empirical information in coarse-grained models	Techniques for extracting emergent quantities (such as membrane enclosures) to be used in further computation.	Input information is often missing about detailed composition or boundary conditions

7b. Simulation integrated design and programming for ChemBioIT

Steen Rasmussen
John McCaskill

Basis of the Approach

Simulation is a general method for investigating any aspect of information processing, communication, computation, (bio)chemical processes and material production. Simulations may be formulated at different levels of description, focus on different time and length scales and may be used to address very different dynamic/functional questions. Very small systems may be investigated with quantum-chemical methods (correlated methods, Hartree-Fock, DFT, semi empirical), small systems via molecular dynamics (MD - many variants), intermediate systems with coarse-grained particle dynamics (e.g. DPD, SPH, lattice gases) and large systems with container-based simulations or via stochastic or deterministic differential equations.

Incorporating information processing into simulations is straightforward as long as the models are particle-based. Systems biology simulations up to whole cell function are now approaching the complexity, but not yet the predictive power, required for multiscale autonomous fabrication.

The full integration of simulation into design and programming for C^hem B^io IT ultimately involves some form of solution of the inverse problem, deciding which structure and parameters of a system will lead to the required performance. Analytical techniques for achieving this, e.g. in control theory, are limited in scope and generally the situation is similar to that faced by symbolic descriptions of nature, such as genetically encoded information in evolution. The ability to iteratively converge on a model description, combined with Occam's rasor, has been a powerful engine when combined with rational thinking. High speed simulation enables simulation, and simulation refinement, to be incorporated as a component in programming complex constructive and information processing systems. One such approach was outlined in Section 4e, in the Evolutionary Design of Experiments. In the 1980s, W. Fontana and McCaskill separately explored combinatorial design in RNA sequences, using secondary structure prediction as a computational engine linking sequence with fitness. P. Stadler et.al. extended this combinatorial space exploration to (Hartree-Fock) quantum mechanical prediction of organic molecular structures in the 90s. More recently, and related to the accompanying program of simulative drug discovery, D. Marx and others have employed more advanced approximations to predict reactivities in combinatorial search of organic molecules, and L.Cronin et.al. has tackled quantum mechanical design in polyoxometalates. Another important step at the next level up has been the incorporation of simulation as a predictive design component in the design and programming of combinatorial multiphase systems, with applications to biological systems involving lipid membranes and many other systems. Recently, H. Lipson has demonstrated that invariants of dynamical systems can often be extracted automatically in an evolutionary procedure, opening a further path to the integration of simulation with programming and design.

Contribution to Central Overall Goal

Further developments of a variety of ChemBio-ICT simulations are critical for a successful roadmap. Simulations are *the most extensively used exploratory, investigative, analysis and design* tool for ChemBio-ICT systems. Below is a schematic overview of the available simulation methods.

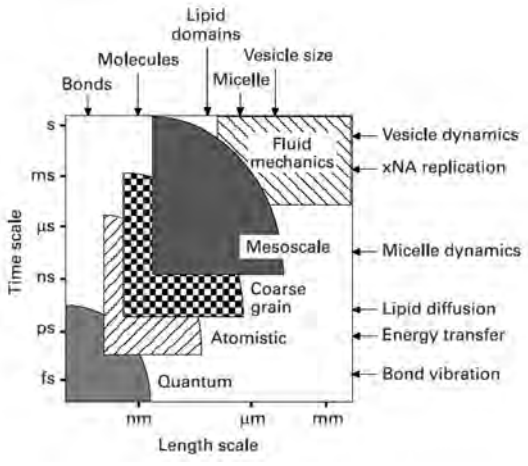

Fig. 7b.1 Schematic of the length and timescales covered by the processes involved in the protocell (from Jiang et al., 2008, Numerical methods for protocell simulations).

Simulations need to be made more modular and able to operate for combinatorially encoded sets of composition, starting conditions or parameters, in order to be used in an integrated way in the design and programming of systems. While the traditional mode of systematic exploration of parameters in a restricted space does provide insight, it must be complemented by simulations moving autonomously into more uncharted terrain, pursuing desired features, to extract their full integrated value.

Main Accomplishments

7b	Main Achievement	Year	By	DS
1.	Molecular Dynamics simulations (up to large molecular aggregates)	Since 1950s	Wide spread	a
2.	Density functional theory. Car-Parrinello MD (quantum) extending Born-Oppenheimer MD	1985 2000 2012	Car & Parrinello D. Marx IBM CPMD	b
3.	(Molecular) lattice gases (up to mesoscale) & lattice Boltzmann	1990s	Many groups	b

4.	DPD simulations (up to mesoscale) Bonded and multipolar DPD	Early 2000s	Many groups	b
5.	Mass-action reaction kinetics Stochastic kinetics Gillespie simulations	Classical 1966, 1977 (1945)	Wide spread Darvey et.al., Gillespie Many groups	a
6.	Multiphase kinetics and Protocell simulations	2000s	Rasmussen et al., Fellermann et al., Sole et al., Jiang et al.,	e
7.	Whole cell simulation (*Mycoplasma Genetalium)*	2014	Covert et. al.	e
8.	Automatic extraction of dynamical invariants from kinetics	2013	H. Lipson	d

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

7b	Strengths	Unknowns	Weaknesses
1.	Simulation can replace (or suggest) experiments, when experiments are expensive or impossible.	It is usually unknown a priori how much detail is needed to model a given phenomenon	Difficult to incorporate all relevant parameters, and fit them, without building results into the simulation.
2.	Approach gains momentum with ongoing decrease in computational cost.	How to manage incremental simulation model refinement most efficiently.	The inverse problem of designing system performance by simulation is hard.

7c. Simulation integrated evolution for ChemBioIT

Rudolf Füchslin
Paulien Hogeweg

Basis of the Approach

Interfacing of microscopic simulation methods with evolutionary processes is obviously important from many points of view. Using simple genetic algorithms for parameter or structural optimization has been done in molecular dynamics from the 90s onwards. In a more open-ended way, generating ensembles of potential 'working' (rather than optimized) systems by evolutionary processes has been less explored but should be useful. Interfacing evolution with large scale simulations is also important to understand evolution itself better.

Natural evolution has no foresight in the sense that e.g. platform strategies can be implemented that only turn out to be beneficial in future evolution steps. This lack of planning is compensated by openness; human engineers are restricted to what can be thought (e.g. the dynamics of a genetic network is hard to understand for humans, networks planned by humans tend to be more modular and hierarchical than actually needed). Simulation integrated evolution, besides all well - known benefits of in silico experiments, may help us to implemenet environments in which evolution is biased towards solutions in which human planning entered at least to some degree. We thereby implement a truly novel hybrid between rational design in engineering (bounded by the capacities of the human brain) and natural evolution that is powerful but blind. It is emphasized that the methods mentioned here apply to chemical as well as mechanical systems. Morphological computing profits heavily from simulation integrated C^hem B^io IT. Furthermore, there is theoretical interest in evolvable chemical networks and their relationship to problems in computation. The role of randomization is of considerable interest in complexity theory (Wigderson). Chemical networks can easily produce randomness. A feedback coupling of simulation and chemical reaction networks may shed

light on potential speed-ups of classes of algorithms (though, at least to my knowledge, people assume that such a speed-up is only polynomial, i.e. P = BPP).

Contribution to Central Overall Goal

Bio - inspired technology requires not only an understanding of the means of nature (materials) but also the ways nature uses (organzational principles). If we want to harvest the potential of bio - inspired ChemBioIT, we must be able to equip artifacts with bio - mimetic organization principles. Evolved networks are somewhat incompatible with our intuition and simulation can help us to explore their phenomenology.

Main Accomplishments

7c	Main Achievement	Year	By	DS
1.	DoE using GA	2007	Poli et al	b
2.	Computational power of compliant systems	2012	Hauser, Helmut	c
3.	MATCHIT calculus	2013	Fellermann, Harold	e
4.	Chemical networks and the P = BPP question	2013	Doty David (based on eg. Nisam and Widgerson 1994)	f
5.	MEMS/NEMS simulations	several	John A. Pelesko	a

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

7c	Strengths	Unknowns	Weaknesses
1.	Dynamic aspects can be emulated	Interactions between parallel processes	Implementation is hard
2.	Evolutionary processes can be studied over numbers of generation not always feasible in the lab	Chemistry (e.g. reaction constants) only known for homogeneous settings.	"Killer applications" such as artificial immune support systems are far away
3.	Focus on evolutionary dynamics without too much bothering about problems of implementation -> Before a technology is implemented, its potential can be explored.		In industry: Laboratory chemists have often a certain idea of what a simulation is; "chemistry as IT" - aspects are hard to convey.

8a. Information encoding and communication of information associated with construction

Peter Wills
Norman Packard

Basis of the Approach

Nature has evolved very sophisticated mechanisms (using both sequence information as well as other non-sequence information) for encoding information associated with construction. Proteins coded by DNA sequences are just a small example; further information encoding is needed for metabolism, membrane, and organelle structures, not to mention encoding for macroscopic structure such as organs, nervous systems, and immune systems.

The essential idea is to develop systems of information encoding and processing analogous to those in natural systems, but generalized to include novel components and physico-chemical functionalities other than those found in nature. One example is the incorporation of programmable electronic components into chemical systems, so that digital information encoding can participate in chemical processes. The ultimate goal is to use this added ability to encode information to manage interactions between different realms of activity (electronic, chemical, molecular transport, etc.) needed for the detailed (molecular-level construction) of artifacts that are complex at the nanometer level (as cells are); to the extent of general purpose self-constructing machines. The current state of development is rather in its infancy, but some theoretical work has been done both in the von Neumann and evolution traditions and several pioneering projects on interfacing electronic and chemical systems have been started.

Contribution to Central Overall Goal

These capabilities are absolutely essential to the roadmap; it is perhaps the central core problem, the way of integrating, with control, different nanoscopic technologies. This area goes beyond merely understanding

how nature encodes information for construction, to extracting principles that enable the engineering of novel technologies that have comparable functionalities and power.

Main Accomplishments

8a	Main Achievement	Year	By	DS
1.	Unravelling the genetic code and protein translation	1961	Nirenberg et al	a
2.	Proof of principle of evolution of genetic coding	2001	Wills, Füchslin, McCaskill	c
3.	Evolution of language in simple artefacts	1997	Steels	d
4.	MICREAgents	2013	McCaskill et. al.	f
5.	EVINCE proposal on nanochains	2013	McCaskill et.al.	f

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

8a	Strengths	Unknowns	Weaknesses
1.	Biological paradigm can serve as a model when it is better understood	Whether effective general (coded) control of information can be achieved across different modes of constructive material processing	Understanding of the overall integration of biological paradigm of this aspect of cells is very very piecemeal; only just being looked at in Systems Biology
2.	Modular encoding of pieces of information is possible, so that such languages are very flexible.		We do not have an example of this being done successfully at the nano-scale

8b. Connecting natural computations (molecular, membrane, cellular etc)

Susan Stepney

Basis of the Approach

One reason for researching unconventional computers is that they promise great advantages, particularly by being able to perform computation that can directly exploit the natural dynamics of the material substrate. However, such "in materio" devices in practice are often limited, they may be non-universal, or special purpose. In particular, they may struggle to perform some necessary functions that another substrate could handle with ease. In particular, unconventional devices are often combined with conventional computers or control systems, acting as special purpose components in a larger system. Consideration needs to be given to the combination of processing power of each device, the communication channels between devices, including encoding, decoding, and translating signals, and the relative timescales of each device. There is currently no general method available to design, perform or analyse such combinations, only substrate-specific (and somewhat ad hoc) approaches.

Contribution to Central Overall Goal

The goal is for "massively parallel information processing and ongoing fabrication". If that massive parallelism includes heterogeneous substrates, rather than assuming each device is a single substrate, then some approach for combining substrates, with their differing physical, chemical, computational, and communication properties is essential.

Main Accomplishments

8b	Main Achievement	Year	By	DS
1.	Position paper on heterotic computing	2012	Susan Stepney, Samson Abramsky, Matthias Bechmann, Jerzy Gorecki, Viv Kendon, Thomas J. Naughton, Mario J. Perez-Jimenez, Francisco J. Romero-Campero, Angelika Sebald	f

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

8b	Strengths	Unknowns	Weaknesses
1.	solid computational/communications	whether a *useful* generic approach that can encompass	

	basis	many orders of magnitude in timescale, and qualitatively different substrates (from photons to bacteria), is possible	
2.	wide variety of unconventional materials considered, to minimise bias		

Additional Comments

(Some of the questions in the radial diagram seem to assume a single substrate, and don't fit well across substrates)

8c. Programmability and programming autonomous systems

Susan Stepney

Basis of the Approach

Essential idea -- programming at one level (high level) so that the artefact behaves in desired ways autonomously, and self-assembles correctly using lower level behaviours. Here that lower level embodied behaviour is (partly) a result of physical laws (eg, exploiting DNA sticky ends), rather than as a result of "compiling down" the high level constraints/requirements into a lower level algorithm (eg, declarative languages) There is the "direct" approach -- designing the behaviours, and then "compiling down" to the correct micro-behaviours There is the "indirect" approach -- designing the behaviours, and then heuristically "evolving" the relevant micro-behaviours

Contribution to Central Overall Goal

If by "programming" we mean "at some level, telling the artefact what it should do", even if at a very high level, then this is essential to the whole goal. We are building functional artefacts, not just "stuff that does its own thing".

Main Accomplishments

8c	Main Achievement	Year	By	DS
1.	DNA tiling	1998	E. Winfree, Jonoska, etc	c
2.	in materio computing	2002	J. Miller, Downing	e

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

8c	Strengths	Unknowns	Weaknesses
1.		scalability	no good "design" process

Additional Comments

The text says "Strictly a contradiction" -- but programming at one level/paradigm, with "compilation" to a different level/paradigm, isn't a contradiction. Do not assume that "programming" means "giving explicit step-by-step instructions on what to do in every case" -- that is merely one paradigm of programming (imperative) -- there are other styles in existence -- this ChemBioIT should result in a further style -- "embodied" (exploiting physical properties in addition to informational ones).

8d. Architectures and optimization for combined computation and construction

John McCaskill

Basis of the Approach

The essential idea of this approach is that complex construction itself is an information process, computations can be performed by construction, and that an interplay between pure information processing and material construction (e.g. through the construction of computing devices) is ultimately necessary to discuss the bootstrapping of complexity in information processing, and to ensure robust and evolvable information processing. This theme dates clearly back to the work of John von Neumann with his Universal Construction Machine and to Alan Turing investigating Chemical Morphogenesis. It was pursued by Varela and Maturana, in connection with cellular autopoeisis. It was taken up by Manfred Eigen, Peter Schuster and his school from a physical chemical perspective in connection with molecular evolution, combined with

spatial pattern forming architectures by Hogeweg and McCaskill, and later extended to many theoretical physics models by F. Dyson, P.W. Anderson, P. Tarazona and many others. The area has provided inspiration, models and constraints for an understanding of the origin of life and is perhaps best known through works such as Hofstädter (Gödel, Escher, Bach) and the Artificial Life research community. The overarching thrust is now being actively pursued in the Artificial Life community. Most architectures for combined construction and computation are bioinspired, and many are very different from the Drexlerian atomic precision construction devices, embracing self-organisation, self-assembly and evolution as formative processes. The idea of genetic information encoding enjoys extended application, with the distinction between components whose structures that can be copied and those which can't a central recurring theme. Implementations of construction systems showing emergent evolved behaviour include the systems of Adamis, Ray, Tangen and many more. The problem of open ended evolution is still hotly disputed, with some measures for this having been proposed (Bedau and Packard).

Contribution to Central Overall Goal

Most of the subtopics are endeavouring, despite significant hardware restrictions to come closer to the goal of an open architecture capable of bootstrapping construction complexity of its information processing. Work on the evolution of a translation apparatus (Wills, McCaskill, Füchslin) for example addresses this in theory, and the MICREAgents project is attempting to implement part of this capability in the interplay of electronics and chemistry. Work on architectures and the optimisation of systems involving computation and construction are either applied directly to given subtopics or act as inspiration of the kind of achievements that can be expected with various types of systems. We are still lacking a comprehensive theory of the integration of construction and computation: formal models make too restrictive assumptions about the way in which natural systems can reveal innovative constellations even at microscopic scales which can be amplified and built on to produce novel computation-construction scenarios. Ideas such as constructive closure, autocatalysis, constructive universality, higher order evolution, robustness, information encoding and open ended evolution play an important role in many areas of the roadmap and require an architectural foundation.

Main Accomplishments

8d	Main Achievement	Year	By	DS
1.	Self-reproducing automata	1949	von Neumann	e
2.	Physical molecular evolution	1971	M. Eigen	b
3.	Cellular morphogenesis	2002	P. Hogeweg	d
4.	Genetic Self-assembly	2006	J. McCaskill	e
5.	Evolutionary emergence of translation	2003	Füchslin, Wills, McCaskill	e

Strengths, Unknowns and Weaknesses. (Enablers and Barriers)

8d	Strengths	Unknowns	Weaknesses
1.	Addresses major weakness of computer science : non-robust processors	Optimal designs for encoding information in complex physical contexts	Absence of universal architectural framework for integrating construction and information processing
2.	Large family of material frameworks and formalisms	Efficiency considerations in stochastic contexts: e.g. next reaction inefficiencies	Lack of robustness in many models based on formal architectures like von Neumann's
3.	Able to bootstrap complexity in principle	Conditions for open-ended evolution of architectural complexity	Computational complexity of calculations in the context of massively parallel detail

7&8. ROLE OF THEORY, SIMULATION AND COMPUTATION IN SUBTOPICS

1a. Systems Chemistry, Supramolecular and Synthetic Chemistry

Günter von Kiedrowski
Andreas Herrmann

Theory is very important: one can do a lot with high level quantum computation, but human creativity is required to set the proper constraints. It is still not completely predictable what can be done by simulation. The main reason is that some phenomena in chemistry require more space than can be fit into a simulation. We need to invent computation and simulation technologies that have a better interface towards quantum level. There are a number of methods that are available, but you need to know about a number of scales.

1b. DNA computing and DNA machines

Friedrich Simmel
Martyn Amos

Simulation: In fact DNA computing/machines are quite advanced in this respect already. There is a huge amount of simulation work already in biology, chemistry, physics which can be utilized for this field. In addition dedicated tools are being developed and interfaced with existing computational approaches. Software tools for molecular/network design will also be required if the field is to progress beyond proof-of-principle, and these will require significant understanding of how multi-scale systems may be simulated. The general problem will obviously require an intelligent multi-scale approach that coarse-grains appropriately over unnecessary degrees of freedom. Already at the moment, one could design DNA nanomachines/molecules with NUPACK, analyze molecular processes such as DNA hybridization using oxDNA, and perform more coarse-grained kinetic studies using standard ODE/systems biology tools (or reaction diffusion modeling with PDE solvers). Simulating large chemical systems is very complex, and it is not clear whether coarse-graining will in general be possible, and/or yield correct results. - computing & construction: Nanotechnology is actually seen as one of the main fields of application for DNA computing and molecular programming. On the one hand the field aims to develop autonomous computing processes that generate complex molecular structures and devices by self-assembly and also self-organization processes. Apart from simple static structures, orchestration of complicated assembly processes, or implementation of "check-points", "decision-points", etc. similar to biological developmental processes are envisioned. Another issue is "external programming" - the field also works on developing computational tools for the design of structures and processes based on DNA and RNA. Together with existing automated synthesis and lab automation technology, genuine "programming" of matter is very well conceivable in this subarea. Several researchers work on encapsulation/microfluidics and also chemical translation into other chemistries. Encapsulation within membranous systems (for cell-scale bioreactors) will naturally blend the field with membrane and cellular computing.

Computation: This is a very diverse subarea. There is a role for theoretical computer science, which may address questions such as "what can be computed with molecules/chemical reaction networks?", "given certain rules, what can be realized by self-assembly?", etc. Theoretical (bio)physics is generally interested in self-organization phenomena and also the dynamics of networks, but also statistical mechanical issues of self-assembly/self-organization. As outlined above, simulation can take place on many levels of abstraction, from molecular (by theoretical/computational chemists) to coarse-grained. Simulations in this field are also performed by physicists, mathematicians, and computational biologists/bioinformaticians. So on the one hand there is a practical demand for the development of design, analysis, and simulation tools (see above), and also for a better theoretical understanding of underlying physicochemical and self-organization processes, and the limits of this approach.

Computer science has a long background of involvement in DNA computing; much early work was motivated by a desire to somehow emulate existing computational models on a new substrate. Since then, theoretical attention has turned more to interrogating the inherent possibilities of molecular substrates (that is, examining their capabilities/limitations), and studying the properties of their interactions.

1c. Inorganic biology and genetic alternatives to nucleic acids

Steen Rasmussen
Lee Cronin

Theory is needed to help map the chemical space understanding the stochastic chemical processes that will need to combine for the first 'functional' adaptive systems and understand the interplay with other units and environments.

1d. Artificial chemistries and formalisms for molecular construction and IT

Peter Stadler

Peter Dittrich

The subarea is entirely concerned with theory, simulation, and computation. Improved capabilities to simulate outcomes of complex designs should be useful to assess likely technical applications of intelligent materials and thus the downstream consequences of their large-scale use.

2a. Reaction Diffusion Computing and Chemical Pattern Formation

Jerzy Gorecki
John McCaskill

Theory and simulation have proved absolutely essential in the development of this area, as experimental intuition is limited with these non-linear spatial systems in the absence of computational models. Many of the key phenomena have been predicted theoretically long before their experimental realisation.

Theory, simulations and algorithms of teaching are very important in reaction-diffusion computing. Theoretical studies on new concepts of computation should answer the basic question about the future role of reaction-diffusion computing. If this type of computation is expected to be universal then we need new theoretical concepts of universal computing machines. If one sticks to a Turing machine, which can be build with logic gates (they can be constructed with excitable medium) then reaction-diffusion processes are too slow to compete with silicon chips. In order to be competitive we need other concepts of universal computing, matching better the properties for the medium and focusing on its self-organization potential. If we treat reaction diffusion computers as instant machines effective for a small number of specific tasks (image processing, labyrinth search) then the future importance of the field will be significantly reduced. Typical computer simulations based on detailed models of chemical kinetics and transport equations are of course important because they allow one to design reaction-diffusion computers in-silico before making experiments. The approach is useful if computation is based on phenomena for which reliable mathematical models exist. In the case of BZ-droplets many processes, like coupling between droplets for different types of surrounding solvents are still missing such models and thus the results of simulations should be treated as qualitative only.

2b. Multiphase chemistry involving self-assembled macroscopic structures

Steen Rasmussen
John McCaskill

The physical simulation of multiphase systems is well advanced, with detailed statistical mechanical models of multiphase amphiphile systems now well established in a hierarchy of discrete (e.g. spin lattice) and continuous frameworks. Rather complex phase diagrams can be qualitatively well predicted in the better studied cases. A recent example of the combination of multiphase assembly with combinatorial evolution of amphiphilic molecules may be found in the work of McCaskill and Rasmussen. Another context where multiphase self-assembly plays a decisive role is in artificial cell modelling. Keeping track of physical action-reaction, or the conservation of momentum, has proved important in describing models that scale appropriately. Here dynamical models such as multipolar reactive dissipative particle dynamics (Füchslin, Maeke, McCaskill) or DNA-extended DPD (Rasmussen) can be useful to gain insight into reaction-extended self-assembly processes.

2c. Surface and interfacial chemical systems: including multilayer fab

Nicolas Plumeré
Itamar Willner

As Heinemann and Panke (2006) point out, the notion of abstraction (as used in its engineering context) is already fundamental to the field, but the distributed computing model will allow us to construct large-scale networked synthetic biology systems. In computer science, distributed systems are characterised by several features, including (1) asychrony (that is, the lack of a global "clock"), (2) local failure of components, without global failure, and (3) concurrency (that is, components work in parallel) (Attiya and Welch, 2004). Findings from CS are already being used to address these issues in population-based synthetic biology. Of course, CS and maths will also be increasingly important in terms of building models and simulations that will allow us to better understand and predict the behaviour of complex interacting (sub-)populations of cells.

2d. Iterative chemical processing systems with integrated separation and cleanup

Uwe Tangen
Steen Rasmussen

Theory and simulation in this subarea are hampered by the multiphase and surface chemistry acting in concert with physical influences from the microfluidic system. Both are extremely challenging and it is not clear a priori that experimentation alone is inferior to fully understand the iterative system. Finally, theory and simulation are required to get this subarea from an experimental stage into a production stage because then error-limits must be imposed onto the system, but a prior simulation to solve all the issues does not seem to be probable.

2e. Computational and theoretical bounds for self-organization and -assembly

Steen Rasmussen

3a. Cellular Synthetic Biology using radical GMOs

Angel Goñi-Moreno

Martyn Amos

Theory and simulation play a vital role in the subarea as it decreases the trial-and-error process to a minimum. Furthermore it helps having ideas which otherwise would be impossible, as it is not easy for most of us to imagine the dynamics of a system and visualize what the impact of changes would be. The notion of "abstraction", which is borrowed from engineering/computer science, has so far underpinned much of the field. Models and simulations are used extensively to both design and refine pathways and circuits.

3b. Cellular computation and Genetic Regulatory Networks involving cell communication

Martyn Amos

As Heinemann and Panke (2006) point out, the notion of abstraction (as used in its engineering context) is already fundamental to the field, but the distributed computing model will allow us to construct large-scale networked synthetic biology systems. In computer science, distributed systems are characterised by several features, including (1) asychrony (that is, the lack of a global "clock"), (2) local failure of components, without global failure, and (3) concurrency (that is, components work in parallel) (Attiya and Welch, 2004). Findings from CS are already being used to address these issues in population-based synthetic biology. Of course, CS and maths will also be increasingly important in terms of building models and simulations that will allow us to better understand and predict the behaviour of complex interacting (sub-)populations of cells

3c. Neural computation in artificial networks

Chrisantha Fernando

Phil Husbands

Theory underpins progress made so far but advances in theory are needed to understand how to achieve the goals outlined above. Simulations have been crucial in establishing the possibilities, the challenge is to move into physical systems.

3d. Artificial tissue engineering using structured chemical/material scaffolds; Additive manufacturing, 3D functional printing, steganography and related fab

Andreas Schober

Theoretic simulation and modelling can show (see Hoehme et al. 2010) that the regenerative capacity of organs like the liver can be understood as interplay of geometric and molecular factors.

3e. Information encoding in cellular systems

Luca Cardelli

The area is fundamentally about (non-standard) theory of computation. Simulation is used extensively to help drive understanding towards theoretical results, to complement theory in practical applications, and as a main engine within supporting tools for discovery and engineering.

4a. Genetic information encoding principles for ongoing construction

Peter Wills

This subarea is fundamentally theoretical and requires considerable computational resources, especially for the many simulation exercises that will be required for progress.

4b. In vitro molecular evolution, combinatorial chemistry

John McCaskill

Theory has played an important role in structuring the area of in vitro molecular evolution, especially since the pioneering work of Eigen, Schuster, Epstein, Szathmary, McCaskill, Stadler and many others. While accurate computation of the genotype to phenotype mapping, and more complex interactions, is still difficult, evolutionary computation has gone a long way to unravelling principles for the optimal design of evolving systems. Simulations have established that (albeit with difficulty) even the cooperative problems such as the origin of genetic translation can be solved through appropriate system dynamics.

4c. Combinatorial functional materials (including polymers)

Andreas Herrmann

Methods developed for modelling small molecules can be very well employed for describing synthetic macro-molecular systems (de Gennes). On the other hand, bioinformatics and structure prediction of biological systems has

advanced very rapidly in recent years. So far less modelling has been pursued in hybrids. Modeling or theory would be a very strong tool if it allows predicting structures and functionalities.

4d. Generative and developmental systems: for integration of production and construction

Peter Dittrich

Currently, simulation is essential, because instantiating an evo-devo process completely in the physical world takes too much time with todays methods (evolvable hardware might be an exception here). Computational studies are essential for designing efficient evo-devo systems. Theory is used only as a guiding principle in the background. However, we believe that a better theoretical quantitative understanding is necessary to develop effective evo-devo systems in the future.

4e. Evolutionary Design of Experiments

Irene Poli

Norman Packard

Theory: In statistical modeling, there are delicate issues regarding limited data sets. These issues are exacerbated when the multivariate data to be modeled is high dimensional. Models must be regularized to avoid overfitting, and an appropriate tradeoff established between exploitation and exploration. These issues are currently handled in a largely ad hoc manner; advances in statistical modeling theory could help in this area.
Evolution in complex fitness landscapes needs development of theory. Questions to be addressed are: (i) how may the ruggedness of a landscape be quantified in terms of its 'difficulty to find a solution by evolution'? (ii) given a landscape with a certain ruggedness, how fast is evolutionary progress, and how does the rate of evolutionary progress depend on meta-parameters such as population size, mutation rate, etc.? Answers to such questions could materially affect the performance of EDoE algorithms.
Simulation: Settling some of the theoretical questions listed above will require substantial simulation using synthetic data with analytically specified fitness functions whose ruggedness may be controlled
Computation: Evolutionary design of experiments computations are significant, mostly for determining the model meta-parameters that are best suited to the landscape as it is discovered in the data. Modern implementations will use multi-processing to substantially parallelize this phase of model-building. Thus enhancements in both hardware and software that facilitate such parallelization will increase the power of the algorithms.

4f. From reconfigurable to self-constructing and self-repairing systems

Uwe Tangen

Currently no real theory exists and all research is more or less ad hoc. The same holds for simulation. It would be great to see some advance in this area but this is not very probable because the problems at hand are 'mind-bogglingly' difficult.

5a. Microfluidics, LOC and other hybrid chemical/physical technologies

Patrick Wagler

Cyril Delattre

Simulation/computation is already playing a major role. As for very complex protocols, it will be easier to let a "machine" (in-silico then in-vivo) decide the location of the droplets at a given time.

5b. Fabricated micro-and nanoparticles interacting with ChemBioIT systems

John McCaskill

Theory is important both in the quantum design of nano particles, in the solution properties of their interfaces and in the description of collective structuring through their self-assembly.

5c. Electrokinetic and electrochemical systems

John McCaskill

Theory, simulation and computation are essential contributors to this area. Excellent texts exist, but still many important phenomena are poorly understood because they involve nonlinear phenomena with numerical instabilities in simulation and because they involve interaction between different physical simulation areas such as electrochemistry, fluid dynamics, molecular water structure, non-equilibrium statistical mechanics, polymer physics, combinatorial synthesis etc. Tools such as COMSOL and other integrative multi physics modelling frameworks will be useful.

5d. Autonomous chemical sensor and actuator networks down to cellular size and intelligent microparticles.

John McCaskill

Itamar Willner

Theory will contribute strongly to the components of physical understanding, evolution, self-assembly and coding theory. Simulation will be essential to understand the complex integration problems involved and the approach will usher in a new type of hybrid computation in which electronic and chemical systems share components of embedded computation.

5e. Hybrid systems involving cells

Andreas Offenhäusser

5f. Information processing principles in hybrid systems

Konrad Szacilowski

Modelling of hybrid devices is crucial. Development in modelling of neural/memristive networks is essential for better understanding of devices, which will lead to better designs.

6a. Chemical robotics, Autonomous Experimentation and Swarm Chemistry

Frantisek Stepanek

Due to large number of parameters that influence the design and functionality of chemical robots, computer-aided design tools and virtual prototyping, as well as direct numerical simulation of the underlying physic-chemical phenomena will be useful as they may significantly reduce the number of experiments as well as lead to the discovery of more general rules and new phenomena, as demonstrated e.g. by Grancic et al., J. Phys. Chem. B 117, 8031-8038 (2013).

6b. Additive manufacturing, 3D functional printing, steganography & related fab

Steen Rasmussen
Andreas Schober
John McCaskill

Simulation plays an important role once local restructuring processes begin to dominate the structure formation initiated by top-instructed 3D printing. 3D printing signals must be simulated to calculate the final structures they induce, and possibly an iterative process of refinement by simulation carried out to achieve good results unless a modular inverse code assigning printing signals to structures can be found.

6c. Multiscale and hybrid robotic systems interacting with chemical construction

Rudolf Füchslin
Serge Kernbach

Theory will certainly help to design and implement hybrid robots. Furthermore, simulations can help us to avoid going astray. We are often inspired by processes observed in biological systems. And one may have an interpretation for what one sees. But I truly believe that one only understands what one can construct. However, constructing in the real world is often difficult. As a, of course somewhat poor substitute, one may rely on virtual construction.

6d. Evolutionary robotics, including functional material modification

Daniel Richards

This subarea exploits computation and simulation of real-world materials, physics and environments to discover functional designs through optimization. A key advantage of this approach relates to sustainability. The ability to "do more with less" with existing materials by combining them in clever ways would significantly help address issues of climate change and environmental design.

6e. Embodiment and chemical information encoding in robotic construction systems

Steen Rasmussen

7a. Simulation of ChemBioIT processes and subsystems

John McCaskill

Theory plays an essential and critical role enabling simulation : without it simulation descends to ad hoc event jungles, without reference to completeness or realism, valid physical conservation laws or methods to extract simplifying principles and unable to extrapolate beyond the limits of computational resources.

7b. Simulation integrated design and programming for ChemBioIT

Steen Rasmussen

7c. Simulation integrated evolution for ChemBioIT

Rudolf Füchslin

Paulien Hogeweg

8a. Information encoding and communication of information associated with construction

Peter Wills
John McCaskill

8b. Connecting natural computations (molecular, membrane, cellular etc)

Susan Stepney

Theory is central -- it is the development of a new theory/design approach necessary for exploitation of multi-substrate, multi scale, ChemBioIT. Simulation is important as a way of determining genuine understanding of the simulated devices (rather than a phenomenological description), and as a way of exploring new devices before committing to costly experimentation, and as a way of exploring risks/consequences of self-assembly/autonomy in a safe environment. Computation is key -- understanding what part of the system is dominated by physical processes, and what by information processing, is key in design and development.

8c. Programmability and programming autonomous systems

Susan Stepney

Theory -- necessary to develop the "emergent programming" area. Simulation -- crucial for exploring the space of the possible.

8d. Architectures and optimization for combined computation and construction

John McCaskill

9. ENERGETICS FOR INFORMED CONSTRUCTION

The C^hem B^io IT roadmap leads towards autonomous fabrication processes and autonomous artefacts, all of which require energy. The Zero Power initiative is already dealing with energy harvesting mechanisms to power electronic devices. While a full integration of a power technology roadmap will be necessary at some point in the future, in the first stage we merely highlight the main issues and facets of this that are especially relevant to ongoing programmed chemical fabrication. The use of synthetic biology for sustainable power is another whole area of technology that will not be addressed here.

9a. Light driven mechanisms (e.g. dye solar films/cells and Si components)

Light provides a sustainable source of power for surface systems that can also be harnessed (as in biology) for programmed construction. Research on matching solar power and artificial light sources to informed local construction should also include investigation of photochemical control mechanisms to gate construction processes as well as self-repair through renewed self-assembly of dye-based photoactive films.

9b. Chemical battery and fuel cell electronics (e.g. enzymatic sugar power) electronics

Biofuel cells consisting of electrically wired enzyme electrodes can be implemented for the conversion of the energy stored in biomass substrates into electrical power. The application of conducting nanomaterials such as mesoporous carbon, carbon nanoparticles, graphene or carbon nanotubes can be implemented to enhance power output of miniaturized biofuel cells. Alternatively, electrically wired dye-modified enzyme electrodes can be used as functional elements to construct photobioelectrical cells that transform light to electrical power or photobiofuel cells transforming light energy into the hydrogen fuel.
As in traditional mobile power electronics a Ragone plot highlights the effective role of fuel cells at the high specific energy density – longer discharge time corner. Chemical power and its management (intelligent accumulation, distribution and exploitation) will be vital for effective autonomous construction.

9c. Energy transduction mechanisms (e.g. Light to electronics and/or chemistry, chemistry to electronics and vice versa).

Energy transduction is crucial to power information processing systems for informed construction. Sources of energy can for example be chemical, electrical, optical or mechanical (vibrational). The inter-conversion of energy sources is important to allow complementary power and information channels and can also be used to regulate construction processes. As in biological systems, the diversity of intermediate forms of energy carriers and construction intermediates means that a fine grained intertwining of energy and information regulation in construction processing can take place.

9d. Capacitive coupling between powered electronics and microparticle chemistry

Capacitive coupling is an alternative already being explored for powering autonomous microparticles intermittently in solution (MICREAgents project), since it also allows electronic communication. Electromagnetic field power should be explored more fully in its relation to ionic currents and other signaling transport networks (cf neural synapses).

9e. Miscellaneous power sources incl. magnetic, vibrational, others.

Research on alternative sustainable energy resources while emphasizing chemical or biochemical opportunities can also make use of a large suite of physical energy sources in the environment for energy scavenging. The C^hem B^io IT smart usage of such additional energy sources for ongoing construction regulation is the specific them

10. ECOLOGICAL & SOCIAL ASPECTS

The significance of the C^hem B^io IT roadmap for society and sustainability has already been introduced in the introduction (Vision for Construction and Computation). A major transition from centralized gigantean fabrication of high technology products to microscopic on site ubiquitous technical fabrication would of course have major effects on society. We view this development as vital to resolve the increasing gaps in society between industrial and personal interests, between global and local economies, between industrial manufacturing and sustainable ecology, between genetic engineering and personal determination, between health industry products and fully personalized medicine. A separate document, submitted to FET as the SPLIT flagship proposal, has dealt with many of these social issues, advocating a major governmental program to address the potential, benefits and hazards of the foreseen inevitable microscopic revolution in high-tech manufacturing. Issues in connection with sustainable C^hem B^io IT are dealt with in more detail in a collection of panel contributions in Part V. Ethical considerations in connection with strong modification to the biological environment are separately underway in the Synthetic Biology and Nanotechnology communities. The technological blurring of the distinction between technical artefacts and organisms will require further intense societal engagement and debate. The authors are already engaged in this process, and hope that through such institutions as the European Center for Living Technology (inaugurated as an EU-FET initiative) and the ISSP in Denmark, a larger engagement with societal interests will be possible.

10a. Sustainable energy and resource systems: "cradle to cradle" & recycling

Information technology will be critical to allow artificial chemical and biological processes to exploit low-density ambient energy and material resources and to manage waste products in a sustainable form. Chemical technologies that can operate efficiently to do construction in complex environments and without destruction of natural balances require combined ecological and chemical research.

10b. Personal fabrication and internet supported fabrication systems

A separate document already describes a roadmap to sustainable personal living technology. The vision here is to move towards universal functional construction on a desktop (the PF augmenting the now ubiquitous PC) through replacing CAD explicit 3D design information with quasi-genetic digital encodings of self-assembling construction process control in a well-defined and replicable construction environment (the personal fabricator). The reproducibility and communicability of construction protocols will allow internet communities to build up and exchange increasingly complex constructions.

10c. Human in the loop personal technical systems: from diagnostics to support

Extending high information chemical content processing from the nascent field of personal medicine (archetype is the parallel paper diagnostics for infectious diseases of Whitesides) to allow dedicated synthesis of appropriate systems and medications for personal therapy will benefit from having humans in the loop to monitor and choose acceptable pathways. Here it is envisioned that in the long term an ecology of devices and control points must be developed.

10d. Social consequences and goals of ChemBioIT e.g. developing countries, young & old

Neil Gershenfeld with personal fabrication, George Whitesides with paper diagnostics and the FET proposed SPLIT initiative (ECLT coordinator) in sustainable personal living technology have implemented or explored the social consequences of injecting IT into fine-grained fabrication and projecting this down to the level of personal solutions and chemicals. The consequences are potentially far reaching, with local fabrication at all scales impacting the fabric of society and the sources of innovation and access and autonomy in technology in numerous ways.

Part III: The Future and Metrics for ChemBioIT

This section collects the material gathered in the roadmap process concerning the future of C^hem B^io IT and how progress can be measured with metrics. The main metrics employed are the development status metrics and the special ChemBioIT metrics introduced in Part I.

After a presentation of the compiled metrics, each subtopic addresses
(i) The 5 and 10 year goals
(ii) Necessary achievements to make the 5- and 10-year goals possible
(iii) Scientific "breakthrough achievements" that could be produced in the process
(iv) Major necessary developments in other areas
(v) Additional comments on the timeline

COMPILED METRICS

The 10 metrics employed are summarized with a key to interpretation of their levels in Table III.1. Many of the subtopics are dependent upon cooperation with other subtopics in order complement weaknesses/bottlenecks in progress towards level 7 in all metrics – the roadmap final goal.

The meaning of the levels 1-7 are different for each metric, as specified in the following table.

Level	robust/flexible	evolvable	creativity	autonomous	fine-grained/ complex	fast/ efficient	stable	sustainable/self-constructing	programmable/ controllable	multi-scale
	towards	regarding	in	w.r.t.	scale/number	time	for time			over factor of
1	optimized lab constancy	sequences	variation	stable trajectories	cm/10s	day	ms	fabricated	switchable	10
2	without stringent control	multi-object	responses	feedback control	mm/100s	hr	s	env. degradable	modulatable	100
3	quantitative lab perturbations	embedded	components	self-assembly	100µm/1000s	min	min	partly	regulatable	1000
4	range of chemicals	information encoding	problem solution	instruction	10µm/10000s	s	hr	needs specialized components	reconfigurable	10000
5	range of mechanisms	multilevel replication	solution paths problem	power	1µm/millions	ms	day	waste control	of operation of	100000
6	new environments	mechanism	choice	architecture	10nm/ 10^8	µs	weeks	self-reproducing	reconstruction	1000000
7	new contexts	open ended	innovations	goals	1nm/10^9	ns	years	component scavenging	fully programmable	1000000000

Table III.1 Metric level key. All of the metrics were determined for each subtopic and period using the level interpretations defined in this table.

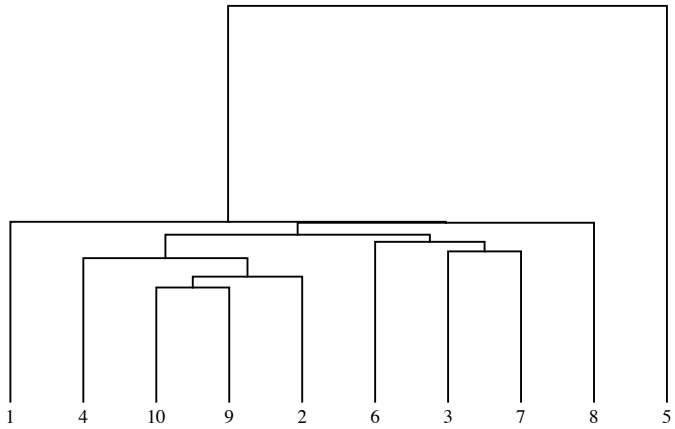

Fig. III.1 Dendrogram of the achievement similarity in the 10 metrics at 10 years.

Only metric 5 on computation and construction efficiency is markedly behind the other metrics, but commensurate with biological construction timescales rather than silicon CPUs.

Fig. III.2 Radar plots of the 10 ChemBioIT metrics
The different subtopics are those of the table of contents refererred to by 2-letter code. The data is compiled from expert panel contributions for the three phases: current, in 5 years and in 10 years.

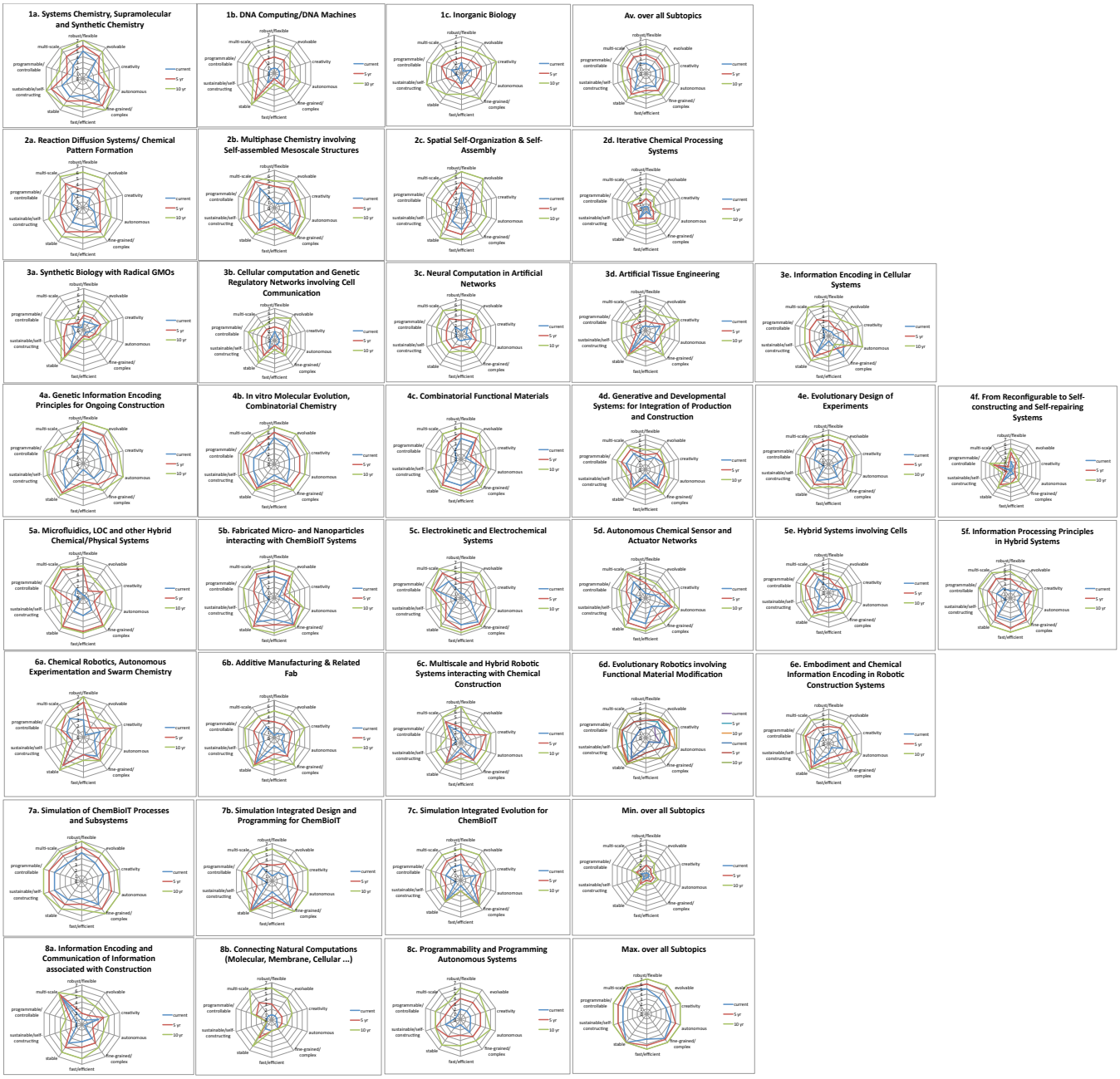

Fig III.3 Radar plots by subtopic for the 10 C^hemB^ioIT metrics
The different subtopics are those of the table of contents referred to by 2-letter code. The data is compiled from expert panel contributions for the three phases: current, in 5 years and in 10 years.

The metrics reveal overall substantial progress in all metrics, if cooperation between the different core technologies can be brought to bear. Efficiency lags significantly behind expectations from computer science computation, but progress in construction time scales is still significant here compared with the generation times for chip development (months). The envelope of all subtopics (last image in Fig. III.3) shows that perfect combination of technologies from all subtopics would yield in 2014 optimal achievement of all metrics, however barriers to effective combination will of course limit progress. The main message remains that a combination of the benefits from the different approaches seems poised to deliver most technological progress towards the goals of the roadmap.

COMPILED FUTURE BY SUBTOPIC

1a. Systems Chemistry, Supramolecular and Synthetic Chemistry – Future Profile

Günter von Kiedrowski
Andreas Herrmann

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Developing modules for robust system construction	Miniplants exhibiting integrated programmable catalysis
2.	Smart chemical pills with integrated control	Programmable reactor able to make chemicals needed in trainable and programmable way

Necessary achievements to make the 5- and 10-year goals possible

1.	Chiral reactor parallel search with feedback loops.
2.	Reverse process of controlling deconstruction by voltage from chip
3.	Light directed chemistry allowing dynamic microsystems controlled during operation by light, orthogonal to electrode control
4.	Combination of 3D printing of experimental apparatus and chemistry

Scientific "breakthrough achievements" that could be produced in the process

1.	Energy harvesting: smart technology to optimise power supply with available resources without massive storage
2.	Basic understanding of water and interfaces
3.	Artificial cells
4.	Exploitation of quantum processing, tunneling, entanglement, collective transitions, at room temperature?

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Physics of water : how does water structure reflect the interface, is there a far ordering beyond 5nm?	Condensed matter physics	Needed
2.	Miniaturization of NMR or other structural characterization tools	Physics	Useful

1b. DNA computing and DNA machines – Future Profile

Friedrich Simmel
Martyn Amos

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Genetic production of nanostructures in vivo or in cell-like systems. Realization of autonomous molecular machines that can transport and assemble materials	Development of free-running (open) systems (having some primitive metabolism, external energy/materials source). Autonomous ("energy scavenging"?) molecular robots.
2.	Orchestration of multistep assembly processes by molecular programs Fully-automated molecular programming	Implementation of evolutionary schemes Artificial evolution (autonomous) Self-replicating systems
3.	Scaling up production of nanostructures Scale-up beyond proof-of-principle Bridging length scales from nanoscopic to macroscopic	Implement learning/trainable systems Learning molecular systems/pattern recognition
4.	Integration with living (mammalian) cells Better standardised software tools for design Better simulation models	Reconfigurable, programmable, multi (or general) purpose systems Programming "on the fly"
5.	Interfacing molecular computing and conventional technology; hybrid systems; autonomous sensor/diagnostic/theranostic	From artificial cells to artificial tissues; artificial development and differentiation; growth and self-replication Information not filled in above

	systems; development of robust, modular, and scalable computing/fabrication schemes; programmable control of dynamical, self-organizing processes; systems with some sort of memory	

Necessary achievements to make the 5- and 10-year goals possible

1.	Realize truly modular systems, reduce/avoid chemical crosstalk Generation of ability for molecular systems to achieve autonomy Improved interfacing/control/screening methods
2.	Autonomous theranostic systems, intelligent drug delivery and "molecular sentinels" Artificial ("unnatural") engineered evolution/self-replication generally, there are many, many chemical/materials challenges involved in order to implement more complicated ideas in the "test tube"
3.	Biological & sustainable production of artificial materials and devices coupling to and utilization of other chemistries (translation from DNA code to "something useful")
4.	Controlled materials/energy exchange & realization of "homeostasis" // utilization of external energy sources (light, chemical, etc.)

Scientific "breakthrough achievements" that could be produced in the process

1.	The applications for this field will most probably lie either in biomimetic (and hopefully sustainable, low-energy consumption, environment-friendly) assembly processes and production systems, or in the realization of autonomous agents, which can interact with their environment (for sensing, theranostics, bioremediation, food & drug safety).
2.	Intelligent therapeutics, autonomous theranostic systems, intelligent drug delivery and "molecular sentinels"
3.	Biological & sustainable production of artificial materials and devices
4.	Artificial ("unnatural") engineered evolution/self-replication. Growth and reproduction of an artificial system.

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Modelling and simulation	CS	Needed
2.	Artificial chemistries	Chemistry	Needed
3.	Microfluidics	Materials/Engineering	Needed
4.	Robotics	Engineering	Useful

1c. Inorganic biology and genetic alternatives to nucleic acids – Future Profile

Steen Rasmussen
Lee Cronin

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Establish the theory and initial proof of concept that evolution of 'inorganics' can be robustly demonstrated using 'computer assisted' robotics	Fully autonomous inorganic machinery allowing evolutionary dynamics to emerge

Necessary achievements to make the 5- and 10-year goals possible

1.	Researchers trained in programming and chemical synthesis
2.	New understanding of what biology is in terms of evolutionary chemistry first Rapid prototyping of chemical robotics
3.	Minimal requirements for functional evolution. New sensor systems
4.	Developments in optimisation algorithms and molecular spectroscopy

Scientific "breakthrough achievements" that could be produced in the process

1.	Inorganic life
2.	New understanding of what biology is in terms of evolutionary chemistry first
3.	Minimal requirements for functional evolution
4.	New understanding of information and link with entropy and evolution (not Shannon or Kolmogorov)

Major necessary developments in other areas

Nr	Development	Area	Need
1.	New theory for self-assembling and self-organising robots	Robotics	Needed
2.	Models for emergent complexity	Complexity Theory	Needed
3.	Control of architecture, programming of evolutionary systems	Evolutionary Computation	Needed
4.	Developments in algorithms	Computer Science	Useful

Additional comments on timeline of necessary achievements

Timeline: 1-2 years - robotics / chemical programming; 2-3 years - modelling and theory for emergent chemical networks (inorganic); 2-3 inorganic replicator systems; 4-6 years for structure-translation-dissipative chemical system (brute force not engineered);6-10 years for rational design of inorganic replicating, mutating, functional system.

1d. Artificial chemistries and formalisms for molecular construction and IT – Future Profile

Peter Stadler
Peter Dittrich

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Inclusion of stereochemistry	Accuracy sufficient to be predictive for technological processes
2.	Inclusion of spatial organization/structures	Models with feedback of chemistry on complex materials
3.	Establish further links between discrete algebraic theory and dynamical systems theory	Develop a unifying theory of molecular computing that joins discrete algebraic descriptions with dynamical systems theory and that is intuitively usable by programmers to predict the behavior of their molecular programs.
4.	Implement computational tools for the design and analysis of C^hem B^io IT.	Implement useful tools following such a theory, i.e., develop computational tools for the design and analysis as well as bio-chemical/electronical tools for the construction of the actual systems ("ChemBioIT compilers").
5.	Combine more symbolic treatments with statistical mechanics and/or quantum mechanical models of molecular structure.	Develop the theory to become more realistic, i.e., include more chemical details like thermodynamics or realistic molecular structures and energies.

Necessary achievements to make the 5- and 10-year goals possible

1.	Spatial organization needs to be modeled in rule based system
2.	New one-pot chemical reactions as contribution to "green chemistry" derivation of rules for spatial (self) organization from simplified physical models.
3.	Theory, algorithms, and tools for constructing and analyzing implicitly defined chemical models including their qualitative dynamics.
4.	Most of the current tools require an explicit representation of the chemical system by a list of reactions.

Scientific "breakthrough achievements" that could be produced in the process

1.	New approaches in heterogeneous catalysis
2.	New one-pot chemical reactions as contribution to "green chemistry"

Major necessary developments in other areas

Nr	Development	Area	Need
1.	DNA machines Molecular modeling Quantum theory	1b Bioinformatics Computational chemistry	Useful Needed
2.	Spatially organized chemistries	2b	Needed
3.	Better understanding of selforg./repairing systems	2e	Useful

4.	Abstract interpretation, temporal logics and theorem proving, formal languages. Information and communication theory	Computer Science	Useful Needed

2a. Reaction Diffusion Computing and Chemical Pattern Formation – Future Profile

Jerzy Gorecki
John McCaskill

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Different variants of information coding, optimized for system dynamics. Self-organization of basic information processing devices from simple elements.	Long distance interactions in chemical medium. Reaction-diffusion medium with on/off property.
2.	Experimental demonstration of coupled phase and RD system evolution. First evolving in vitro morphogenetic system with Turing structures.	Evolutionary optimization of evolved Turing structures Evolutionary optimization of multiphase RD
3.	Sustained operation of reaction-diffusion computer with reactants delivered and products removed. Sustainable RD system with self-repair	Coupling chemistry with mechanical properties in order to produce required outputs. Self-maintaining RD system with in-built product cleanup.
4.	Discovery of new physico-chemical phenomena that can be used for external control of reaction-diffusion medium (information input). Significant computation by RD system used in directing construction	Strategies of training that can be applied to self-organized structures composed of nonlinear elements. Programmable RD computer with external interface
5.	Investigation on new types of nonlinear media for information processing applications. Flattened RD systems in microfluidics	Self-organized 3D computing media. Hybrid RD systems showing emergent structure

Necessary achievements to make the 5- and 10-year goals possible

1.	New variants of nonlinear media (for example BZ reaction and surrounding artificial tissue) that can proceed in a encapsulated space (like a nerve cell), but exchange substrates and products with the neighborhood, thus allowing for sustained activity. New variants of nonlinear media that can be controlled with external factors. DNA-directed chemical reactions : with rate control via sequence
2.	Formulation of general teaching strategies for compartmentalized media with different types of interactions. Understanding the influence of surface structures on RD systems. Scale-bridging pattern formation between molecules and macroscopic structures.
3.	Experimental demonstration of self-repair phenomena in a computing reaction-diffusion medium. Autonomous pattern forming systems that can process information.
4.	3D-printing control of system geometries. A "printing" technology allowing one to generate a medium with arbitrary defined non homogeneous concentrations of reactants. Efficient techniques of reconstruction and visualization of 3D droplet structures. Electrochemical and optical control of RD systems.

Scientific "breakthrough achievements" that could be produced in the process

1.	Experimental demonstration of a reaction-diffusion computer that can be switched off and next turned on with an external stimulus. Formulation of general teaching strategies for compartmentalized media with different types of interactions.
2.	Scale-bridging pattern formation between molecules and macroscopic structures. Artificial cells exploiting RD systems
3.	Experimental demonstration of self-repair phenomena in a computing reaction-diffusion medium. The integration of evolution and chemical pattern formation.
4.	Experimental demonstration of a system that can self-generate multiple copies of reaction-diffusion computers. Autonomous pattern forming systems that can process information.

Major necessary developments in other areas

Nr	Development	Area	Need

1.	Microfluidics, LOC and other hybrid chemical/physical Technologies Optical nanoparticle labelling	5a 5b	Useful
2.	Reconfigurable, self-constructing and self-repairing systems Neural computation in artificial networks. Information encoding in cellular systems.	4f 3c	Needed
3.	All types of simulations, especially Simulation of ChemBioIT processes and subsystems. 3D-printing control of system geometries.	7, 7a 6b	Needed
4.	Autonomous smart microparticles for distributed control of RD systems Active transport control	5d, 6a 5c	Useful

2b. Multiphase chemistry involving self-assembled macroscopic structures – Future Profile

Steen Rasmussen

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Robust ChemBio-ICT component self-assembled that creates new functions Examples of new programmable self-assembly structures	Molecular self-assembly engineering design principles More general programmable self-assembly
2.	Realize a minimal self-reproducing protocell Expand "standard" self-assembly modules	Vastly expand "standard" self-assembly modules
3.	Couple metabolic processes with self-assembly	Expand coupling between metabolic processes with self-assembly
4.	Robust self-assembly of ICT and ChemBio joint components. Expand ICT-molecular self-assembly processes	Programmable ICT-molecular self-assembly processes
5.	Controlled ICT component self-assembly	Programmable ICT component self-assembly

Necessary achievements to make the 5- and 10-year goals possible

1.	More collaborative work between experimentalists and theorists.
2.	Assembly of robust functional ChemBio-ICT components that are better / can do more / than pure ICT or ChemBio components. More focused scientific activities towards the large scientific milestones. Expansion of theoretical (e.g. exact solvable) self-assembly processes.
3.	ICT controlled self-assembly. ICT-molecular energy transfer.
4.	More exploratory activities in ICT component self-assembly and coupled ICT-molecular self-assembly.

Scientific "breakthrough achievements" that could be produced in the process

1.	Assembly of an autonomous self-reproducing protocell in the test-tube (create life from scratch)
2.	Assembly of robust functional ChemBio-ICT components that are better / can do more / than pure ICT or ChemBio components
3.	ICT controlled self-assembly. ICT-molecular energy transfer.
4.	Novel functionalities through ICT-molecular self-assembly structures ICT-molecular information exchange

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Better understood systems chemistry and supramolecular chemistry	Systems and Supramolecular chemistry	Needed
2.	Better micro and nano electronics	Better micro and nano electronics	Needed
3.	Better materials	Engineering/Materials	Needed

2c. Surface and interfacial chemical systems: including multilayer fab – Future Profile

Nicolas Plumeré

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals

1.	Electrocatalytic layer with full biomimetic properties	Layer as reactor for multistep chemical synthesis triggered via external stimuli
2.	Self renewing sensing layer for continuous in vivo monitoring	Triggering self assembled layer activity via external stimuli
3.	Complete mimic of the photosynthetic Z-scheme in biomimetic layersection in situ	Semi-artificial photosynthetic layers
4.	Adressability of multiple functionality via specific stimuli	Non limiting Electron transfer layers in analogy to multicenter redox enzymes
5.	Synthetis of biomolecules in (electro-) catalytic layer	Electrochemical energy conversion in biomimetic layers

Necessary achievements to make the 5- and 10-year goals possible

1.	Precise control of 3D layer self assembly.
2.	Concepts for Self renewing sensor for continuous in vivo monitoring Development of external stimuli triggered chemistry for activation with high 3D resolution
3.	Fully automated total synthesis of proteins Simulation to predict needed functionality to achieved a precise self assembly of 3D structures

Scientific "breakthrough achievements" that could be produced in the process

1.	Catalytic active layer with enzyme-like properties
2.	Concepts for Self renewing sensor for continuous in vivo monitoring
3.	Fully automated total synthesis of proteins
4.	Insights into the nature of biological pattern formation

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Optogenetics	Biology/Engineering	Needed
2.	Microfluidics	Engineering/Materials	Needed
3.	Formal models of bacterial consortia	Computer Science/Mathematics	Useful
4.	Directed evolution	Biology	Needed

2d. Iterative chemical processing systems with integrated separation and cleanup – Future Profile

Uwe Tangen
Steen Rasmussen

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Amplification and separation combined	Switchable amplification and separation

Necessary achievements to make the 5- and 10-year goals possible

1.	Master the surface problems of amplification and potential separation
2.	Programmable compartments with defined inside surfaces and outside behavior

Scientific "breakthrough achievements" that could be produced in the process

1.	Programmable surfaces with modules added changing its properties
2.	Programmable compartments with defined inside surfaces and outside behavior

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Surface chemistry	Chemistry	Needed
2.	Multiphase	Chemistry	Needed

Additional comments on timeline of necessary achievements

Expected achievements and development status:

- amplification in microstructures (today, d)
- iterative amplification, (2015, d)
- integrated amplification and cleanup (2018, d),(2020, c),(2022, b), (2032, a)

Cleanup is simpler in principle than amplification but integrating cleanup seems to be as difficult as integrating amplification. I expect that the integration of both together will take at least 5 years to succeed.

3a. Cellular Synthetic Biology using radical GMOs – Future Profile

Angel Goñi-Moreno
Martyn Amos

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Standardise measurements techniques Routine gene circuit synthesis	Standardise in-vivo activity Development of complex functional materials
2.	Expand orthogonality modules Agreed vision of scope of field	Scale up intracellular circuits Effective clinical therapies
3.	Improve mammalian syn. bio. Stable regulatory framework	Medical apps. based on mammalian cells Tissue engineering and regenerative medicine
4.	Unify in-silico representation Global adoption of standards	Bacterial chassis General public acceptance of value
5.	Environmental apps Established routes to market	Automate protocols Movement into mammalian cells

Necessary achievements to make the 5- and 10-year goals possible

1.	It is needed to make governments understand that education & science cuts are bad. Promote inter-disciplinary work (mainly in mixed labs)
2.	Better DNA synthesis capabilities. More hosts/chassis organisms/synthetic genomes. Mammalian-cell circuits aiming at medical applications.
3.	Accurate computational tools Promote "computational biology" in academia (University subjects, Master, ...) More extensive databases
4.	Achieve reliable tools for information sharing among labs More refined models of metabolism

Scientific "breakthrough achievements" that could be produced in the process

1.	General-purpose chassis (almost-"empty" and standard bacteria to use as chassis for circuits) Personalised medicine/drugs
2.	Mammalian-cell circuits aiming at medical applications. Water security/desalination
3.	Accurate computational tools Novel crops
4.	Standard robust-like biological engineering Synthetic genomes

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Software tools and libraries High throughput screening	IT Biology	Needed
2.	DNA Synthesis Systems biology	Chem BIology/CS	Needed
3.	Standard protocols Computational modelling	Bio CS	Needed
4.	DNA synthesis/assembly	Molecular Biology	Needed

Additional comments on timeline of necessary achievements

Robustness is the key issue of 3a. Although researchers are working fast on this and small elements are very reliable (as in point IV), bigger examples that are to come (5yr and 10yr) will face this very first problem. In order to know if something is robust or not we must measure it. If we are going to measure it, we need to conclude in 1) a number and 2) some units. Till now, most of the units are "arbitrary". Necessary things to do to connect with 5yr and 10yr: - Find a way to turn the "arbitrary units" into "absolute units". - When the previous is achieved, we will be able to engineer parts robust enough in different labs (we do not know if they are robust or not if we cannot measure them). - Dynamic studies (computational biology) will inform

on how to build those parts. - Previous dynamic studies will also help joining parts together in bigger circuits. - Synthetic circuits must be coupled with natural systems in order to suit applications. That is the timeline for 10yrs.

3b. Cellular computation and Genetic Regulatory Networks involving cell communication – Future Profile

Martyn Amos

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Adaptive distributed biosensors	Practical demo of bacterial metabolic "chemical plant", made up of multiple consortia
2.	Reliable synthesis of non-trivial, distributed logic circuits	Tissue engineering demo
3.	Multiple cellular communication schemes in wide use, including horizontal gene transfer	Practical demo of therapeutic application of engineered consortia (eg. pathogen detection and destruction in situ)
4.	Better interfacing with consortia (perhaps using optogenetics)	Regular demonstration of engineered inter-kingdom communication
5.		Programmed bacterial population that mimics development/differentiation in multi-cellular organisms

Necessary achievements to make the 5- and 10-year goals possible

1.	Better real-time monitoring of genetic circuit components (interfacing and screening)
2.	Programmed pattern formation Methods for incorporating stable genomic changes into "non-standard" organisms
3.	Distributed cellular "decision making" and actuation Better understanding of fundamental processes underling pattern formation, and thus more realistic models and simulations

Scientific "breakthrough achievements" that could be produced in the process

1.	Directed tissue engineering
2.	Programmed pattern formation
3.	Distributed cellular "decision making" and actuation
4.	Insights into the nature of biological pattern formation

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Formal models of bacterial consortia	CS/Maths	Needed
2.	Microfluidics	Engineering/Materials	Needed
3.	Optogenetics	Biology/Engineering	Useful
4.	Directed evolution	Biology	Needed

3c. Neural computation in artificial networks – Future Profile

Chrisantha Fernando
Phil Husbands

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Understand structural plasticity of the brain and develop algorithms to explain it.	Integrate symbol systems with connectionist approaches to make a unified approach
2.	Determine whether there is copying/replication of supra-synaptic information in the brain	
3.	programmable R-D demonstrator	robust, evolvable chemically controlled robot.
4.	physically realised volume signalling systems	robust, reconfigurable processor networks with electrical and chemical signalling

Necessary achievements to make the 5- and 10-year goals possible

1.	A method to produce genuine collaboration between distantly related discliplines in a manner which is more than superficial.
2.	Radical new type of programmable information processors This requires not only the standard grant

	funding methodology, but a physically localised group of individuals working on a long term 10 year goal with performance related bonuses.
3.	Development of hybrid 'hardware'/chemical information processing systems
4.	Suitable sustainable R-D systems capable of rapid pattern formation

Scientific "breakthrough achievements" that could be produced in the process

1.	The ability to exhibit general artificial intelligence, creativity, and adaptivity.
2.	Radical new type of programmable information processors

Major necessary developments in other areas

Nr	Development	Area	Need

3d. Artificial tissue engineering using structured chemical/material scaffolds; Additive manufacturing, 3D functional printing, steganography and related fab – Future Profile

Andreas Schober

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Design and construction of functional sinussoidal structures	The scientific community working in this area is highly focusing on the creating functional tissue islands with that can maintain their function for reasonable time.
2.		Common bioprinted tracheas
3.		Functional liver lobula

Necessary achievements to make the 5- and 10-year goals possible

1.	Surface driven control on the cellular adhesion of different cell types
2.	Constructive cell experiments, which solve biological questions like Cue for the self-organization of cellular material
3.	Cell cell interaction or neuronal cell communication producing devices like Perfect scaffolding technique for multipurpose applications
4.	Structuring of porous material, multilayer technology

Scientific "breakthrough achievements" that could be produced in the process

1.	Organ like models
2.	Constructive cell experiments, which solve biological questions
3.	Cell cell interaction or neuronal cell communication producing devices
4.	3D multicellular, multifunctional devices implementing partial brain functions

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Better theoretical models for the geometric and molecular interaction of evolving cellular networks	Theoretical Biology	Needed

3e. Information encoding in cellular systems – Future Profile

Luca Cardelli

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Understanding of genetic algorithms.	(Re)Engineering of genetic functionality.
2.	Understanding of proteomic signal processing.	(Re)Engineering of proteomic functionality.
3.	Understanding of membrane algorithms.	(Re)Engineering of membrane-driven fabrication.

Necessary achievements to make the 5- and 10-year goals possible

1.	Increased knowledge of fundamental biology (e.g. ongoing sequencing efforts)
2.	A theory of proteomic circuits akin in power to the theory of electronic circuits. Developments in the theory of computation by molecular assemblies, in addition to experimental progress.
3.	Flexible, programmable, highly gain, multi-channel tagging techniques for subcellular structure, such as via DNA computing. Increased biological knowledge, including dynamical imaging techniques for subcellular structures.

Scientific "breakthrough achievements" that could be produced in the process

1.	Ability to reprogram the genome.
2.	A theory of proteomic circuits akin in power to the theory of electronic circuits.
3.	Flexible, programmable, highly gain, multi-channel tagging techniques for subcellular structure, such as via DNA computing.

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Experimental techniques.		Needed
2.	Nanotechnology.	DNA	Needed

4a. Genetic information encoding principles for ongoing construction – Future Profile

Peter Wills

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Demonstrate, in silico, the co-emergence of a general system of constructive computation and the 'genetic' programme needed by the system to construct itself.	Demonstrate, in silico, a co-emergent system that continues to generate more refined descriptions and self-constructive computations.
2.	Demonstrate the existence of a minimal autocatalytic system that has all of the essential features of co-emergent genetics and self-construction.	Build a complex autocatalytic co-emergent genetically programmed self-constructive system capable of transitioning to dynamic states reflecting self-definitions that are increasingly information-rich.

Necessary achievements to make the 5- and 10-year goals possible

1.	Achievement of the 5-year goal 1 and 10-year goal 1
2.	Evolution of type II von Neumann machines Achievement of the 5-year goal 2 and 10-year goal 2
3.	Construction of general purpose type II von Neumann machines

Scientific "breakthrough achievements" that could be produced in the process

1.	Construction of a type II von Neumann machine
2.	Evolution of type II von Neumann machines
3.	Construction of general purpose type II von Neumann machines

Major necessary developments in other areas

Nr	Development	Area	Need

Additional comments on timeline of necessary achievements

Rapid development (in 5 years) to achieve in silico examples of evolved, genetically programmed systems able to self-construct in a highly structured environment (stable; sustainability/self-construction). Over the next few years it should be possible to "wean" the systems so that they are able to construct more of their components from variable energy sources, rather than relying on being supplied with ready-made elementary parts (autonomy; programmable/controllable). This will have to be accompanied by advances in understanding how such systems can progressively evolve, becoming progressively more information-rich (complex) in all of their functions and interactions with the outside world (evolvable; creativity).

4b. In vitro molecular evolution, combinatorial chemistry – Future Profile

John McCaskill

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Incorporation of evolution into ongoing construction process	Evolution of a metabolic system with self-sustaining properties
2.	Evolution of polymerase ribozymes	Evolution of a high fidelity DNAzyme polymerase
3.	Integration of genetic and container evolution	Evolution of an artificial cell
4.	Coupled reaction-diffusion controlled evolution	Spatially evolving in vitro systems
5.	Evolution of information encoding	Artificial integrated evolution and translation

Necessary achievements to make the 5- and 10-year goals possible

1.	Effective coupling of in vitro evolution with high throughput sequencing
2.	Better understanding got the origin of life and artificial life Integration of programmable separation technologies with evolution on chip
3.	Rapid pre-clinical production and screening of pharmaceuticals for function Integration of real-time parallel selection control (e.g. electrochemical)
4.	Autonomous micro scale chemical evolution processors for 10 year goal

Scientific "breakthrough achievements" that could be produced in the process

1.	First enzyme free high fidelity evolution system
2.	Better understanding got the origin of life and artificial life
3.	Rapid pre-clinical production and screening of pharmaceuticals for function
4.	Extension of chemical evolution to physical processes

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Printable environments	3D printing & electronic microsystems	Needed
2.	Evolutionary encoding design	Evolution theory/ Biomathematics	Useful
3.	Click chemistry of ligation	Organic synthesis	Useful
4.	Sensitive compositional label-free detection	Spectroscopy	Useful

4c. Combinatorial functional materials (including polymers) – Future Profile

Andreas Herrmann

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Combining supramolecular hybrid systems that exhibit several of the functionalities of replication, compartmentalization, and information transfer.	Fully artificial cell that is composed of one or several hybrid materials and self-sustained
2.	DNA materials that act as drug delivery vehicle	Several artificial cell types communicating with each other and performing joint functionalities.

Necessary achievements to make the 5- and 10-year goals possible

1.	Prediction of assembly of biohybrid systems
2.	Stabilize and reduce immunogenicity of biohybrid structures in the body
3.	Creating enzymes or electronic synthesis systems that can fabricate biohybrid structures
4.	Electronic integration of synthesis and other sensing functions of bioorganic hybrids

Scientific "breakthrough achievements" that could be produced in the process

1.	Novel sensor technologies because of better interfacing of electronics with receptors
2.	Accelerated and improved gene synthesis for synthetic biology
3.	Catalytic nano-reactors for multistep catalysis
4.	Biodegradable electronics

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Prediction of body immunological response to artificial materials	Immunology	Useful
2.	Integration of polymer characterization on biomaterial synthesis chip including e.g. DLS, fluorescence & mass spectroscopy, AFM	Engineering	Useful

4d. Generative and developmental systems: for integration of production and construction – Future Profile

Peter Dittrich

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Quantitative insight (experimental/theoretical)	Directed evo-devo demonstration in (synthetic)

	concerning factors influencing the performancs of evo-devo	biology
2.		Quantitative theory of evo-devo performance

Necessary achievements to make the 5- and 10-year goals possible

1.	Benchmark problems for evo-devo.
2.	Standardized experimental computing platforms for evo-devo studies: virtual environments, electronics, program evolution.
3.	Standardized experimental platforms of physical artefacts for evo-devo studies: molecular systems, robotic systems, orgnic systems.

Scientific "breakthrough achievements" that could be produced in the process

1.	A creative evo-devo system exploiting unknown functions of a given bio/chem/mechano/electronic substrate.

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Molecular and cellular computing for instantiation at molecular level	Roadmap 1-3	Needed
2.	Virtual world simulation	Roadmap 7, Computer Science	Needed
3.	Synthetic biology	Roadmap 1, Biology / Computer Science	Useful
4.	Bioelectronics	Roadmap 8, Engineering	Needed

Additional comments on timeline of necessary achievements

Development of an evo-devo theory that allows to derive more effective evo.-devo mechanisms: 5 Years : Basic theoretical advancement joining evolution theory and theory of evolutionary computation 10 Years: Quantitative theoretical insights Development of evo-devo benchmarks and quantitative studies: 5 Years: Standardized benchmark problems Moving evo-devo from virtual to the physical world: 5 Years: Novel self-assembling / structurally developing robotic systems 10 Years: Biological or BioChemIT evo-devo substrates Note: The development in this area depends substantially on a better understanding of evo-devo (cf. the progress so far). Progress in understanding is difficult to predict, so is the future of this subarea.

4e. Evolutionary Design of Experiments – Future Profile

Norman Packard
Irene Poli

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Small molecule drug discovery campaign driven subtaintially by EDoE	All small molecule drug discovery campaigns driven substantially by EDoE
2.	Use of EDoE to discover effective chemistry-container combinations for protocell research	Use of EDoE to produce a fully evolvable protocell
3.	One significant scientific result for evolving systems, driven by EDoE	Dissemination of EDoE techniques to all evolutionary experimental contexts

Necessary achievements to make the 5- and 10-year goals possible

1.	Integration of several models (binding, toxicity, ADME), into multiobjective optimization.
2.	Identification of appropriate structures and variables to be explored, encoding of this information into a genome for EDoE.
3.	Interface built for the particular evolutionary experiment (whether peptides, proteins, or DNA) to a genomic representation for EDoE

Scientific "breakthrough achievements" that could be produced in the process

1.	New level of productivity for preclinical pharmaceutical research.
2.	A Protocell
3.	Chemical evolutionary engineering

Major necessary developments in other areas

Nr	Development	Area	Need

1.	Effective encoding of small molecules, databases of binding results	Chemo-informatics	needed
2.	Set up experimental protocols to be explored via high throughput experiments, and to be genetically encoded for EDoE	MEMS	needed
3.	High throughput infrastructure for chemical evolution	MEMS	needed

4f. From reconfigurable to self-constructing and self-repairing systems – Future Profile

Uwe Tangen

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Self-repair of silicon-chips will become a major research area	Self-repair of silicon chips will be deployed in space applications
2.	Reconfigurability will be used to help managing complexity	Reconfigurability will become a common sub-feature of high-end electronic devices
3.	Autonomy of sensor-networks will become a major issue in research	Sensor-networks will become semi-autonomous
4.	Adjustable and reconfigurable sensors will become an research issue	Reconfigurable biochemical sensors will become mainstream research

Necessary achievements to make the 5- and 10-year goals possible

1.	New concepts on self-repair must be developed, especially the routing-problem of the signal-pathways
2.	Better insight into parallel decision making and parallel conflict management the dichotomy between programmable and autonomous must be settled, perhaps by inventing semi-programmability
3.	Perhaps some parts of the computation can already be implemented in chemistry intrinisic fault detection is a difficult task.
4.	The machinery to detect and repair faults should not be orders of magn. larger than the normal device

Scientific "breakthrough achievements" that could be produced in the process

1.	It could be learned in principle how nature managed to solve the problem of repair systems smaller and simpler than the machines to be repaired.
2.	Better insight into parallel decision making and parallel conflict management
3.	Perhaps some parts of the computation can already be implemented in chemistry

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Surface coating	Chemistry	Needed
2.	Parallel computing	Computer sciences	Useful
3.	logic reasoning	Philosophy and mathematics	Useful

5a. Microfluidics, LOC and other hybrid chemical/physical technologies – Future Profile

Patrick Wagler
Cyril Delattre

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Manipulate individual liquid volumes of scale 10cm and 50nm on the same device. Very small volumes to manipulate single cell/element manipulation Very large volumes to store everything necessary. (Multiscale Fine Grained)	Dedicated software translating needs into droplet manipulation on matrix (resilient, fault recovery, ...) System usable without the knowledge of the technology. (Evolvable)
2.	Use a 10 MPixels matrix for electrowetting (pixel size ca 200µm). Become design agnostic. (Evolvable Flexible) Use of electrochemical display technology with active CMOS-Faradaic pixels less than 10µm on cm-sized chips.	Have a feedback on the liquid volumes for parameters such as position, content, activity. Increase resilience Allow system to react when sensing. (Evolvable, Self-Constructing)
3.	3D ink jet printing of complex LOCs Fabrication of BioNEMS Self-powered MEMS-robots	Supramolecular self-assembling nanorobots Digestable sensors Programmable nanosensors
4.	Programmable nano-containers	Use a living system to generate charges for

		electrowetting with on-chip supply chain management. Manage resources such as energy, food, nutrients, waste, ... (Autonomous)
5.	Removing dependencies on complex external connections (pipes, wires, …) to generate true LoC, not chip in a lab (Autonomy, compare 5d)	Electrowetting system capable of handling all kind of solvents. Full versatility towards the nature of liquids that can be handled (access to all kind of chemical processes). (Creativity, Complexity)

Necessary achievements to make the 5- and 10-year goals possible

1.	Nanoliter scale fluidic handling 5 yr: Manipulate individual liquid volumes of 10cm and 50nm on the same device. Transition in size of liquid droplets. Manage the voltage locally
2.	Newly autonomous, parallel MEMS/NEMS fabrication technologies nanoscale positioning tools based on self-assemby 5 yr: Use a 10 MPixels matrix for electrowetting (pixel size ca 200µm). Materials. Adaptation of current TFT technology
3.	"active nanoparticles" "intelligent energy harvesting" 10 yr: Dedicated software translating needs into droplets manipulation on matrix (resilient, fault recovery, ...). Computer Aided Design of protocols and droplets manipulation
4.	10 yr: Have a feedback on the liquid volumes for parameters such as position, content, activity, etc... Sensors (physical, chemical, biological) compatible with electrowetting and materials

Scientific "breakthrough achievements" that could be produced in the process

1.	3D nano printing technology with combined(hybrid materials
2.	newly autonomous, parallel MEMS/NEMS fabrication technologies
3.	"active nanoparticles"
4.	Computation, microelectronics, materials science, biology (synthetic biology to change/add functionalities in cells/bacteria)

Major necessary developments in other areas

Nr	Development	Area	Need
1.	power management	9c-e	Needed
2.	Autonomous chemical sensor and actuator networks	5d	Needed
3.	Evolutionary Processing	4	Useful
4.	Programmability and programming autonomous systems	8c	Needed

5b. Fabricated micro-and nanoparticles interacting with ChemBioIT systems – Future Profile

John McCaskill

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Use DNA & NPs to assemble electronic circuitry	Deployment of NP-self-assembly in nanoelectronics fabrication
2.	NP based iterative chemical processing	Ongoing fabrication and deployment including NPs
3.	Construction of combinatorial NP-polymers	Evolution of NP polymers
4.	Rich repertoire of amplifying NP molecular sensors	Single molecule autonomous sensing with NPs
5.	Autonomously powered NPs	Smart NPs acting as MICREAgents

Necessary achievements to make the 5- and 10-year goals possible

1.	In solution synthesis of NPs with defined properties
2.	Ultimate detection limit in customized molecular sensing Further developments of NP internal structure beyond Janus NPs
3.	Extension of robotics to the sub-micrometer domain Separation of raw NP synthesis and in situ decoration/ customisation
4.	Establishment of end-user programmable NPs

Scientific "breakthrough achievements" that could be produced in the process

1.	Novel self-assembly paradigms
2.	Ultimate detection limit in customized molecular sensing
3.	Extension of robotics to the sub-micrometer domain
4.	Novel paradigms for artificial living systems and living technology

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Parallel particle manipulators	Physics	Useful
2.	Characterisation of NP-solution interface	Surface Science	Needed
3.	Novel multiphase synthetic	Physical organic synthesis	Needed
4.	Quantum NP programming	Quantum physics	Useful

Additional comments on timeline of necessary achievements

Nanoparticles and micro particles are already a large area of research with many applications. The step towards their integrated synthesis and deployment should be possible in the next 5-10 years and herald a new phase of chemical integration towards user-programmability.

5c. Electrokinetic and electrochemical systems – Future Profile

John McCaskill

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Hybrid electronic chemical cell	Fully autonomous nanomorphic cell
2.	Nanopore directed synthesis	Nanopore integrated chemical construction systems
3.	Microscale electronic chemical agents	Medical diagnostics and drug release with MICREAgents
4.	Ambient powered autonomous micro scale chemical hybrids	Autonomously moving micro scale electrochemical robots
5.	Programmable complex electrochemical coatings	Complex electrochemical construction control involving NPs

Necessary achievements to make the 5- and 10-year goals possible

1.	Detailed molecular theory (involving water structure) of electrokinetic/electrochemical phenomena
2.	Programmed control of cell interactions by autonomous particles Demonstration of efficient electrochemical molecular amplification processes e.g. DNA
3.	Fundamental understanding of nonlinear surface chemistry and phase effects Progress in system integration in nanofluidics, surface coatings and NP structuring
4.	Development of bootstrapping information encoding between electrical and chemical signals

Scientific "breakthrough achievements" that could be produced in the process

1.	Nanoionic based information processing in adaptive devices
2.	Programmed control of cell interactions by autonomous particles
3.	Fundamental understanding of nonlinear surface chemistry and phase effects
4.	High density and improved interface to neural systems and the human brain

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Evolutionary optimisation	Directed evolution	Useful
2.	DNA machines to modulate nanoionics	Biophysics, DNA	Useful
3.	Nanoparticle design	Nanoscience	Useful
4.	Multiscale simulation tools	Theory and simulation	Needed

5d. Autonomous chemical sensor and actuator networks down to cellular size and intelligent microparticles. – Future Profile

John McCaskill
Itamar Willner

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	To develop a self-reproducing autonomous lablet technology at the 100 µm scale	To establish an autonomous electronic artificial cell at the scale of 10µm
2.	To achieve electronically controlled translation of nanoscale objects on the 10µm scale	To demonstrate its electronic programmability via (a) pre-programming (b) programming during operation
3.	To complete an electronic chemical cell combining simple metabolism, containment and a genetic component on an electronic active surface	To demonstrate self-assembly and self-reproduction of such a cell, in an environment containing the raw electronic component substrates
4.	To develop an optical interface to hybrid electronic artificial cells	To demonstrate useful applications of ongoing construction and environmental sensitivity in such an HECC population
5.	To establish an interface between lablet technology and biological cells AND To develop a theory of information bootstrapping in such hybrid systems, building on evolution theory	To open up a route to sustainable personal fabrication of such entities

Necessary achievements to make the 5- and 10-year goals possible

1.	Autonomous electrical power and intermediate storage to particles without cables from chemical, photo, electrical or other sources.
2.	New understanding of biological systems (in particular the information flows and translations in biological systems) through a second translation system (electronic-chemical). Reversible control of particle docking and undocking by means of self-assembly.
3.	A nanoscale solution of von Neumann's universal construction automata Efficient local communication between particles via electrical signals.
4.	Control of interactions between smart particles and bio-objects such as cells.

Scientific "breakthrough achievements" that could be produced in the process

1.	Novel artificial life form and general platform for artificial life
2.	New understanding of biological systems (in particular the information flows and translations in biological systems) through a second translation system (electronic-chemical)
3.	A nanoscale solution of von Neumann's universal construction automata
4.	The basis for a new kind of neuromorphic-electronic computation combining the best of both worlds

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Progress in DNA machines and DNA based self-assembly	DNA Computing	Useful
2.	Progress in modeling and understanding of nanoelectrochemistry and nanoionics	Nanoionics	Needed
3.	Progress in chemical amplification and systems chemistry	Systems Chemistry	Needed
4.	Architectures for noisy low power circuitry and advances in low power electronics AND The achievement of protocell closure with a complex metabolism AND Progress in the evolutionary design of experiments	Low power electronics and Applied evolution	Useful

5e. Hybrid systems involving cells – Future Profile

Andreas Offenhäusser

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Sensors for neuropharma screening	Brain implants
2.	Controlled neuronal communication between individual cells	Controlled neuronal communication between cell populations
3.	Better interfacing with neuronal cells and tissue	Longterm functionality of BCI systems

Necessary achievements to make the 5- and 10-year goals possible

1.	Better interfacing of cellular components with electronic components
2.	Neuronal diodes Controlling cellular processing
3.	Neuronal tissue engineering Designing cellular function
4.	Improved nanoelectronic devices

Scientific "breakthrough achievements" that could be produced in the process

1.	Perfect bidirectional communication
2.	Neuronal diodes
3.	Neuronal tissue engineering
4.	Simple information processing based on neuronal circuitries

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Microfluidics	Material Science	Needed
2.	Microelectronics	Material Science	Needed
3.	Optogenetics	Synthetic Biology/Engineering	Useful
4.	Neuroscience	Biology	Needed

5f. Information processing principles in hybrid systems – Future Profile

Konrad Szacilowski

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Development of generic platform for integration/concatenation of various molecular-scale devices	Fabrication of VLSI devices containing molecular/biosystem components
2.	Implementation of different computing approaches within molecular systems (e.g. combination of reservoir computing with molecular switches)	Development of all-molecular computing systems of high complexity
3.	Development of molecular-scale interfaces with neurons and other types of cells	Molecular interfacing of animal brains with molecular electronic systems
4.	Interfacing of molecular logic/informaton processing systems with semiconducting electronics	Integration of molecular devices with all-optical processing devices

Necessary achievements to make the 5- and 10-year goals possible

1.	Concatenation of molecular-scale logic devices
2.	Interrogation with neurons/synapses at molecular level construction of biocompatible neurointerface operating at moleuclar level

Scientific "breakthrough achievements" that could be produced in the process

1.	Understanding of multiscale operation of nervous system
2.	Interrogation with neurons/synapses at molecular level

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Development of synthetic/biomimetic neurotransmitters for interogation of neurons at the molecular level	1d	Needed
2.	nanofluidics at single cell level	5e	Needed

Additional comments on timeline of necessary achievements

There are numerous issues to be addressed in the subfield 5f. The timescale of operation of molecular-scale devices, their minaturization and long term stability should not present any problems/obstacles. Usually molecular systems are very stable and their specific chemical reactivity may be tuned using standard synthetic strategies. Miniaturization is also not a serious issue - most of the molecular devices already operate at the molecular scale, but the signal detection is a bottleneck of miniaturization. Their operation is diffusion-controlled and miniaturization will automatically bring about an increase in their operation speed. The most problematic are their autonomity and evolution. At present there are some reports of evolvable/self-reproducitng molecular systems, but evolution in biological systems is extremely slow. It is

difficult to predict the evolution of artificial systems. Autonomity of molecular/hybrid systems is a direct function of their stability, robustness, good interfacing with environment and computing power. The progress in this area will be rather slow (at least slower than in other fields) due to stringent requirements.

6a. Chemical robotics, Autonomous Experimentation and Swarm Chemistry – Future Profile

Frantisek Stepanek

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	increase range of applications	commercialisation
2.	implement principles of artificial chemotaxis	autonomous locomotion
3.	develop reversible particle aggregation	reconfigurable swarming behaviour
4.	implement basic programmability	fully flexible chemical programmability

Necessary achievements to make the 5- and 10-year goals possible

1.	chemically robust vesicles with sharp phase transition
2.	direct control over biochemical pathways in tissues and biofilms efficient chemo-mechanical coupling for locomotion
3.	self-assembly of multicellular materials switchable surfaces robust in chemically complex environments
4.	embedding of complex reaction networks including excitable and oscillatory ones

Scientific "breakthrough achievements" that could be produced in the process

1.	control of (bio)chemical reactions in "inaccessible" environments
2.	direct control over biochemical pathways in tissues and biofilms
3.	self-assembly of multicellular materials

Major necessary developments in other areas

Nr	Development	Area	Need
1.	3D printing with sub-micron resolution	engineering	Useful
2.	chemical oscillator with bio-compatible components	chemistry	Needed
3.	stimuli-responsive polymers with a sharp phase transition	chemistry	Needed
4.	massively parallel microfluidic fabrication	engineering	Useful

6b. Additive manufacturing, 3D functional printing, steganography & related fab – Future Profile

Steen Rasmussen
Andreas Schober
John McCaskill

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Manufacturing of convincing combined top-down bottom-up hybrid materials (not "just" printing organs with stem cells)	Self-reproducing and self-assembling 3D printers
2.	Printing with multiple materials	More universal construction - or closer to that ultimate goal
3.	Printing semiconductors / transistors	Printing organic electronics and structures
4.	Printing self-assembling material	Integration of 3D printing and self-assembly
5.	Printing structures capable of ongoing reactive structuring	3D printing as reproducible programming system for setting up self-sustaining construction systems

Necessary achievements to make the 5- and 10-year goals possible

1.	Basic science and technology activities closely collaborate with (marked driven) industrial development of additive manufacturing activities
2.	Self-replicating and self-assembling 3D printers

Scientific "breakthrough achievements" that could be produced in the process

1.	Self-replicating 3D printer, initially "just" printing all its parts
2.	Self-replicating and self-assembling 3D printers

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Material functionalities from large scale (long range) self-assembling materials	Material science	Needed
2.	More intuitive interfaces (virtual reality) for programming additive manufacturing	Computer science / virtual reality	Needed
3.	Novel biomaterials and organs	Synthetic biology	

6c. Multiscale and hybrid robotic systems interacting with chemical construction – Future Profile

Rudolf Füchslin
Serge Kernbach

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Physical refill of energy, e.g. via radiation	Energy metabolism with refill from the environment
2.	Selective take up of material from the environment	Programmable selective take up of material from the environment.
3.	signal transduction from environment into agent	Processing of signal, e.g. via susceptible chemical networks.

Necessary achievements to make the 5- and 10-year goals possible

1.	Creating autonomous, self-supporting, self-replicating, sustainable systems is a great challenge. To some extent, understanding life means not only being able to create it from scratch, but also improving, supporting, saving it, or even making it even more advanced. This can be thought of as a long-term goal of hybrid autonomous systems: connection of ICT and bio-/chemo- developments, embodied artificial evolution of soft and wet"robots, integration of material science into developmental robotics, and potentially, addressing the self-replication in autonomous systems.
2.	Selective transport into agent. Transport into agent must depend on agent's content (feedback). Artificial membrane channels
3.	Steps towards an artificial immune system Repeatable signal transduction, real chemical sensing (not by using up some component that cannot be refilled)
4.	Self-surveying chemical networks with susceptible sub-network

Scientific "breakthrough achievements" that could be produced in the process

1.	Self-controlling chemical networks
2.	Artificial membrane channels
3.	Steps towards an artificial immune system

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Formation of vesicular/micellar/droplet structures	2b	Needed
2.	Scaffolds for efficient formation of chem. robots	3d	Useful
3.	functionalized nano particles	5b	Useful
4.	Self surveying reaction networks	6d	Needed

Additional comments on timeline of necessary achievements

From the viewpoint of a short-term and middle-term (e.g. 5-years) research agenda, it would make sense to undertake a step-wise transition from current mechatronic collective systems towards hybrids. The list of open research questions and achievements here is long, below are some examples: Which properties of materials are useful for collective robotics? Capabilities of a minimal cognition by using simple (even molecular) systems? Self-replication: from wet hardware to soft hardware Are there artificial structural elements that are absolutely plastic in the developmental sense, analogous to biological amino acids? Is a natural chemistry (i.e., a high complexity of evolutionary processes) important for adaptability and self-

development? What are the driving forces of long-term developmental processes? Are they controllable? Is the embodied evolution controllable? Is there any developmental drift due to emergence of artificial sociality and self-recognition? Is there an artificial chemistry that is able to adapt software in-situ? Do artificial homeostasis and rules of ecological survival lead to self-identification and to emergence of different self-phenomena (denoted as self): self-replication, self-development, self-recovering? We would like also to address the issues of a long-term controllability of hybrid autonomous systems. Artificial adaptive systems with a high degree of plasticity demonstrate a developmental drift. There are many reasons for this, like long-term developmental independence and autonomous behavior, emergence of artificial sociality, mechanisms of evolutionary self-organization. Such systems are very flexible and adaptive, but they also massively increase their own degree of freedom. New challenges in this area are related to a long-term controllability and predictability of self principles of making plastic purposeful systems, predictability of structural development and goal-oriented self-developing self-organization. These challenges have a great impact on the human community in general (cf. the Terminator scenario) as well as in different areas of embodied evolution, like synthetic biology or evolvable and reconfigurable systems.

6d. Evolutionary robotics, including functional material modification – Future Profile

Daniel Richards

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals

Necessary achievements to make the 5- and 10-year goals possible

Scientific "breakthrough achievements" that could be produced in the process

1.	high-performance bio-inspired materials for engineering applications (medical implants, prosthetic limbs, military armors, aerospace and navel technologies, machine parts, structural and civil engineering...etc)

Major necessary developments in other areas

Nr	Development	Area	Need

6e. Embodiment and chemical information encoding in robotic construction systems – Future Profile

Steen Rasmussen

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Making such systems more programmable	Information/control exchange between chembio and ICT
2.	More ChemBio-ICT integration	Power exchange between ChemBio and ICT
3.	Self-replication	
4.	Onboard complex computing	Swarming collective intelligence and problem solving with micro chembio-ICT robots
5.	Initial sustainable recycling of materials	Sustainable recycling of materials

Necessary achievements to make the 5- and 10-year goals possible

1.	Robust programmable microscopic motility
2.	Advances in both ICT hardware, chembio self-assembly and metabolic (power providing) processes self-replicating micro-robots
3.	Programmable chembio-ICT micro-robots
4.	Artificial mucles / medical repair / environmental remidiation

Scientific "breakthrough achievements" that could be produced in the process

1.	Better programmablility of funcionalities at the microlevel
2.	Advances in both ICT hardware, chembio self-assembly and metabolic (power providing) processes

Major necessary developments in other areas

Nr	Development	Area	Need

7a. Simulation of ChemBioIT processes and subsystems – Future Profile

John McCaskill

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	A verified simulation toolbox for subsystem engineering relevant to ongoing integrated fabrication.	Extension of toolbox to embrace all candidate including quantum technologies.
2.	First simulations of ongoing fabrication systems.	A verified simulation model of evolving ongoing fabrication.
3.	Full integration of SBML-style reaction kinetics with physical multiphase equilibria.	Extension of multiphase-integration with SBML to non-equilibrium phases.
4.	Computer language for the evolution of coding in ongoing fabrication systems.	Programming environment for simulation of ongoing fabrication systems.
5.	Computer design of functional subsystems for ongoing fabrication	Multi-scale simulation of integrated ongoing fabrication.

Necessary achievements to make the 5- and 10-year goals possible

1.	Modular interface development for multiphase simulation of subprocesses
2.	Fundamental theory of efficient stochastic simulation Autonomous identification of emergent dynamical quantities
3.	General framework for modelling emergent phenomena Automated model refinement mechanism as hierarchy : especially w.r.t. combinatorial chemical reactions
4.	Combination of multi-scale deterministic and event driven stochastic simulation

Scientific "breakthrough achievements" that could be produced in the process

1.	Understanding how life channels physical information processing power to explore self-construction
2.	Fundamental theory of efficient stochastic simulation
3.	General framework for modelling emergent phenomena
4.	New ChemBioIT processes and subsystems, found and/or understood by simulation

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Computer directed and autonomous experimentation	Extensions to Lab on a Chip Technology	Needed
2.	Evolutionary Design of Experiments	Experimental design	Useful
3.	World wide web database of models and simulations	Internet	Useful
4.	Ground-breaking implementations of novel living technology concepts	Artificial Life	Useful

Additional comments on timeline of necessary achievements

Only effective in conjunction with the main experimental threads 1-6.

7b. Simulation integrated design and programming for ChemBioIT – Future Profile

Steen Rasmussen

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals

Necessary achievements to make the 5- and 10-year goals possible

Scientific "breakthrough achievements" that could be produced in the process

Major necessary developments in other areas

Nr	Development	Area	Need

7c. Simulation integrated evolution for ChemBioIT – Future Profile

Rudolf Füchslin
Paulien Hogeweg

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Generation of a list of industrially relevant applications beyond search for key - lock structures in pharmacology	Implementation of some show cases
2.	Description and simulation of a self - surveying chemical network	Simulation supported programming of such networks
3.	A more lab oriented investigation of the P=BPP question with respect to real chemistry	
4.	Design of a set of chemical primitives for the construction of reaction networks	Simulation supported demonstration of programmability
5.	Proper analysis of how simulation integrated CBT can be embedded in industrial processes	Embedding in industrial processes

Necessary achievements to make the 5- and 10-year goals possible

1.	Construction of a support system which does only interact with chemical system in a manner that is understood quantitatively
2.	Self - surveying chemical networks Identification of chemical primitives
3.	Toolbox for the implementation of customizable chemcial networks Clarification of role/vision of ChembioIT in economical context, we need compatibility with present research schemes.
4.	Realistic picture of relation of chemical networks to abstract problems in complexity theory

Scientific "breakthrough achievements" that could be produced in the process

1.	Artificial immune system
2.	Self - surveying chemical networks
3.	Toolbox for the implementation of customizable chemcial networks

Major necessary developments in other areas

Nr	Development	Area	Need
1.	support system for chemical networks	2b, 3ab, 0, 4cde, 6de, 8	Needed
2.	Chemical primitives which can used for evolved networks	1a, 1c, 3abe, 0, 4cde, 6de, 8	Needed

Additional comments on timeline of necessary achievements

I probably don't answer the question in the intended sense, partially because topic 7c is not easy to interface with metric radial diagram. I "dream" of evolved chemical networks; networks that can be (chemically) interfaced with other, e.g. industrial chemical processes. The idea is to create a sort of artificial immune systems (by no means equivalent to the biological IS). I think of networks which, qua their sensibility to external parameters, analyze processes in their environment.

8a. Information encoding and communication of information associated with construction – Future Profile

Peter Wills

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Design/evolve "transducers" through which coded information corresponding to elementary physical processes/operations can be communicated	Build operational transducers
2.	Demonstrate controlled transfer of (coded) information between electronic, chemical and mico-fluidic modes	Build a single system able to perform a simple nano-detailed construction task and deliver the product to the environment

Necessary achievements to make the 5- and 10-year goals possible

1.	5 yr: For information transfer between each pair of modes, construct means of information transfer and

	find modes of generality (coding)
2.	10 yr: [experts will have to define the necessary achievements]

Scientific "breakthrough achievements" that could be produced in the process

1.	Coded transfer of information between any two of the specified modes of controlled processing/operation (electronic, chemical, micro-fluidic)

Major necessary developments in other areas

Nr	Development	Area	Need

8b. Connecting natural computations (molecular, membrane, cellular etc) – Future Profile

Susan Stepney

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Outline theory	Full theory
2.	Diverse demonstrators designed using theory	Routinely used design and analysis approach

Necessary achievements to make the 5- and 10-year goals possible

1.	Development of theory
2.	Validation of theory in multiple combinations of multiple substrates

Scientific "breakthrough achievements" that could be produced in the process

Major necessary developments in other areas

Additional comments on timeline of necessary achievements

Within 5+ years: development of a good theory of multiple interconnected substrates, plus multiple demonstrations, involving multiple diverse substrates, of its use and applicability. This development will require the close working of computaitonal theorists and substrate-specific experimenters. 10+ years -- theory routinely in use in designing novel heterogeneous computational devices.

8c. Programmability and programming autonomous systems – Future Profile

Susan Stepney

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Design theory	Scalability to suitably macroscopic artefacts

Necessary achievements to make the 5- and 10-year goals possible

1.	Theory of "emergent programming" -- how to convert the desired properties of emergent artefacts into the required properties of micro-components
2.	Theory of "embodied programming" -- how to incorporate physical processes/properties of the substrate in the design and analysis

Scientific "breakthrough achievements" that could be produced in the process

1.	"Emergent engineering" would be a massive breakthrough

Major necessary developments in other areas

Nr	Development	Area	Need

8d. Architectures and optimization for combined computation and construction – Future Profile

John McCaskill

Goals for 5 and 10 years

Nr	5 Year Goals	10 Year Goals
1.	Theory applied to embedded construction problem	General theory of embedded information processing and construction

2.	Optimal encoding theory for construction in specific contexts : e.g. self-assembly	Construction encoding language for general purpose encoded construction
3.	Results on optimal architectures for programming construction	Design toolbox for construction systems
4.	Evaluation of tradeoff between autonomy and programming precision ion construction	Omega machine deployment as general purpose bootstrapping tool for construction systems
5.	Efficient implementations of a family of construction models for exploration	Results on optimal architectures for construction systems

Necessary achievements to make the 5- and 10-year goals possible

1.	Advances in stochastic computation and modelling : efficient multi-purpose platforms
2.	Nanoscale computation in embedded systems Full understanding of evolutionary stability in cooperative structures
3.	Proof of principle for technological open-ended evolution of architecture Robust implementations of real world instant ions as testable model systems
4.	Integration of conventional (e.g. 3D printing, lithographic) construction with autonomous processes

Scientific "breakthrough achievements" that could be produced in the process

1.	New adaptive computer architectures
2.	Nanoscale computation in embedded systems
3.	Proof of principle for technological open-ended evolution of architecture
4.	Better understanding of guiding principles in brain architecture

Major necessary developments in other areas

Nr	Development	Area	Need
1.	Intelligence foundation in adaptive neural processing	Cognitive science	Useful
2.	Embedded computation architecture	Robotics	Useful
3.	Evolving genetic encoding	Evolution and language	Useful
4.	Biological morphogenesis theory	Biological Development	Useful

Part IV: Case studies from recent EU projects

BACTOCOM – Bacterial Computing with Engineering Populations.

Martyn Amos, Manchester Metropolitan University.

BACTOCOM was a project funded by the FP7 FET Proactive Biochemistry-based Information Technology (CHEM-IT) programme (ICT-2009.8.3), project reference 248919. The roadmap areas of specific relevance to the project are 3a (Cellular Synthetic Biology using radical GMOs), 3b (Cellular computation), 3e (Information encoding in cellular systems, 4d (Hybrid systems involving cells), and 7a (Simulation of $C^{hem}B^{io}IT$ processes and subsystems).

Various *natural computing* paradigms exist that are inspired by biological processes (e.g., artificial neural networks, immune systems, genetic algorithms, ant colony algorithms). However, we can now go further than mere inspiration: instead of developing computing systems that are loosely *modelled* on natural phenomena, we can now directly *use* biological substrates and processes to encode, store and manipulate information.

Since the work of Adleman and others, the feasibility of using biological substrates for computing has been well established. More recent work on *synthetic biology* has shown that the living cell may now be considered as a programmable computational device, capable of sophisticated, human-controlled individual and collective behaviour. However, such biological engineering is inherently difficult, due to the nature of the biological substrate. Attempts at rational design are often thwarted by factors such as crosstalk, cell death, mutation, noise and other external conditions, and bio-engineers sometimes adopt what has been called a "design then mutate" approach.

The BACTOCOM (Bacterial Computing with Engineered Populations) project (2010-2013) was one attempt to address these issues. In this three-year work programme, we outlined a framework for engineering biological computation, by harnessing the inherent stochasticity of the underlying biological system.

We begin with a population of *E. coli* bacteria, which forms the core of our framework. We engineer a set of computational plasmids; circular strands of DNA representing "components", which may be combined together within the cell to form a simple logical circuit. These components may be exchanged between individual bacteria via the process of conjugation; the transfer of genetic material via direct cell-cell contact. By introducing large numbers of these computational plasmids, we initialise the system. Over time, the bacteria integrate the components into their genomes, thus "building" logical ciruits. The "output" of these circuits is measurable, and by defining "success" in terms of correlation with a desired signal profile, we allow successful components to flourish via a process of selection. Crucially, this selection is not performed manually (as before), but by an in-built comparator device, which increases a cell's output of "good" computational plasmids (which may then be taken up by neighbouring cells). By controlling the desired signal profile, we direct the evolution of the population towards novel, robust computational structures.

We have a cyclical workflow structure, where computational components (plasmids) are introduced to a population of bacteria, which then integrate them to build internal logical circuits. Sections of these circuits are then exchanged throughout the population, facilitating system evolution. In order to monitor system outputs and direct the

evolutionary process, the system may be externally observed through microscopy, and controlled via external signals (light, chemical, temperature, etc.) We inform the construction of the components and the choice of laboratory parameters through extensive observation and computational modelling of the system, in a continual cycle of refinement.

Our specific objectives were as follows:

1. Demonstrate the introduction of computational plasmids into bacteria.
2. Demonstrate external control and read-out of bacterial states.
3. Engineer the local exchange and expression of computational plasmids, facilitating evolutionary search.
4. Develop computational models to predict the dynamics and behaviour of individual engineered bacteria and whole microbial populations.
5. Apply our findings to the development of significant novel applications.

A full list of publications arising from the project is available at

http://www.bactocom.eu/docs.html

Software developed by the project is available at

http://www.bactocom.eu/software.html

The BACTOCOM project was led by **Prof. Martyn Amos**, Manchester Metropolitan University, UK, along with the following partners: Charite-Universitätsmedizin Berlin, Germany (Group of Systems Biology of Molecular Networks and Institut für Pathologie & Institut für Theoretische Biologie, **Dr Nils Blüthgen/Dr Ilka Axmann**); Universite d'Evry Val d'Essonne-Genopole®-CNRS, France (Synth-Bio Group, Institute of Systems and Synthetic Biology, **Prof. Alfonso Jaramillo**); Universidad Politécnica de Madrid, Spain (Artificial Intelligence Research Group, Faculty of Informatics, **Prof. Alfonso Rodríguez-Patón**); Universidad de Cantabria, Spain (Intergenomics Group, Institute of Biomedicine and Biotechnology, **Prof. Fernando de la Cruz**); Technischen Universität München, Germany (Physics of Biomolecular Systems and Bionanotechnology, **Prof. Dr. Friedrich C. Simmel**).

Project website: http://www.bactocom.eu

MATCHIT - MATrix for CHemical IT

Steen Rasmussen, University of Southern Denmark

The institutional teams were lead by the work package leaders: Günter. v. Kiedrowski (Bochum University), Martin Hanczyc (University of Southern Denmark), Pierre-Alain Monnard (University of Southern Denmark), Benny Gill (Weizmann Institute), John McCaskill (Bochum University), Doron Lancet (Weizmann Institute) and Harold Fellermann (University of Southern Denmark), while the coordinator was Steen Rasmussen (University of Southern Denmark). The project website can be found at: http://www.fp7-matchit.eu

The MATCHIT (MATrix for CHemical IT) project has developed and implemented a programmable MEMS and biochemistry based hybrid system that seamlessly integrates information processing and material production. MATCHIT was funded by the FP7 FET Proactive Biochemistry-based Information Technology (CHEM-IT) programme (ICT-2009.8.3).

The roadmap areas of specific relevance to the project are 1a (Systems Chemistry, Supramolecular and Synthetic Chemistry, 1b (DNA computing and DNA machines), 1d (Artificial chemistries and formalisms for molecular construction and IT), 2b (Multiphase Chemistry involving self-assembled mesoscale structures), 2c (Surface and interfacial chemical systems: including multilayer fabrication), 2d (Iterative chemical processing systems with integrated separation and cleanup), 2e (Computational and theoretical bounds for self-organization and –assembly), 4a (Microfluidics, LOC and other hybrid chemical/physical technologies), 4b (Fabricated micro- and nanoparticles interacting with ChemBioIT systems), 4c (Electro-kinetic and -chemical systems), 4d (Autonomous chemical sensor and actuator networks & intelligent microparticles), 4f (Information processing principles in hybrid systems), 5e (Generative and developmental systems: for integration of production and construction), 5f (From reconfigurable to self-constructing and self-repairing systems), 6a (Chemical robotics, Autonomous Experimentation and Swarm Chemistry), 6c (Multiscale and hybrid microrobotic systems interacting with chemical construction), 7a (Simulation of ChemBioIT processes and subsystem) and 7b (Simulation integrated design and programming for ChemBioIT).

The inspiration for this project comes from biology. A biological subcellular matrix functions through an intricately coordinated material transportation, information processing and material production system. We seek to mimic these fundamental properties utilizing a hybrid biochemical and information technological system. We introduce an integrated programmable information- and production chemistry by having DNA addressable chemical containers (chemtainers) interfacing traditional electronic computers via microelectromechanical systems (MEMS) with regulatory feedback loops (Amos et al., 2011). DNA tags anchored in the chemtainers make them addressable with respect to each other through complementary DNA interaction as well as addressable within a MEMS microfluidics matrix through DNA tags anchored in the micro fluidics channels.

The different types of chemtainers employed are: DNA nano-cages, vesicles (lipid and fatty acid), oil-in-water emulsion droplets and water droplets in ionic liquids. The micro fluidic MEMS matrix with immobilized single stranded DNA represents the interface between the chemtainers and the electronic computers by controlling the attachment of DNA-coated chemtainers.

The abovementioned chemtainers vary significantly in terms of scale and functionality. At the nanoscale, DNA single strands are both the building blocks of the containers and the instance to functionalize them. These DNA cages can open and close controlled by external signals and when closing encapsulate macromolecules as cargo. For the microscale containers, DNA is not used as building material but to address the surface of the chemtainers. These microscopic chemtainers act as either hydrophilic or hydrophobic reaction vessels, which can themselves determine their next processing steps. DNA labeling and addressing of the larger water droplets is also possible (Wagler et al., 2013). DNA-directed fusion of chemtainers will replace fusion events already shown to be

triggered by electrostatic interactions between artificial vesicles (Caschera et al., 2011). Fission and fusion of chemtainers are formally Membrane computing operations (Paun, 1998).

A key point for all these technologies is the use of DNA addresses to coordinate the specific assembly of chemtainers in space and time. As an example, we have developed a modular DNA addressing system for supramolecular chemtainers. DNA single strands are incorporated into the surface both of artificial vesicles (Hadorn and Eggenberger Hotz, 2010) and of oil-in-water emulsion droplets (Hadorn et al., 2012). In this way we can program the assembly of chemtainers using local base paring rules. Both the sequence and length of the DNA addresses can be modified to ensure both specificity and robust hybridization against denaturing thermal effects (Chan et al., 2007). The same methodology directing the assembly of chemtainers is applied to immobilize them to a solid support. Conditions that disfavor the DNA base pairing (i.e. increase of temperature, decrease in salt concentration, addition of competitive DNA) is used to reverse the assembly process of chemtainers. In addition, we have demonstrated that the DNA addresses can be detached from the surface and replaced by new addresses. This allows for altered programmed assembly and a recyclability of our system. Dissipative Particle Dynamics (DPD) simulations are used e.g. to simulate oil-droplets tagged with DNA molecules, using a novel dynamic bonding DNA model (Svaneborg, 2012).

Using DNA addresses a common language of the diverse types of chemtainers combined with chemical reactions controlled by programmable fusion of chemtainers opens up for a new kind of computing. This computing allows parallel chemical and internal material production programming in a multilevel architecture. Through autonomous DNA address modification (utilizing the usual DNA computing operation) and resolution at the container-container, container-surface, and container-molecule levels, the architecture provides a concrete embedded application for integrated information processing, computing and material production. Self-organizing container addressing can allow micro- and nanoscale processing of any collection of chemicals that can be packaged in the containers. We are developing a calculus that expands, but closely follows the line of Brane Calculi (Cardelli, 2004), for expressing nested addressable membrane systems. The extension of the Brane Calculus is necessary to accommodate the electronic feedback between the chemtainers and the monitoring-actuating MEMS matrix as well as the spatial addressing.

Making living materials from nonliving materials and the implementation of living processes in other media e.g. hybrids between biochemistry and ICT both address and pose fundamental epistemological questions. However, the potential usefulness of novel engineered living processes in mixed ChemBio-ICT media stem from the tantalizing properties of life itself. Living systems are characterized by energy efficiency, sustainability, robustness, autonomy, learning, local intelligence, self-repair, adaptation, and most importantly evolution through self-replication (Bedau et al., 2010 & Bedau et al., 2010a). Unfortunately, these are desirable properties current technology lacks, which over the last centuries have created an increasing variety of problems for our societies. MATCHIT seeks to address one step in this direction.

Some of the other early and ongoing activities within the emerging Chembio-ICT area can be followed e.g. at the European Commission sponsored project web pages for PACE, ECCell, BACTOCOM, COBRA (Chembio-ICT) and in Amos et al., 2011. Common to these projects is an investigation of how to create and utilize living processes in a variety of hybrid bio-chemical, computational, and robotic systems. As our technology becomes more life-like, it also brings us a variety of new safety, environmental, and ethical challenges. These issues are addressed by one of the research networks at the Initiative for Science, Society and Policy (ISSP) and the general area of living technology is address at the European Center for Living Technology (ECLT).

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MICREAgents - Microscopic Chemically Reactive Electronic Agents

Self-assembling smart microscopic reagents as pourable electronics for chemical computation.

John S. McCaskill, Ruhr Universität Bochum

MICREAgents is a project that combines several of the subtopic threads towards the overall roadmap goal. The project deals with or employs results from aspects of many roadmap subtopics that do not involve biological cells: 1a-d, 2a-e, 4a,c,e,f 5a-f, 6a-e, 7a-c and 8a-c. Especially the subtopics "DNA computing and machines" (1b), "Autonomous chemical sensor and actuator networks" (5d) and "Chemical robotics" (6a) are central themes of the project.

The goal of the project is to give electronics and chemistry an equal autonomous say in programming complex chemical constructions, processes and analyses at the nano and microscales: the same scale where information processing in living systems occurs – where "to construct is to compute". To do this MICREAgents (MIcroscopic Chemically Reactive Electronic Agents) will develop novel electronically active microreactor components, called ***lablets***, that self-assemble at a scale less than 100 µm, approaching that of living cells. The project will integrate the necessary components to ensure autonomous action of millions of these "very smart chemicals", including electronic logic, supercapacitors for power, pairwise coupling for communication, programmable chemical sensors and electronic actuation of chemical processing. Key examples of MICREAgent actuation are to reversibly switch their association, load or dose chemicals, modify surfaces, initiate reactions and control locomotion in complex chemical environments. MICREAgents *lablets* can join forces to communicate both chemicals and electronic information in order to solve complex tasks, acting as smart collective agents of chemical change. Like cells, they are essentially genetically encoded, but with chemical and electronic memories, translating electronic signals into constructive chemical processing and recording the results of this processing. They also reversibly employ DNA molecules as chemical information, for example to control surface-surface binding of *lablets*, or to program chemical sensors, rather than to synthesize proteins as in cells.

The project is building autonomous self-assembling electronic microreagents that are only 100µm in diameter. They will exchange chemical and electronic information to jointly and autonomously direct complex chemical reactions and analyses in the solutions they are poured into. The project heralds a major step beyond macroscopic Lab-on-a-Chip devices, towards the integration of chemistry and information technology in unconventional computation. John von Neumann envisioned information devices that can construct more complex machines than themselves, in his theory of self-reproducing automata[10], but he did not arrive at a robust architecture for this. The MICREAgents project represents the next major research program towards these overarching initiatives, one that could change the level of fine-grained algorithmic control in chemical construction, bringing the important social goal of sustainable personal fabrication one step closer.

In order to create this programmable microscale electronic chemistry, MICREAgents contain electronic circuits on 3D microchips (called **lablets**, diameter ≤ 100 µm) that self-assemble in pairs or like dominos to enclose transient reaction compartments, using

[10] J. von Neumann in "Self-reproducing automata" edited and completed by A.W. Burks Univ. Illinois Press, Urbana and London (1966).

the electronics to control chemical access, surface coatings and reactions via physical and chemical processes such as electroosmosis, electrowetting and electrochemistry. Chemicals will be able to be selectively concentrated, processed and released into the surrounding solution, under local electronic control, in a similar way to which the genetic information in cells controls local chemical processes. The reversible pairwise association in solution of electronic surfaces in the nm range are also used to avoid the prohibitive energetic costs of broadcast communication, allowing lablets to transfer information (including heritable information) from one to another. The *lablet* devices integrate transistors, supercapacitors, energy transducers, sensors and actuators, involving electronically constructed nanofilms, and will be essentially genetically encoded, translating electronic signals into constructive chemical processing and recording the results of this processing. Instead of making chemical reactors to contain chemicals, the smart MICREAgents will be poured into chemical mixtures, to organize the chemistry from within. Ultimately, such microreactors, like cells in the bloodstream, will open up the possibility of controlling complex chemistry from the inside out.

MICREAgents will provide an unconventional form of computation that microscopically links reaction processing with computation in autonomous mobile smart reactors. This corresponds to a radical integration of autonomous chemical experimentation, a very recent research area, and represents a novel form of computation intertwined with construction. The self-assembling smart micro reactors can be programmed for molecular amplification and other chemical processing pathways, that start from complex mixtures, concentrate and purify chemicals, perform reactions in programmed cascades, sense completion, and transport and release products to defined locations. The project defines a continuous achievable path towards this ambitious goal, making use of a novel pairwise local communication strategy to overcome the limitations of current smart dust and autonomous sensor network communication. It will provide a technical platform spawning research in new computing paradigms that integrate multilevel construction with electronic ICT.

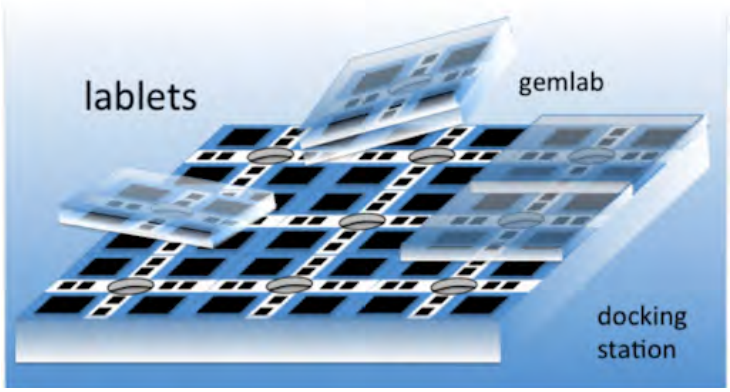

Fig. IV.1 MICREagents lablets and dock

The MICREAgents project involves chemical reactive electronic agents (lablets) that can pair to form gemlabs or associate with a smart docking interface (docking station) to be programmed or powered up or to deliver information or chemical payloads.

The MICREagents project addresses key issues of bridging the molecular and microscopic scales and the worlds of electronics and chemistry in hybrid autonomous systems. Although the silicon circuitry is not fabricated in an ongoing process, the MICREagents particles are built to approach universally customizable electronic functionality with run-time programming and reprogramming able to specify a very diverse range of functional properties. Although the geometry and initial coatings of the lablets are also mass-produced off-line, the operation of the microparticles is capable of modifying and programming the surface coating modifications that determine functionality. From this perspective, one can regard the mass-production as producing a shell or chassis for the lablets that is changed and specialized during operation. Raw lablets can then be regarded as a resource that does not contain significant information about the environmental or

synthetic functions the run-time customized lablets are modified to fulfil. This approach ties in with the perspective of employing reconfigurable systems to economize on fabrication effort. Future lablets may be able to use organic or graphene based electronics that can be co-synthesized on site and during operation. The first generations of MICREAgents lablets will indeed support the active making and breaking of communication connections between lablets.

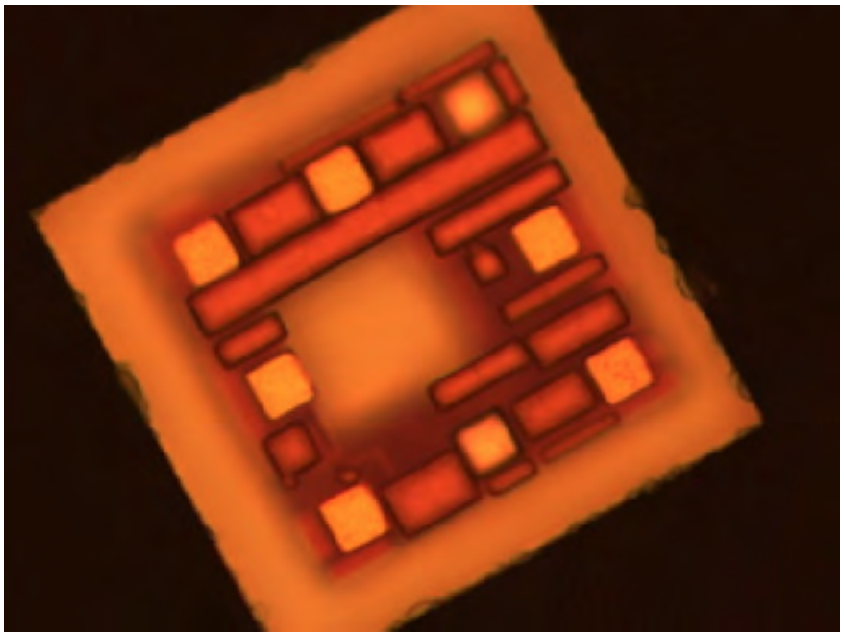

Fig. IV.2 First CMOS MICREAgent lablets with eight gold-coated electrodes for actuation and sensing (size ca. 100µm). Conventional Europractice CMOS in 180nm resolution processing was implemented with test circuitry for autonomous charging, actuation, sensing and communication. The lablets were diced from thinned (40 µm) 5x5 mm chips.

The other participants in MICREAgents are teams led by Leroy Cronin (Univ. of Glasgow), Andreas Herrmann (University of Groningen), Itamar Willner (Hebrew University of Jerusalem), Steen Rasmussen (Southern Denmark University), Frantisek Stepanek (Institute of Chemical Technology, Prague), Norman Packard (European Centre for Living Technology), and Peter Wills (University of Auckland). Together with the teams at the Ruhr Universität Bochum, led by Günter von Kiedrowski, Jürgen Oehm and John McCaskill, they are all pioneers in the multidisciplinary areas required to achieve the project goals, with a common grounding in IT. The project website can be found at: http://www.MICREAgents.eu An introduction to the project was published (2012) in the J. Unconventional Computing.[11]

[11] J.S. McCaskill et.al. "Microscale Chemically Reactive Electronic Agents" (2012) Intnl. J. Unconventional Computing **8**(4) 289-299.

Part V: Impact, Sustainability, Society and Conclusions

The potential payoff from this field will be information processing and production systems that are evolvable, self-replicating, self-repairing and responsive to their environment (as well as having local intelligence), whilst also being capable of interfacing with existing silicon based ICT systems. Such capacity will open up a radically new form of technology that couples information processing with physical control and production at both the micro- and macro-levels. Such integration is currently only seen in natural, living systems, and this achievement may well trigger a seismic shift in ICT. The prevalent vision of computation as something that deals primarily with *information* will be transformed into a view in which it is also intimately linked to hardware changes that influence a system's *material structure*, and therefore its future processing potential. A breakthrough in this area would allow ICT specialists programmable algorithmic entry to the world of nanoscale chemical processes, as well as the self-organized power of cellular assemblies. In the future, we will require not top-down, directed assembly of structures, but the utilization of interactions between components to *self-assemble* functional information processing materials of immense complexity. The impact will be a major increase in the complexity and programmability of engineered nano and micro-systems in all areas of application.

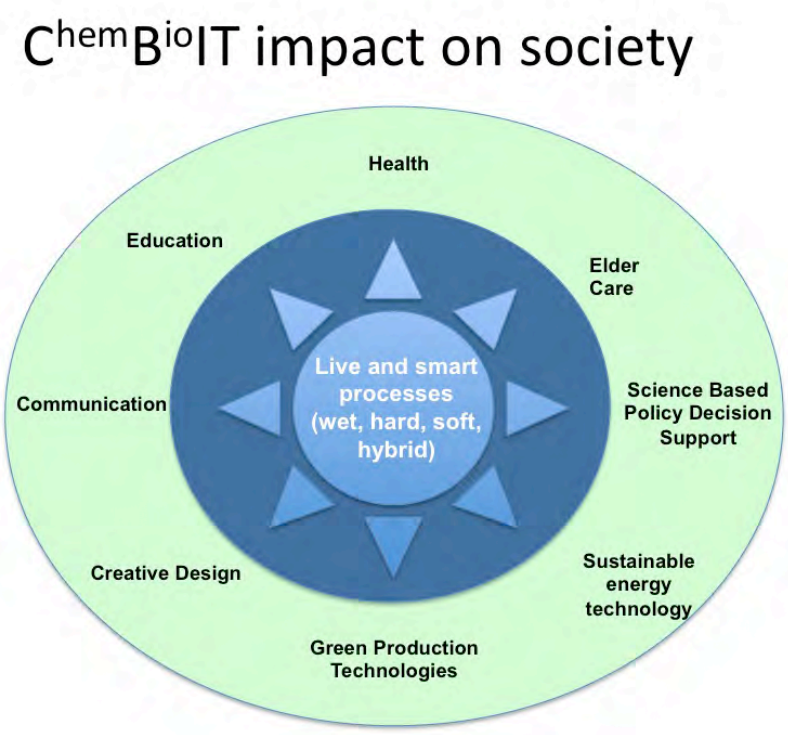

Fig. V.1 Impacts of ChemBioIT on society.

The impact on society and sustainability has been raised already in Topic 10 in Part II. In this section, to preserve a broad perspective from experts in this roadmap document, we asked panelists to comment on the contribution of the subtopics to sustainability and socioethical responsibility. Responses varied over a wide range of positions, but it is clear that a common concern to address issues of environmental and social sustainability is pronounced amongst the ChemBioIT community. Many experts are strongly motivated by the increasing needs in society to bridge the gap between high technology development and microscopic, individual and local fabrication and deployment.

Some of the major impact areas of ChemBioIT on society are depicted in Fig. V.1. If computers have now either strongly influenced or transformed almost every facet of our lives, the impact of ubiquitous programmed embedded construction addressed by C^{hem}B^{io}IT in this roadmap will be significantly greater inside this century. It is important to the panel of experts to emphasize the magnitude of the impact on society that this will involve, while not at the same time overstating the case as to the timescale over which the problems in the technology will be mastered. In 2014, we expect that this technology will be visible to the global investment community as an emerging transformative force on society, and already beginning to influence the makeup of the industrial sector. We do not yet expect that every individual will be directly confronted with the benefits of the technology: ten years later this will be the case, while at the same time C^{hem}B^{io}IT technology will be very much in its infancy.

The authors are aware of the problems associated with technology push versus societal pull, and the need for early engagement with the public sector. We hope that this document will encourage the wider community to engage with this process, by making the scope of the potential and its current emerging proximity and integration clear. Prior to this roadmap, explicit engagement has been limited to a number of prominent subfields, such as in the areas of Artificial Cells, Synthetic Biology, Nanotechnology and Living Technology. Active sponsoring of institutions and consortia engaging with the public are required: example sof our own activity here include the European Center for Living Technology (ECLT) in Venice and the Institute of Science and Social Policy (ISSP) in Denmark.

Internationally, the global community is already quite strongly engaged with the issues raised in this roadmap, albeit perhaps nowhere as coherently as brought together in this document. Europe, with its special early competencies – in systems chemistry, DNA and spatial self-organization (ever since the Prigogine school and Eigen), in synthetic biology (at cellular and tissue scales) and in evolution research, in micro and nanosystems fabrication and in robotics, in simulation and computation, in autonomous energy power and sustainability research – are well poised to play a leading integrative role in this development.

In future activity, following further rounds of research funding, it may be possible to approach the technological focus associated with the Silicon Roadmap, but this is not possible or advisable at this stage. The field is in a state of a creative crucible of ideas, and progress is distributed and rapid. Our recommendations for the short term are the identification in 5 years time of significant progress towards the roadmap goal and the strong inclusion of industrial players and societal layers in the launch of an ongoing incrementally updated roadmap to accompany the field at that stage.

1a. Systems Chemistry, Supramolecular and Synthetic Chemistry – Future Profile

Günter von Kiedrowski

Impact on other areas of ChemBioIT, science and society

I can only summarize my general impression on the technology which might develop from CBIT lines of research. It seems to have two sides of a coin. On one side nanoscale to microscale robotics could help to improve the quality and longevity of human life. If one thinks about architectures that cure cancer, dissolve plaques in blood vessels, Alzheimer in the brain, etc., only a few will object that such approaches are useless. The long term vision however might result in the step by step conversion of a human being into a transhuman cyborg like entity seeking to immortalize its existence. Will such a being experience the same level of human connectedness, empathy, and freedom of decision? Or will it be a slave engine whose existence is limited to work for the sake of its corporate owner? This thought is especially important if the implants or injects - targeting and replacing the function of a human organ including the brain - are equipped to send and receive messages to the outside world. It would mean the transition from the internet of things to the internet of living beings and it could not exclude the option of total control of human life. A singularity in which the internet of beings wakes up as a conscious global entity starting to transform human existence into a nightmare. This is why any development in this direction – especially when linked to FET projects such as the Human Brain Project – should include ethical considerations and ethical laws for technology applications from the very beginning.

On the other side it may come out that developments in these lines will be challenged and stimulated by fundamentally novel insights that could seriously affect the way we think in science. My impression here is that we might face a 2nd Kopernican revolution during our lifetime. The first meant the transition from the geocentric to the heliocentric view. The second might address the transition from the anthropocentric to a post-anthropocentric view. In the Darwinian narrative homo sapiens sapiens is the crown of evolution of life, the latter having originated in the systems chemistry of the warm little pond 3 to 4 billions of years ago. What, if the picture is wrong or at least incomplete? While we have learned to let emerge autocatalysis, self-replication, and (to some degree) Darwinian evolution, we often neglect the existence of the chemist who put things together so that it happens indeed. We forget the enormous labour involved. Evolution in the lab so far only works as "directed evolution" where the director is the selection constraint defined by the experimenter. Evolution in silico is not different: Any metric which defines fitness is not based on an undefined condition. Similar considerations must have brought Francis Crick & Leslie Orgel to the idea of directed panspermia, which meens seeding the earliest forms of life by intelligent intervention.

The Darwinian narrative thus might be incomplete – it might be a reduction to a physical materialism which of course is helpful to understand evolution. A number of us discussed this issues on a workshop at CERN in Feb. 2013. There are several other incompletions in science relating to reductionistic materialism. The three that are directly relevant to systems chemistry at interfaces within CBIT are the following. (1) Between 1895-1910 analytical chemist Landoldt tested whole series of autocatalytic chemical reactions leading to the metallization of glass vials. He was interested in the question on the conservation of mass during chemical reactions and he found systematic deviations in the ppm range which were reproducible, well documented, but disappeared from our common knowledge. In 1910 Max Planck decided to discontinue research in the direction of an electromagnetic "ether" celebrating the success of Einstein's special relativity which finally fixed the constancy of the speed of light in vacuum as a natural constant. Landoldt had died a few month before – as a consequence the law of mass conservation during chemical reactions was fixed as a paradigm. Any research in "etheric matter or energy" became "esoteric" from then on. Still research continued. Hauschka reported mass changes between germination and death of cress sprouts in air-sealed vials and found that these changes are time dependant reflecting the moon cycle. Volkamer reproduced both Landolts and Hauschka's experiments with digital scales (comparators) directly connected to a computer allowing to monitor the kinetics of mass changes. His results further show that these mass changes are most pronounced during solar eclipses. (2) The structure of water at interfaces is believed to have a different order compared to bulk water. Textbooks refer to such ordered water as a spline of hydration and attribute a characteristic length scale of a few nanometers. This is in contrast with experiments by Pollack and by now two dozens others labs who claim water ordering at hydrophilic interfaces in the range of 50 µm (typical). The build up of such exclusion zones occurs in the order of seconds and is driven by infrared radiation, as electrical charge separation between EZ and bulk water requires energy. The charge separation is attributed to negative fluid-crystalline EZ (hexagonally ordered layers of composition $H_3O_2^-$) and adjacent mobile protons in the positive bulk. The technological implications of this finding are enormous – an engineering approach has not even started yet. (3) In Feb. 2012 a Korean team reported a case of a nanoscale "overunity LED" , viz. a LED that gives more photonic energy than electrical energy put in. To my best knowledge, the results have not been falsified yet. The authors explain their finding as a phonon-photon coupling, viz. the extra energy needed must come from lattice vibration which then, however, is in contrast with the second law of thermodynamics according to which physical work is not extractable from heat by cooling a reservoir under adiabatic control.

My suspicion is that the three phenomena are manifestations of a type of physics which interventors seem to have perfect

control while we have to learn it. They certainly don't use kerosene in their vehicles. Their propulsion is not based on combustion. They seem to have control over the macroscopic quantum state, allowing to decohere and to cohere (viz. pop in and out of material existence) at will. We have to learn these "spooky" technologies. A focus on chemical quantum effects, coherence, resonance, interference, coupling, entanglement, tunneling is therefore a reasonable extension.

Contribution to sustainability/ socioethical responsibility

Disposable technology for analysis of chemical end environmental data make an important contribution to sustainability.

1b. DNA computing and DNA machines – Future Profile

Friedrich Simmel

Impact on other areas of ChemBioIT, science and society

As stated in the more detailed description above, has strong relations to and will have impact on many of the points listed in (1)-(6). Nucleic acids systems (DSD circuits, genelets, etc.) can be seen as an example of systems chemistry (1a), the developments in this field will certainly inspire alternative information chemistries (1c) and may also require translation into this in some applications. Formalization already takes (took) place in the field (1d). Applications in self-assembly and self-organization are already there or are actively pursued (2a), and integration into higher order assemblies is also currently done (2b). Also implementation of, e.g., RNA circuits within cells (3a) is conceivable, and artificial neural network computation (3c) can, in principle, be done. In relation to point (0), the field will probably utilize microfluidics and microfabrication in general, and potentially there is some feedback to this point. Interfacing with biosensing/electrochemistry is something that some researchers in the subarea work on. Several people in the area in fact have a background in in vitro evolution, and evolutionary approaches, and related fields such as "DNA display" implement combinatorial ideas. So it can be expected there will be some impact on at least (4a-c). People are already using the term (DNA) nanorobots for some of the structures in the field. It appears that a combination of the structural, mechanical, and information-processing capabilities of DNA systems would automatically result in something like a molecular robotic system (6c).

Contribution to sustainability/ socioethical responsibility

In the best case, DNA/RNA computing/machines are biocompatible, of course. I am not sure about the environmental cost of artificial DNA molecules (nucleotides come from salmon sperm - so how much fish do we have to kill for world-wide production?). Also transfer to other materials always requires additional chemistry (which requires energy and often hydrocarbons as starting materials). It appears to me that an implementation in cells might be favorable. In principle, a sustainable, biomimetic technology should be possible, though …

1c. Inorganic biology and genetic alternatives to nucleic acids – Future Profile

Steen Rasmussen
Lee Cronin

Impact on other areas of ChemBioIT, science and society

New tool box for theory / modelling; Embodiment of evolution in inorganic chemistry / artificial chemistry; Interplay of agent based systems.

Contribution to sustainability/ socioethical responsibility

One contribution of inorganic biology is to create a greater distance between the organic chemistry of life and artificial living systems based on very different chemistry : this may enable an application in areas where there would otherwise be a danger of biological proliferation and escape into the environment. At the same thime, this distance also provides unique experimental opportunities and a separate perspective on what is essential in living systems.

1d. Artificial chemistries and formalisms for molecular construction and IT – Future Profile

Peter Stadler
Peter Dittrich

Impact on other areas of ChemBioIT, science and society

Artificial/rule based chemistry models will be a key ingredient in more elaborate self-organizing systems/ In the long run, they will also influence work on synthetic biology - in fact very recent advances in rational design of e.g. riboswitches and other nucleic-acid based gadgets show that rule-based design based on effective theories is feasible -- albeit only in particular systems -- already with current technologies.

Achievements here will serve as "plugins" in cellular computing systems and hybrid bio-electronic systems. Theories and tools will be also valuable in synthetic biology, systems biology, prebiotic chemistry, systems chemistry, chemoinformatics, and protocell research.

Contribution to sustainability/ socioethical responsibility

2a. Reaction Diffusion Computing and Chemical Pattern Formation – Future Profile

Jerzy Gorecki
John McCaskill

Impact on other areas of ChemBioIT, science and society

The results obtained within reaction diffusion computing can contribute to the other core technologies on the ChemBioIT shortlist. Of course the closest links are with the tasks of Spatial Self-Organization & Self-Assembly. For example computational and theoretical bounds for self-organization and self-assembly can be verified with experiments on reaction-diffusion medium. Also the other theoretical concepts like those grouped under "Genetic information encoding principles for ongoing construction", "From reconfigurable to self-constructing and self-repairing systems" or "Information encoding in cellular systems" can be verified with reaction-diffusion media. Moreover, reaction diffusion computers can be used in hybrid technologies.

Developments in RD systems can be used as a component process in other areas: in DNA molecular systems (1), both intra- and extra-cellular in cellular systems (3), in conjunction with microfluidic and autonomous micro particle systems (0), in connection with evolutionary optimisation (5) and with robotic systems, either as hybrid systems or as an intercommunication mechanism for robots. Developments may also contribute to our understanding of the origin of life.

Contribution to sustainability/ socioethical responsibility

Reaction-diffusion systems may be used not only to explore sustainable morphogenesis per se, but also to explore resource scavenging and sustainability in chemically reacting systems. In connection with controlled experimentation in specific geometries, this area contributes to an understanding of ecological processes and the broader societal consequences of opening laboratory processing to the wider world.

2b. Multiphase chemistry involving self-assembled macroscopic structures – Future Profile

Steen Rasmussen
John McCaskill

Impact on other areas of ChemBioIT, science and society

Multiphase chemistry is seen as essential to multiscale $C^{hem}B^{io}IT$, as it allows the structuring of locally communicating regions in space via barriers (such as lipid membranes). Combinations with DNA computing in the information control of gel phases (cf Area 1) are already being made. Its mastery will allow extensions to cellular systems (Area 3). Work on evolving multiphase chemical systems is gathering way (Area 4), both in pre-cellular and cellular contexts, and multiphase systems are being explored fruitfully in the context of hybrid systems (Area 5 e.g. microfluidics) and robotics (Area 6). Dynamic multiphase systems challenge computation limits in physical multi-scale simulation (Area 7) and will play an increasing role in future models of embedded computation (Area 8).

Contribution to sustainability/ socioethical responsibility

Full control of multiphase chemistry will allow more intelligent recycling and sustainable solutions for problems currently solved by hard plastic and metallic systems with diverse chemical composition. Cells are completely recyclable because of their ability to be decomposed into non-toxic multiphase building materials

2c. Surface and interfacial chemical systems: including multilayer fab – Future Profile

Nicolas Plumeré
Itamar Willner

Impact on other areas of ChemBioIT, science and society

Energy: Biosinspired catalytic systems based on self assembly of artificial active sites, artificial electron transfer chain, artificial substrate/product channel and artificial protecting shells in structured 3D films. Evolvable design toward self assembled 3D interface with catalytic activity and selectivity comparable to enzyme for H2 evolution/oxidation, CO2 reduction, light harvesting. Diagnostics: Continuous sensing based on 3D functional layers providing energy, sensor renewal and information transmission in non invasive devices (e.g contact lense sensors) for accurate (self)-diagnostic. Synthesis: catalytic layer with in-built functionalities for external control of activation, reaction, separation.. Information: High density 4D layers with individual dots bearing multiple or continuous information content. special contribution of the approach to sustainability and/or socioethical responsibility.

Contribution to sustainability/ socioethical responsibility

2d. Iterative chemical processing systems with integrated separation and cleanup – Future Profile

Uwe Tangen
Steen Rasmussen

Impact on other areas of ChemBioIT, science and society

Without the development of stable, push-button iterative processing, which always requires amplification and cleaning, all the other subareas will remain in the classical chemical context. Sustained iteration, even better replication, is a prerequisite for studying evolution and sustained chem-bio computation to be possible. At a later stage, when entering the autonomy domain, this iteration and cleanup must be integrated into the individual entities. It is then situated and parallel. Control then must be done locally.

Contribution to sustainability/ socioethical responsibility

The integrated iteration of amplification and cleanup is at the heart of all sustainability or ethical considerations because it is the watershed of whether classical chemistry or biochemistry is being applied or the entire new area of ChemBioIT is entered. As long as this iteration is controlled by fixed external machinery and not autonomous sustainability and ethical considerations can be neglected. In the moment these integrated iterative amplification and cleanup systems become autonomous and are deployed serious controlling, rules and oversight has to be set into existence because these entities then can evolve and interact with the environment.

3a. Cellular Synthetic Biology using radical GMOs – Future Profile

Angel Goñi-Moreno
Martyn Amos

Impact on other areas of ChemBioIT, science and society

The hard inter-disciplinary work needed will stablish protocols and methodologies useful for any science. Point 3a strongly affects point 3b as they are basically one. Point 3a strongly affects point 3e and vice versa. Point 3a is kind of a basic point before area 0 which sounds like an application of 3a developments. Point 3a may "join forces" with other basic-science areas in order to be used in application based sciences as medicine or ecology.
Developments in Synthetic Biology will help to encourage an emerging group of interdisciplinary researchers with a broad set of capabilities and expertise. Need for automation->scale up will drive developments in robotics, microfluidics and high throughput screening. Requirement for large-scale DNA synthesis/assembly capabilities will benefit many other areas of biology.

Contribution to sustainability/ socioethical responsibility

As long as this science stays in the lab, the ethical concerns will not be touched. When the application era comes, then the ethical issues would be on the first line.
Synthetic biology can contribute to sustainability through addressing issues such as water/food security (eg. desalination, resistant crops). Ethical considerations form a significant branch of synthetic biology; this is especially salient given previous experience with Genetic Modification. Risk management, safety and bio-security are high-profile areas of interest, and there is growing involvement in synthetic biology from so-called "DIY biologists" (ie. interested amateurs).

3b. Cellular computation and Genetic Regulatory Networks involving cell communication – Future Profile

Martyn Amos

Impact on other areas of ChemBioIT, science and society

The ability to engineer and control mixed populations of microbes will shed new light on the fundamental underlying processes, as well as offering a large number of possible "test-bed" systems for biological investigations.

3c. Neural computation in artificial networks – Future Profile

Chrisantha Fernando
Phil Husbands

Impact on other areas of ChemBioIT, science and society

Developments in machine learning and neural computation can have application for structure prediction and discovery, prediction, and compression of data. Progress in this area will benefit core technologies 1-6 as there are clear overlaps.

Contribution to sustainability/ socioethical responsibility
Neural networks can process data related to sustainability and socieoethical responsibility, allowing insights to be gained. By exploiting high degrees of reconfigurability, the approach has the potential for great efficiency in use of resources, contributing to sustainability.

3d. Artificial tissue engineering using structured chemical/material scaffolds; Additive manufacturing, 3D functional printing, steganography and related fab – Future Profile

Andreas Schober

Impact on other areas of ChemBioIT, science and society
The ability to engineer and to construct arbitrarily designed tissue like structures /scaffolds in reasonable time (definitely under the constraint of vascularization and self evolvability and self adaptation of multicellular 3D cultures) may help to design new experimental set ups for answering question according to self organization and self assembly, cellular computation, evolutionary processing. The construction of hybrid Mems should allow to design mixed systems made of cellular interacting populations like neurons with embedded artificially, technical devices like man made synapse structures as one example.

3e. Information encoding in cellular systems – Future Profile

Luca Cardelli

Impact on other areas of ChemBioIT, science and society
The greatest future changes in our society, both in technology and healthcare, will come from the convergence of Biology, Nanotechnology, and Computing. The latter should not be confused with software production, no more than Biology is glassware production. Computing is the theory and practice of information processing, in this case applied to the molecular level. There is no question that great societal transformations will result from nano-engineered materials and molecularly-programmed diagnosis and cure. But an essential part of this convergence, along with the understanding of metabolic and nano-physical processes, is a fundamental understanding of computation at the molecular, cellular, level.

Contribution to sustainability/ socioethical responsibility
Application of these theories to synthetic biology will impact sustainable material production. Moreover, a theoretical understanding of computational processes is required (as is well practiced in software engineering) to establish methodologies that guarantee safe and ethical use of procedures and resources.

4a. Genetic information encoding principles for ongoing construction – Future Profile

Peter Wills

Impact on other areas of ChemBioIT, science and society
This subarea is at the heart of ChemBioIT - it requires the development of a deep understanding of how artificial systems that truly function like biological systems, can be constructed. Achievement of these subarea goals will only be possible if there are concomitant technological breakthroughs. However there are close synergies, in terms of our understanding of how these systems will operate and evolve, with subareas 2c, 3e, 4f, 5f, 8a & 8d.

Contribution to sustainability/ socioethical responsibility
In terms of sustainability and socioethical responsibility, this subarea comes in at a fundamental philosophical level, raising questions about the place of both humans and their artifacts as parts of nature and modifiers of nature. A general purpose type II von Neumann machine would have an autonomy, but also be disposably directed, suitable for almost any human purpose, either good, morally neutral, or evil. History shows that the purposes for which a technological capability is developed often dominate, through economic force, its deployment. Therefore ChemBioIT must develop in a truly reflective, critical and responsive fashion, led by emerging insights in this subarea.

4b. In vitro molecular evolution, combinatorial chemistry – Future Profile

John McCaskill

Impact on other areas of ChemBioIT, science and society
In vitro evolution is already being applied to molecular systems (1), and has been proposed to evolve components such as DNA, RNA and proteins for deployment in cells (3). In the latter context it often competes with cellular directed evolution which benefits from high fidelity copy processes, but suffers from difficulties in ensuring selection pressures are maintained and smaller population numbers. An intermediate level is phage display molecular evolution. Spatial and multiphase evolution processes allow a direct combination with (2), but are still in their infancy, despite rapid progress in droplet based evolutionary protocols. These have already allowed first example of cooperative evolution through compartmentation to be demonstrated experimentally (Griffiths). Combinations of in vitro evolution and microfluidics (4) have been pioneered by

McCaskill, by Joyce and others. Projects are now underway to examine the combination of in vitro evolution and autonomous chemical robotics (6) (e.g. MICREAgents) and we expect this to be a growth area in future, since it allows the experimental microenvironment to be coevolved with the molecules. In general in vitro evolution will contribute to our understanding of both the origin of life and artificial life, and in connection with evolutionary ecology to the safe deployment of self-sustaining and self-reproducing entities in the environment.

Contribution to sustainability/ socioethical responsibility

The socio-ethical implications of evolution in creating new molecules and even organisms still requires extensive analysis. While so-called "irrational" design is seen by some as uncertain in outcome, others maintain that the evolved molecules are more likely to be robust in performance and somewhat less likely to harbour unforeseen artefacts than their more narrowly tested rationally designed molecular competitors.

4c. Combinatorial functional materials (including polymers) – Future Profile

Andreas Herrmann

Impact on other areas of ChemBioIT, science and society

Combinatorial functional materials can be seen as an extension to the systems chemistry approaches (1A) since instead of small molecules larger macromolecular building blocks are investigated in this subdiscipline. All the findings, especially those relating to supramolecular chemistry, are directly relevant for systems chemistry as well. It is also expected that this research area has impact on surface and interfacial chemical systems (2C) since hybrid material building block are ideal candidates to be molecularly engineered to be directed to interfaces. For the same reason such materials might be very useful for fabricated micro- and nanoparticles interacting with ChemBioIT systems (5B) since they are ideal to function as surface coating for such particles. Finally, since it is easier to adjust mechanical properties by selecting the right synthetic materials than evolving biomaterials one might speculate that these types of materials are very valuable for artificial tissue engineering (3D)

Contribution to sustainability/ socioethical responsibility

Combinatorial materials can be either synthesized by chemical means or produced by biotechnology processes. Since oil is usually the raw material for the former processes it might be necessary to find solutions to fabricate such materials with biological systems. However, itself combinatorial materials might be useful to act as catalytic reactors allowing more benign synthesis of a range of valuable compounds.

4d. Generative and developmental systems: for integration of production and construction – Future Profile

Peter Dittrich

Impact on other areas of ChemBioIT, science and society

Roadmap 3: Evo-devo as a design method for cellular systems. But also as a method to achieve adaptation and other self-* properties. Roadmap 6: Evo-devo approach for autonomous robot construction. Especially for multi-scale, dynamically reconfigurable, modular robotic systems (incl. small scale or molecular robots).

Contribution to sustainability/ socioethical responsibility

Sustainability and ethical issues appear when evo-devo systems will be build on a molecular scale and/or using synthetic organisms. Misuse of intellectual property rights and patenting are another sociopolitical issue arising in this and similar context.

4e. Evolutionary Design of Experiments – Future Profile

Irene Poli
Norman Packard

Impact on other areas of ChemBioIT, science and society

Developments in Evolutionary Design of Experiments should have impact across the board in ChemBioIT. Experimental infrastructure is naturally evolving toward high throughput, roboticized automation. These developments will necessitate a principled methodology to guide the infrastructure toward desired scientific and engineering goals. Evolutionary design of experiments is exactly such a methodology.

The science of complex systems is in the process of recognizing itself as a different kind of science from the science of strong laws (e.g. Newton's laws, Schrödinger's equation, etc.) that has traditionally been used to derive desired engineering goals. Instead, such derivation is impossible, and progress must be made through exploratory design processes such as evolutionary design of experiments. Progress in this area will elucidate complex systems science as a whole, and clarify what is possible and how it may be achieved.

Contribution to sustainability/ socioethical responsibility

Sustainability requires an understanding of how our technological developments affect and create our environment. Since the environment itself is a complex system, its behavior cannot be derived from first principles, and experiments on it are either performed blindly (the traditional approach), or they may be performed with attention to how experimental variations may affect outcomes. Evolutionary design of experiments offers a framework for incorporating statistical modeling in this loop of experimental interaction, to provide the necessary attention and achieve positive effects with higher probability. Experimentation can have serious adverse effects on environment, and involve living organisms (animals or humans), so an efficient method that can drastically reduce the set of experimental points to test and achieve the target will be a real benefit to the society.

4f. From reconfigurable to self-constructing and self-repairing systems – Future Profile

Uwe Tangen

Impact on other areas of ChemBioIT, science and society

Reconfigurable hardware and electronic construction can help as bridges to better understand the processes occurring in ChemBio-devices. Many principal intellectual achievements can and must be made before a ChemBio-devices can become working and manageable. As such this sub-area has an important bridging capability in future ChemBioIT-research. The main driving motor though is and will be silicon-industry. The production of ever finer structured silicon-chips forces the foundries to solve the problem of increasingly unreliable hardware. Classic concepts are already at their limit and it might well be that these people much earlier come to incorporate cellular structures and biochemistry into their devices than the bio-community can imagine.

Contribution to sustainability/ socioethical responsibility

As long as the devices in this sub-area are mainly electronic devices, socioethical issue will not come up, because already the unsolved power-supply issue will not allow these devices to proliferate uncontrolled in the environment. Regarding the sustainability question: All these devices require highly specialized materials, e.g. rare-earths etc.. Environmental neutral product life cycles are not yet implemented and a re-utilization of these devices is not yet possible, but it might be possible in the future.

5a. Microfluidics, LOC and other hybrid chemical/physical technologies – Future Profile

John McCaskill

Impact on other areas of ChemBioIT, science and society

LoC developments facilitate both chemical and cellular approaches to the overall roadmap goal through fostering miniaturization, parallelization, integration of experiments in synthesis and analysis down to single molecule and single cell levels, and by the integration with electronic programming. They could also play a decisive role in distributing material in a kind of artificial blood system for construction, but to do this they would need to develop more sophisticated interplay of self-construction and fluid handling. One type of system where this could be achieved is with reversible gel containment.

Contribution to sustainability/ socioethical responsibility

5b. Fabricated micro-and nanoparticles interacting with ChemBioIT systems – Future Profile

John McCaskill

Impact on other areas of ChemBioIT, science and society

Nanoparticles and micro particles will make an important contribution to each of the other main threads towards the roadmap goal. They will contribute to both molecular level analytics and synthesis, and keeping track of combinatorial molecular synthesis. They will contribute to extended chemical systems in providing packets of chemicals amenable to packaging and controlled release in iterative chemical processing. They will contribute to cellular systems as both internal sensors (already widespread) and actuators (e.g. radio release) as well as manipulators (e.g. magnetic particle attachment). They will contribute to evolution of ongoing fabrication , through their ability to act as addressable containers for sequence programmed chemicals, and potentially also to form sequence directed structures at a meta-level. They will contribute to the micro- and nano systems thrusts, as components, as coatings and as characterisation devices. They will contribute as low-level chemical robots with autonomous power to automated distributed experimentation, and via self-assembly to the extensions of additive manufacturing to include sophisticated programmed macro scale synthesis. Ongoing synthesis involving NPs could provide a general platform for making high tech (fine resolution) user-customisable chemical synthesis available to everyman.

Contribution to sustainability/ socioethical responsibility
While noxious and non-degradable nano particles provide a major potential environmental hazard. Their ability to package chemicals in resortable quantities, means that they may play a decisive role in recycling. Their use in user-printable systems could greatly limit the environmental waste associated with industrial scale remote synthesis and local usage mismatch.

5c. Electrokinetic and electrochemical systems – Future Profile

John McCaskill

Contribution to sustainability/ socioethical responsibility
The area makes a key contribution to sustainability, through developing solutions to such key problems as water recycling (desalination), power production (see also photovoltaics topic 9), and interfaces to cellular systems. Electrochemical systems involving disposable organic components are both possible and commensurate with the overall roadmap goals of achieving fully self-constructing systems.

5d. Autonomous chemical sensor and actuator networks down to cellular size and intelligent microparticles. – Future Profile

Itamar Willner

Impact on other areas of ChemBioIT, science and society
(i) achieving this goal will invert chemical experimentation: you add EACs to perform an experiment in solution, rather than placing your solution in an experimental setup (ii) these entities will open up a powerful interface to all manner of nanoscale systems, allowing both data collection and microscale engineering, ultimately impacting on our understanding of tissue organization and medical questions as well as providing mechanisms for modulating the growth of biological crops and a wealth of other applications (iii) this direction will allow a greater exchange of reproducible experimental protocols between groups and also sponsor sustainable personal living technology

5e. Hybrid systems involving cells – Future Profile

Andreas Offenhäusser

Impact on other areas of ChemBioIT, science and society
Progress in all fields of material research and bioengineering will further the progress in life and cell science

5f. Information processing principles in hybrid systems – Future Profile

Konrad Szacilowski

Impact on other areas of ChemBioIT, science and society
The development of hybrid systems can be possible only in the case of parallel progress in other subfiels, including (but not limited to): micro/nanofluidics, synthetic chemistry and analytical chemistry of neurotransmitters, development of molecular scale complex computing systems with a possibility of molecular-scale concatenation. These may be achieved directly within 5f and be "exported" to other subfields or may be "inherited" by 5f from the others.

6a. Chemical robotics, Autonomous Experimentation and Swarm Chemistry – Future Profile

Frantisek Stepanek

Impact on other areas of ChemBioIT, science and society
Developments in chemical robotics will provide a platform for the embodiment of chemical computing -- instead of a beaker or a test tube, the reactions that implement chemical IT will take place in autonomous micro particles (chemical robots) that can move in the environment, send and respond to chemical signals, and reversibly assemble into multi-cellular structure. Chemical robots can also provide an interface between chem/bio IT and "traditional" silicon-based microelectronics IT.

6b. Additive manufacturing, 3D functional printing, steganography & related fab – Future Profile

Steen Rasmussen
Andreas Schober
John McCaskill

Contribution to sustainability/ socioethical responsibility
3D printing can play a major role in sustainability and social responsibility. Firstly it is consistent with an open source policy to encourage local user groups to gain high tech control of their own problems which cannot be solved by other means. It will also foster constructive activity in all segments of society. Secondly, 3D printing with internet exchangeable

libraries of printing protocols can make a real contribution to sustainability by fostering the production of customized repair parts, local manufacturing and manufacturing with novel sustainable materials. These issues have been explored in the SPLIT proposal for a flagship action: coordinator N. Packard.

6c. Multiscale and hybrid robotic systems interacting with chemical construction – Future Profile

Rudolf Füchslin
Serge Kernbach

Impact on other areas of ChemBioIT, science and society

The progress in 6c will interact with all other areas in various ways. I pick out an important one (as a proponent of applied sciences): 6c is a somewhat understandable, probably in the future rather cheap way of mimicking many functionalities presently only attributed to truly living systems. Because one can argue that living systems a) exist and b) are of technological interest and the presented concepts already reached a certain state of maturity, parts of the industry may be willing to contribute bridging the gap between the present state and future systems. In other words: hybrid or chemical robots do not look like purely academic exercises. This is not only about money, it is also about ideas and engineering coming in from social structures that know how to make complex technologies running in the real world.

6d. Evolutionary robotics, including functional material modification – Future Profile

Daniel Richards

Impact on other areas of ChemBioIT, science and society

Contribution to sustainability/ socioethical responsibility

6e. Embodiment and chemical information encoding in robotic construction systems – Future Profile

Steen Rasmussen

Impact on other areas of ChemBioIT, science and society

Contribution to sustainability/ socioethical responsibility

7a. Simulation of ChemBioIT processes and subsystems – Future Profile

John McCaskill

Impact on other areas of ChemBioIT, science and society

The role of simulation is in support of the main experimental threads tackling the overarching roadmap goal. In Area 1, simulation will continue to be used in Systems Chemistry to explore novel and evolving kinetic systems; In molecular design (as in DNA design) including increasingly complex interacting molecular systems, in inorganic biology including quantum computation, and in expiring artificial chemistries. In Area 2, coarse-graining, stochastic and multi-scale simulations will become increasingly important in reaction-diffusion modelling, in self-assembly and its links with chemical kinetics, and especially in interfacial systems. In Area 3, we expect SBML-style modelling to be expanded to include physical modelling of collective phenomena in subsystems (as in biophysical phase modelling of membranes, to include complex systems network models of randomised component equivalent systems, to embrace more realistic models in communication, multicellular, tissue and hybrid systems. In Area 4 we expect simulation to be crucial in linking evolution with real experimentation, e.g. in connection with the EDoE. In Area 5, simulation should be extended from microscopic to integrated molecular and microscopic simulation. In Area 6, simulation can be divided between autonomous process-accompanying simulation (on robot) and simulation by the scientist or engineer to understand or design a system. Both will be important.

Contribution to sustainability/ socioethical responsibility

Simulation plays an important role in socioethical responsibility through projecting the consequences of new subsystems and subprocesses on overall systems dynamics, including the ecological context. Sustainable scenarios can be explored without existential environmental issues using simulation, to narrow the scope in choosing between alternatives and to avoid some of the potential hazards to conservation in interfacing technology with the natural world.

7b. Simulation integrated design and programming for ChemBioIT – Future Profile

Steen Rasmussen
Norman Packard

Impact on other areas of ChemBioIT, science and society

The use of simulation for integrated design and programming should become an integral part of design infrastructure. As such it will have a strong impact on most areas of ChemBioIT, particularly those where implementation is expensive relative to simulation. The rapid ongoing decline in the cost of computation will ultimately increase pressure to use simulation.

Contribution to sustainability/ socioethical responsibility

Issues of sustainability are concerned with interaction of technology with the environment. Unfortunately, we only have one environment, and cannot do multiple parallel experiments on it. Simulation is thus a necessary tool for integrated design and programming of technological interactions and interventions with the environment.

7c. Simulation integrated evolution for ChemBioIT – Future Profile

Rudolf Füchslin
Paulien Hogeweg

Impact on other areas of ChemBioIT, science and society

The most important general aspect is in my opinion to learn how rational design in engineering can be combined with the combinatorial and functional structure of evolved networks. Again, I emphasize the fact that human foresight in engineering is powerful and limiting at the same time. Working with engineers, I developed the conviction that most people, including myself, have not yet understood the difference between technology and biology.

8a. Information encoding and communication of information associated with construction – Future Profile

Peter Wills

Impact on other areas of ChemBioIT, science and society

Contribution to sustainability/ socioethical responsibility

8b. Connecting natural computations (molecular, membrane, cellular etc) – Future Profile

Susan Stepney

Impact on other areas of ChemBioIT, science and society

The main benefits will be in the principled design and understanding of multi-substrate computations and assembly. Technology advances by constructing artefacts from a variety of specific components (with specific application properties) -- this is necessary in these novel technologies, and we need a theoretical underpinning to achieve this.

Contribution to sustainability/ socioethical responsibility

Simulation is important as a way of exploring risks/consequences of self-assembly/autonomy in a safe environment

8c. Programmability and programming autonomous systems – Future Profile

Susan Stepney

Contribution to sustainability/ socioethical responsibility

Ethics -- providing a solid basis for safety critical systems engineering of self-replicating, self-(dis)assembling technology.

8d. Architectures and optimization for combined computation and construction – Future Profile

John McCaskill

Impact on other areas of ChemBioIT, science and society

This area provides the fundamental theoretical underpinning required in all the main experimental approaches 1-6 to the roadmap goals as discussed above. We can expect a major impact on science and engineering as the transformation to self-constructing computer architectures take place, and a more complete understanding of the biological domain.

Contribution to sustainability/ socioethical responsibility

Architectures for integrating construction and information processing will help address the current societal issues associated with sustainability, by achieving local integration of construction, deployment and operation, to allow reuse of materials, full customisation of applications for enhanced utility, minimisation of transport and maximisation of human intelligence resources. These issues have been expounded in the SPLIT proposal on Sustainable Personal Living Technology submitted to FET.

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Part VI: Appendices

1. Template for Detailed Roadmap Sections 1-8

The purpose of the detailed-level roadmap summaries is to provide a short description of each of the 6 main approaches, and 4 overarching subjects, an evaluation of each approach in terms of the common metrics for ChemBioIT and, for both approaches and overarching subjects, descriptions of the likely developments over the next decade. We envisage teams of 2-3 panel members working on each of the detailed roadmaps and other overall topics in three phases: (i) initial draft (ii) revision after feedback from whole panel on integration issues (iii) revision after feedback from community.

The proposed common issues to be addressed in each of the 6 detailed roadmaps:

1. The researchers working on this approach, their location and group size,
2. The essential idea of the approach and how far it is developed,
3. A summary of how this approach contributes to the common roadmap goal,
4. A list of what has been accomplished, when it was accomplished, and by whom, underpinning the development status metrics,
5. The "special strengths" of this approach, the unknowns and weaknesses of this approach,
6. The 5-year goals for this approach, the 10-year goals for this approach, including current, 5yr and 10yr radar-metric diagrams for the approach
7. The necessary achievements to make the 5- and 10-year goals for the approach possible,
8. Scientific "breakthrough achievements" that could be produced,
9. Developments in other areas of ChemBioIT or other areas of science that will be useful or necessary in this approach,
10. How developments within this approach will have benefits to others areas of ChemBioIT or other areas of science in general,
11. The role of theory, simulation and computation in this approach, and
12. A timeline that shows the necessary achievements and makes connection to the development and objective status metrics.

The four overarching subjects (7-10) should follow this template for 1, 3-10, and 12 but replace points 2 and 11 by

2a. The central contribution of this subject to the overall roadmap and its current status
11a. An assessment of how and how strongly it contributes to each of the 6 fundamental approaches

The next pages contain a pictorial representation of the template form on Adobe Forms Central that was employed. In addition to what can be seen, drop down choices and information buttons were made available on the form.

ChemBioICT Roadmap Input on Subtopic

Please type in the subarea title, making any suggestions to improvements to the title that you deem necessary.

DATE

Subarea code (e.g. 6c)

Subtopic of ChemBioICT Roadmap

FIRST NAME

LAST NAME

Email (required for processing)

Use the help buttons marked with a question mark for additional contextual information on entry.

I. Please list main research teams (5-10) working in subtopic (=subarea)

5-10 main researchers, one for each main team, list each name on a separate line (ensuring the unambiguity of each name)

II. What is the essential idea of this approach and its state of development?

III. How does this approach contribute to the common roadmap goal?

Please type in the subarea title, making any suggestions to improvements to the title that you deem necessary.

IV. Please list accomplishments in subarea, when, by whom, and development status (DS) choice (a-f)

Development Status: choose one of six levels a-f

a) an approach amenable to modular integration and automation
b) an approach robustly transferrable between labs
c) an approach firmly established scientifically
d) an approach with some experimental evidence as to viability
e) an approach verified by simulation and quantitative estimates
f) a hypothetical approach, no known implementation so far.

1.		Yr		By		DS	c	
2.		Yr		By		DS	c	
3.		Yr		By		DS	c	
4.		Yr		By		DS	c	
5.		Yr		By		DS	c	

V. List a) strengths b) unknowns c) weaknesses of this approach

a) strengths

1.
2.
3.

b) unknowns

1.
2.
3.

c) weaknesses

1.
2.
3.

VI. List 5 and 10 year goals. 5yr 10yr

1. 1.
2. 2.
3. 3.
4. 4.
5. 5.

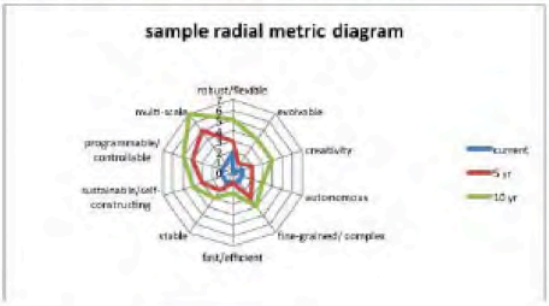
Need Needed

ill have benefits to others areas of C hem Bio IT, eneral.

Please now also complete the metric table in the excel file provided in the invitation email. You will only need to enter a few integers to complete the diagram.

You will only need to fill out a short matrix of integer responses in the range 0 to 7, giving your assessment according to defined criteria of the subarea now, in 5 years and 10 years.

sample radial metric diagram



Attachment Select File

and computation in the subarea, and outline the or socioethical responsibility.

VII. List the necessary achievements to make the 5- and 10-year goals possible

1.
2.
3.
4.

VIII. Which scientific "breakthrough achievements" could be produced in the process?

1.
2.
3.
4.

IX. Major developments in other areas of ChemBioICT or science and engineering that will be useful or necessary to implement this approach

tments in the subarea and makes connection to nd to the metric radial diagram defined under

1. Area Need Needed
2. Area Need Needed
3. Area Need Useful

Additional comments

Submit

2. Compiled Main Research Groups by Subtopic

Subtopic	Team Leader	Column1	Institution	Country	Web page
1a	von Kiedrowski	Günter	Ruhr Universität Bochum	DE	http://www.ruhr-uni-bochum.de/oc1
1a	Herrmann	Andreas	Univ. Groningen	NL	http://www.rug.nl/research/polymer-chemistry-bioengineering/herrmann
1a	Kauffman	Stuart	Univ. Calgary, emer. Univ. Pennsylvania	CAN, US	http://stuartkauffman.com/
1a	Lehn	Jean Marie	Univ. Freiburg	DE	http://www.frias.uni-freiburg.de/en/people/present-fellows/lehn
1b	Benenson	Yaakov	ETH Zurich	CH	http://www.bsse.ethz.ch/synbio/people/kobibe
1b	Benenson	Yaakov	ETH Zurich	CH	http://www.bsse.ethz.ch/synbio/people/kobibe
1b	Cardelli	Luca	MSR, Cambridge	UK	http://www.lucacardelli.name/
1b	Church	George M.	Harvard	US	http://arep.med.harvard.edu/gmc/
1b	Phillips	Andrew	MSR Cambridge	UK	http://research.microsoft.com/en-us/people/aphillip/
1b	Rothemund	Paul	Caltech	US	http://www.dna.caltech.edu/~pwkr/
1b	Seeman	Ned	NYU	US	http://seemanlab4.chem.nyu.edu/
1b	Simmel	Friedrich C.	Univ. München	DE	http://www.e14.ph.tum.de/en/group-members/friedrich-c-simmel/
1b	Turberfield	Andrew	Univ. Oxford	UK	http://www2.physics.ox.ac.uk/research/self-assembled-structures-and-devices
1b	Turberfield	Andrew	Univ. Oxford	UK	http://www2.physics.ox.ac.uk/research/self-assembled-structures-and-devices
1b	Willner	Itamar	Univ. Jerusalem	Israel	http://chem.ch.huji.ac.il/willner/
1b	Winfree	Erik	Caltech	US	http://www.dna.caltech.edu/~winfree/
1b	Yan	Hao	Univ. Arizona State	US	http://yanlab.asu.edu/index.html
1c	Cronin	Lee	Univ. Glasgow	UK	http://www.chem.gla.ac.uk/cronin/
1c	Cronin	Lee	Univ. Glasgow	UK	http://www.chem.gla.ac.uk/cronin/
1c	Maselko	Jerzy	Univ. Alaska	US	http://www.uaa.alaska.edu/chemistry/directory/maselkoinfo.cfm
1c	Company		JPL (Jet Propulsion Lab)	USA	http://www.jpl.nasa.gov
1c	Company		NASA Ames Research Center	US	http://www.nasa.gov/centers/ames/home/
1c	Company		Cambridge Microsoft Research Centre	UK	http://research.microsoft.com/en-us/labs/cambridge/
1d	Banzhaf	Wolfgang	Memorial Univ. of Newfoundland	CAN	http://www.cs.mun.ca/~banzhaf/
1d	Banzhaf	Wolfgang	Memorial Univ. of Newfoundland	CAN	http://www.cs.mun.ca/~banzhaf/
1d	Cardelli	Luca	MSR, Cambridge	UK	http://www.lucacardelli.name/
1d	Danos	Vincent	Univ. Edinburgh	UK	http://homepages.inf.ed.ac.uk/vdanos/home_page.html
1d	Dittrich	Peter	Univ. Jena	DE	http://users.minet.uni-jena.de/~dittrich/
1d	Dittrich	Peter	Univ. Jena	DE	http://users.minet.uni-jena.de/~dittrich/
1d	Feret	Jérôme	INRIA, Paris	FR	http://www.di.ens.fr/~feret/
1d	Flamm	Christoph	Univ. Vienna	AU	http://www.tbi.univie.ac.at/~xtof/
1d	Flamm	Christoph	Univ. Vienna	AU	http://www.tbi.univie.ac.at/~xtof/
1d	Fontana	Walter	HMS, Boston	US	http://fontana.med.harvard.edu/www/index.htm
1d	Hinze	Thomas	(Cotbus)	DE	http://www.informatik.tu-cottbus.de/~hinzet/
1d	Ikegami	Takashi	Univ. Tokyo	Japan	http://sacral.c.u-tokyo.ac.jp/~ikeg/
1d	Ikegami	Takashi	Univ. Tokyo	Japan	http://sacral.c.u-tokyo.ac.jp/~ikeg/
1d	Merkle	Daniel	Univ. of Southern Denmark	DK	http://www.imada.sdu.dk/~daniel/
1d	Merkle	Daniel	Univ. of Southern Denmark	DK	http://www.imada.sdu.dk/~daniel/
1d	Winfree	Eric	MPAAAA Team	US	http://molecular-programming.org
1d	Nagpal	Radhika	Harvard	US	http://www.eecs.harvard.edu/~rad/
1d	Phillips	Andrew	MSR Cambridge	UK	http://research.microsoft.com/en-us/people/aphillip/
1d	Rothemund	Paul	Caltech	US	http://www.dna.caltech.edu/~pwkr/
1d	Speroni di Fenizio	Pietro	Dublin City Univ.	Ireland	http://home.pietrosperoni.it/
1d	Stadler	Peter	Univ. Leipzig	DE	http://www.bioinf.uni-leipzig.de/
1d	Suzuki	Hideaki	National Institute of Information and CommUniv.cation	Japan	National_Institute_of_Information_and_Communications_Technology
1d	Teuscher	Christoph	Univ. Portland	US	http://www.teuscher.ch/christof/ext/
1d	Winfree	Erik	Caltech	US	http://www.dna.caltech.edu/~winfree/
2a	Adamatzky	Andrew	Univ. of West of England, Bristol	UK	http://uncomp.uwe.ac.uk/adamatzky/
2a	Agladze	Konstantin	Kyoto Univ.	Japan	http://www.icems.kyoto-u.ac.jp/e/ppl/grp/agladze.html
2a	deKepper	Patrick	CNRS Bordeaux	FR	http://www.crpp-bordeaux.cnrs.fr/~dekepper/
2a	Dittrich	Peter	Univ. Jena	DE	http://users.minet.uni-jena.de/~dittrich/
2a	Epstein	Irving R.	Univ. Brandeis	US	http://www.bio.brandeis.edu/faculty/epstein.html
2a	Epstein	Irving R.	Univ. Brandeis	US	http://www.bio.brandeis.edu/faculty/epstein.html
2a	Gizynski	Konrad	Inst. Phys. Chem. Polish Academy of Sciences	PL	http://ichf.edu.pl/res/res_en/depart/zd-8/cheminfo_lab/index.html
2a	Gorecki	Jerzy	Inst. Phys. Chem. Polish Academy of Sciences	PL	http://ichf.edu.pl/person/gorecki.html
2a	Gruenert	Gerd	Univ. Jena	DE	http://www.biosys.uni-jena.de/Members/Gerd+Gruenert.html
2a	Grzybowski	Bartosz A.	Univ. Northwestern	US	http://dysa.northwestern.edu/index.html
2a	Herminghaus	Stephan	Max-Planck-Institute for Dynamics and Self-Organisation	DE	http://www.dcf.ds.mpg.de/index.php?id=239
2a	Hogeweg	Pauline	Univ. Utrecht	NL	http://www-binf.bio.uu.nl/ph/
2a	Husbands	Phil	Univ. Sussex	UK	http://www.sussex.ac.uk/informatics/people/peoplelists/person/1334
2a	Krinsky	Valentin	Max-Planck-Institute for Dynamics and Self-Organization	DE	http://www.bmp.ds.mpg.de/full-list.html
2a	Maini	Philip K.	Univ. Oxford	UK	http://people.maths.ox.ac.uk/maini/
2a	McCaskill	John S.	Ruhr Universität Bochum	DE	http://www.biomip.de
2a	Meijer	E. W. (Bert)	Univ. Eindhoven	NL	https://www.tue.nl/en/research/research-institutes/top-research-groups/institute-for-complex-molecular-systems/research/groups/meijer-research-group/
2a	Meinhardt	Hans	Max-Planck-Inst. of Dev. Biology	DE	http://www.eb.tuebingen.mpg.de/?id=79
2a	Mikhailov	Alexander S.	Max-Planck-Institute of Phys. Chemistry	DE	http://www.fhi-berlin.mpg.de/complsys/mik/
2a	Murray	J. D.	Univ. Washington	US	http://depts.washington.edu/amath/staff-members/james-d-murray
2a	Showalter	Kenneth	Univ. West Virginia	USA	http://heracles.chem.wvu.edu/showalter.html
2a	Steinbock	Oliver	Univ. Göttingen	DE	http://www.chem.fsu.edu/steinbock/hp1.htm
2a	Toth	Agota	Hungarian Academy of Sciences	Hungary	http://www.staff.u-szeged.hu/~atoth/indexh.html
2a	Vanag	Vladimir	Univ. Brandeis	US	http://www.brandeis.edu/departments/chemistry/directory/research.html
2a	Winfree	Arthur T.	Regents	US	http://uanews.org/story/regents-professor-arthur-winfree-dies
2a	Yoshikawa	Kenichi	Univ. Kyoto	Japan	https://www.math.kyoto-u.ac.jp/en/people/profile/yosikawa
2a	Zauner	Klaus Peter	Univ. Southampton	UK	http://www.ecs.soton.ac.uk/people/kpz
2a	Zhao	Xin	Nankai Univ., Tianjin, Inst. Robotics and Auto. Inf. Sys.	China	http://it.nankai.edu.cn:8080/itemis/English/IRAIS.aspx
2b	Cronin	Lee	Univ. Glasgow	UK	http://www.chem.gla.ac.uk/cronin/
2b	Herrmann	Andreas	Univ. Groningen	NL	http://www.rug.nl/research/polymer-chemistry-bioengineering/herrmann
2b	McCaskill	John S.	Ruhr Universität Bochum	DE	http://www.biomip.de
2b	Monnard	Pierre-Alain	Univ. of Southern Denmark	DK	http://findresearcher.sdu.dk:8080/portal/en/person/monnard
2b	Mouritsen	Ole	Univ. of Southern Denmark	DK	http://www.memphys.dk/
2b	Packard	Norman H.	ECLT, Univ. Ca'Foscari di Venezia	Italy	http://www.ecltech.org
2b	Rasmussen	Steen	Univ. of Southern Denmark	DK	http://www.sdu.dk/en/Om_SDU/Institutter_centre/C_FLinT.aspx
2b	Stepanek	Frantisek	ICT Praque	CZ	http://www.chobotix.cz/
2b	Svaneborg	Carsten	Univ. of Southern Denmark	DK	http://flint.sdu.dk/index.php?page=carsten-svaneborg
2b	von Kiedrowski	Günter	Univ. Bochum	DE	http://www.ruhr-uni-bochum.de/oc1/kiedro.html
2b	Willner	Itamar	Univ. Jerusalem	Israel	http://chem.ch.huji.ac.il/willner/
2d	McCaskill	John S.	Ruhr Universität Bochum	DE	http://www.biomip.de
2d	Rasmussen	Steen	Univ. of Southern Denmark	DK	http://www.sdu.dk/en/Om_SDU/Institutter_centre/C_FLinT.aspx
2e	Fellermann	Harold	Computing Science New Castle Univ.	UK	http://harold.teerun.de/index.html
2e	McCaskill	John S.	Ruhr Universität Bochum	DE	http://www.biomip.de
2e	Rasmussen	Steen	Univ. of Southern Denmark	DK	http://www.sdu.dk/en/Om_SDU/Institutter_centre/C_FLinT.aspx
3a	Benenson	Yaakov	ETH Zurich	CH	http://www.bsse.ethz.ch/synbio/people/kobibe
3a	Church	George M.	Harvard	US	http://arep.med.harvard.edu/gmc/
3a	Collins	James J.	Harvard	US	http://www.bu.edu/bme/people/primary/collins/
3a	Collins	James J.	Harvard	US	http://www.bu.edu/bme/people/primary/collins/
3a	deLorenzo	Victor	CNB, Madrid	Spain	http://www.cnb.csic.es/~meml/meml/Victor.html
3a	Elowitz	Michael	Caltech	US	http://www.elowitz.caltech.edu/
3a	Endy	Drew	Stanford	US	http://www.stanford.edu/~endy
3a	Endy	Drew	Stanford	US	http://www.stanford.edu/~endy
3a	Freemont	Paul	Imperial College	UK	http://www.imperial.ac.uk/AP/faces/pages/read/Home.jsp?person=p.freemont
3a	Hasty	Jeff	UCSD	US	http://biodynamics.ucsd.edu/
3a	Hasty	Jeff	UCSD	US	http://biodynamics.ucsd.edu/
3a	Keasling	Jay	Berkeley	US	http://cheme.berkeley.edu/faculty/keasling/
3a	Lu	Timothy K.	MIT	USA	http://www.rle.mit.edu/sbg/
3a	Serrano	Luis	CRG, Barcelona	Spain	http://serrano.crg.es/
3a	Smolke	Christina	Stanford	US	https://med.stanford.edu/profiles/Christina_Smolke
3a	Solé	Ricard	Pompeu, Barcelona	Spain	http://complex.upf.es/~ricard/Main/RicardSole.html

3a	Voigt	Chris	MIT	US	http://web.mit.edu/voigtlab/
3a	Voigt	Chris	MIT	US	http://web.mit.edu/voigtlab/
3a	Weiss	Ron	MIT	US	http://groups.csail.mit.edu/synbio/
3a	Weiss	Ron	MIT	US	http://groups.csail.mit.edu/synbio/
3b	Benenson	Yaakov	ETH Zurich	CH	http://www.bsse.ethz.ch/synbio/people/kobibe
3b	Collins	James J.	Harvard	US	http://www.bu.edu/bme/people/primary/collins/
3b	Danino	Tal	MIT	US	http://tal.mit.edu/
3b	Fussenegger	Martin	ETH Zurich	CH	http://www.bsse.ethz.ch/department/people/detail-person.html?persid=88479
3b	Hasty	Jeff M.	UCSD	US	http://biodynamics.ucsd.edu/
3b	Solé	Ricard	Pompeu, Barcelona	Spain	http://complex.upf.es/~ricard/Main/RicardSole.html
3b	Voigt	Chris	MIT	US	http://web.mit.edu/voigtlab/
3b	Weiss	Ron	MIT	US	http://groups.csail.mit.edu/synbio/
3c	Adamatzky	Andrew	Univ. of West of England, Bristol	UK	http://uncomp.uwe.ac.uk/adamatzky/
3c	Marder	Eve	Univ. Brandeis	US	http://www.bio.brandeis.edu/faculty/marder.html
3c	Schweighofer	Nicolas	USC	US	https://www.usc.edu/programs/neuroscience/faculty/profile.php?fid=61
3d	Bhatia	Sangeeta	MIT	US	http://ki.mit.edu/people/faculty/bhatia
3d	Chikov	Boris	Laser Zentrum Hannover	DE	http://www.lzh.de/en/departments/nanotechnology
3d	Khademhosseini	Ali	MIT	US	http://www.tissueeng.net/
3d	Liefeith	Klaus	Iba Heiligenstadt	DE	http://www.iba-heiligenstadt.de/fachbereiche/biowerkstoffe/
3d	Mironov	Vladimir	CIT San Paulo	Brasil	http://icpro-am.com.sg/vladimir.html
3d	Yamanaka	Shinya	Gladstone	US	http://labs.gladstone.ucsf.edu/yamanaka
4a	McCaskill	John S.	Univ. Bochum	DE	http://www.biomip.de
4a	Wills	Peter	Univ. Auckland	NZ	http://www.science.auckland.ac.nz/people/p-wills
4b	Benner	Steven A.	Foundation for Applied Molecular Evolution	US	http://www.ffame.org/sbenner.php
4b	Breaker	Ronald	Yale	US	http://breaker.sites.yale.edu/
4b	Eigen	Manfred	Max-Planck-Institute for Biophysical Chemistry Göttingen	DE	http://www3.mpibpc.mpg.de/groups/eigen/manfred_eigen/german.html
4b	Ellington	Andrew	Univ. Texas Austin	US	http://ellingtonlab.org/index.html
4b	Famulok	Michael	Univ. Bonn	DE	http://www.famuloklab.de/
4b	Joyce	Gerald	Scripps	US	http://vivo.scripps.edu/display/JoyceGerald
4b	Lehman	Niles	Univ. Portland	US	http://web.pdx.edu/~niles/Lehman_Lab_at_PSU/Home.html
4b	McCaskill	John S.	Ruhr Universität Bochum	DE	http://www.biomip.de
4b	Stadler	Peter	Univ. Leipzig	DE	http://www.bioinf.uni-leipzig.de/
4b	Szostak	Jack W.	Harvard	US	http://molbio.mgh.harvard.edu/szostakweb/
4b	von Kiedrowski	Günter	Ruhr Universität Bochum	DE	http://www.ruhr-uni-bochum.de/oc1/kiedro.html
4d	Banzhaf	Wolfgang	Memorial Univ. of Newfoundland	CAN	http://www.cs.mun.ca/~banzhaf/
4d	Bentley	Peter	Univ. College London	UK	http://www0.cs.ucl.ac.uk/staff/P.Bentley
4d	Furusawa	Chikara	RIKEN, Osaka	Japan	http://www.qbic.riken.jp/mbd/furusawa/index_e.html
4d	Hogeweg	Paulien	Univ. Utrecht	NL	http://www-binf.bio.uu.nl/ph/
4d	Kaneko	Kunihiro	Univ. Tokyo	Japan	http://chaos.c.u-tokyo.ac.jp/
4d	Maree	Stan	John Innes Centre	UK	https://www.jic.ac.uk/scientists/stan-maree/
4d	Pfeifer	Rolf	Univ. Zürich	CH	http://www.ifi.uzh.ch/ailab/group/professors/rolfpfeifer.html
4d	Pollack	Jordan	Gregory	US	http://www.cs.brandeis.edu/~pollack/
4e	Chomtee	Boonorm	Dep. of Statistics, Kasetsart Univ. Bangkok	Thailand	http://pirun.ku.ac.th/~fsciboc/
4e	Green	D.V.S.	GSK Medicines Research Centre	UK	http://www.gsk.com/research/r-and-d-locations.html
4e	Herrera	Frederico	ITQB	Portugal	http://www.itqb.unl.pt/research/biology/cellular-neurobiology
4e	Lazic	Zivorad R.	BASF catalysts LLC	US	http://www.catalysts.basf.com/p02/USWeb-Internet/catalysts/en/
4e	Lewis	Sue	Univ. Southampton	UK	http://www.personal.soton.ac.uk/sml2/
4e	Montgomery	Douglas C.	Arizona State Univ.veristy	US	http://masmlab.engineering.asu.edu/montgomery/
4e	Packard	Norman H.	Protolife, USA Wynn, H. London School of Economics	US,UK	http://www.protolife.com/
4f	Higuchi	Tetsuya	AIST	Japan	t-higuchi@aist.go.jp, http://itri.aist-go.jp/en/about.html
4f	Keymeulen	Didier	JPL (NASA's Jet Propulsion Laboratory)	US	http://www.jpl.nasa.gov
4f	Mange	Daniel	EPFL	CH	http://lslwww.epfl.ch/pages/staff/mange/home.html
4f	Meier	Karlheinz	Univ. Heidelberg	DE	http://www.kip.uni-heidelberg.de/~meierk/?lang=en
4f	Miller	Julian F.	Univ. York	UK	http://www.cartesiangp.co.uk/index.html
4f	Sipper	Moshe	Univ. Ben Gurion	Israel	http://www.moshesipper.com/
4f	Stoica	Adrian	JPL (Jet Propulsion Lab)	US	http://www-robotics.jpl.nasa.gov/people/Adrian_Stoica/index.cfm
4f	Thompson	Adrian	Univ. Sussex	UK	http://mazsola.iit.uni-miskolc.hu/~vajo/html/ade.html
4f	Wunderlich	Hans Joachim	Univ. Stuttgart	DE	http://www.iti.uni-stuttgart.de/abteilungen/rechnerarchitektur/mitarbeiter/hans-joachim-wunderlich.html
5a	de Mello	Andrew J.	ETH Zurich	CH	http://www.demellogroup.ethz.ch/en/
5a	Fair	Richard B.	Univ. Duke	US	http://www.ece.duke.edu/faculty/richard-b-fair
5a	Fan	Shih Kang	Univ. Taiwan	Taiwan	http://fan-tasy.org/nanotas/member/advisor/shih-kang-fan
5a	Fouillet	Yves	CEA - Grenoble	FR	http://www-leti.cea.fr/en ???
5a	Hyoung Kang	Kwan	Pohang Univ. of Science and Technology	Korea	http://wwwhome.postech.ac.kr/web/eng/ecad_01_06
5a	Kim	Chang-Jin	UCLA	US	http://cjmems.seas.ucla.edu/
5a	Krupenkin	Tom N.	Univ. Wisconsin	US	http://www.krupenkin.com/Default.aspx
5a	Lee	Abraham	Univ. Irvine	US	http://biomint.eng.uci.edu/people.html
5a	Muegele	Frieder	Univ. Twente	NL	http://www.utwente.nl/tnw/pcf/
5a	Papathanasiou	Athanasios G.	Univ. Athens	Greece	http://www.chemeng.ntua.gr/people/pathan/
5a	Quake	Stephen	Univ. Stanford	US	http://thebigone.stanford.edu
5a	Senez	Vincent	IEMN - Lille	FR	http://exploit.iemn.univ-lille1.fr/en/scientific-management
5a	Steckl	Andrew J.	Univ. Cincinnati	US	http://www.nanolab.uc.edu/members/Steckl/Steckl.html
5a	van den Berg	Albert	Univ. Twente	NL	http://www.utwente.nl/ewi/bios/
5a	Weitz	David A.	Univ. Harvard	US	http://weitzlab.seas.harvard.edu/research/microfluidics
5a	Wheeler	Aaron	Univ. Toronto	CAN	http://microfluidics.utoronto.ca/
5a	Whitesides	George M.	Univ. Harvard	US	http://gmwgroup.harvard.edu
5a	Zengerle	Roland	IMTEK Freiburg	DE	https://www.imtek.de/research/research-topics/microfludics
5a	Company		Advanced Liquid Logic	FR	http://www.liquid-logic.com/
5a	Company		Varioptic/Parrot	FR	http://www.varioptic.com/
5a	Company		Liquavista/Samsung	NL	http://www.liquavista.com/
5a	Company		Optilux	US	http://optilux.com/
5a	Company		InStep Nanopower	US	http://instepnanopower.com/
5a	Company		Gamma Dynamics	US	http://gammadynamics.net/
5a	Company		Sharp Lab & Univ. Southampton (Lab on chip collab. resea	UK	http://www.singularityweblog.com/microfluidics-chip-sharp/, http://blogs.rsc.org/lc/2012/08/07/hot-artic
5a	Company		Kapplex	CAN	http://www.kapplex.com/
5b	Furuya	Takeshi	AIST	Japan	https://unit.aist.go.jp/nri/member/member_e.html
5b	Maeda	Hideaki	RIKEN, Osaka	Japan	http://protein.gsc.riken.jp/AboutUS/Organization/researchteams.html
5b	Watanabe	Kosuke	Univ. Kyushu	Japan	not found (perhaps: http://www.tj.kyushu-u.ac.jp/en/igses/c_research/mms.php)
5b	Willner	Itamar	Univ. Jerusalem	Israel	http://chem.ch.huji.ac.il/willner/
5b			Affymetrix	US	http://www.affymetrix.com/estore/
5c	Bayley	Hagan	Univ. Oxford	UK	http://bayley.chem.ox.ac.uk/hbayley/
5c	Bazant	Martin Z.	MIT	US	http://web.mit.edu/~bazant/www/
5c	Beunis	Filip	Univ. Ghent	NL	http://lcp.elis.ugent.be/filipb
5c	Biesheuvel	Maarten	Univ. Wageningen	NL	http://www.maartenbiesheuvel.nl/
5c	Compton	Richard G.	Univ. Oxford	UK	http://research.chem.ox.ac.uk/richard-compton.aspx
5c	Dekker	Cees	Delft Univ. of Technology	NL	http://ceesdekkerlab.tudelft.nl/
5c	Dietz	Henry G.	Univ. Kentucky	US	http://www.engr.uky.edu/research/researchers/henry-gordon-dietz/
5c	Edwards	Brian F. P.	Univ. Wayne State	US	http://biochem.med.wayne.edu/profile.php?id=42760
5c	Fromherz	Peter	Max-Planck-Institute BioChem	DE	http://www.biochem.mpg.de/en/eg/fromherz/
5c	Heller	Michael	UCSD	US	http://www.jacobsschool.ucsd.edu/faculty/faculty_bios/index.sfe?fmp_recid=1
5c	Kassegne	Samuel K.	Univ. San Diego	US	http://www.digitaladdis.com/sk/
5c	Liedl	Tim	LMU	DE	http://www.softmatter.physik.uni-muenchen.de/personen/senior_scientists/liedl/index.html
5c	McCaskill	John S.	Univ. Bochum	DE	http://www.biomip.de
5c	Schiffbauer	Jarrod E.	Technion	Israel	http://meeng.technion.ac.il/peoplen/S/
5c	Schuhmann	Wolfgang	Univ. Bochum	DE	http://www.ruhr-uni-bochum.de/elan/
5c	Shepard	Kenneth L.	Univ. Columbia, NY City	US	http://bme.columbia.edu/kenneth-l-shepard
5c	Willner	Itamar	Univ. Jerusalem	Israel	http://chem.ch.huji.ac.il/willner/
5d	Cavin III	Ralph Keary	SRC	US	https://www.src.org/about/management-team/cavin-ralph/
5d	Cronin	Lee	Univ. Glasgow	UK	http://www.chem.gla.ac.uk/cronin/
5d	Dekker	Cees	Delft Univ. of Technology	NL	http://ceesdekkerlab.tudelft.nl/
5d	Herrmann	Andreas	Univ. Groningen	NL	http://www.rug.nl/research/polymer-chemistry-bioengineering/herrmann

5d	McCaskill	John S.	Univ. Bochum	DE	http://www.biomip.de
5d	Oehm	Jürgen	Univ. Bochum	DE	http://www.ais.ruhr-uni-bochum.de/arbeitsgruppe/
5d	Packard	Norman H.	ECLT, Univ. Ca'Foscari di Venezia	Italy	http://www.ecltech.org
5d	Rasmussen	Steen	Univ. of Southern Denmark	DK	http://www.sdu.dk/en/Om_SDU/Institutter_centre/C_FLinT.aspx
5d	Stepanek	Frantisek	ICT Praque	CZ	http://www.chobotix.cz/
5d	von Kiedrowski	Günter	Univ. Bochum	DE	http://www.ruhr-uni-bochum.de/oc1/kiedro.html
5d	Willner	Itamar	Univ. Jerusalem	Israel	http://chem.ch.huji.ac.il/willner/
5d	Wills	Peter	Univ. Auckland	NZ	http://www.science.auckland.ac.nz/people/p-wills
5d	Zhirnov	Victor V.	SRC	US	https://www.src.org/about/management-team/zhirnov-victor/
5e	Benfenati	Fabio	Genova	Italy	http://www.iit.it/en/people/fabio-benfenati.html
5e	Claverol-Tintur	Enric	FCRI Barcelona	Spain	http://www.fundaciorecerca.cat/en/Patronat.asp
5e	Lieber	Charles	Harvard	US	http://cml.harvard.edu/people/charles-m-lieber/
5e	Offenhäusser	Andreas	FZ Juelich	DE	http://www.fz-juelich.de/pgi/pgi-8/EN/Home/_node.html
5e	Peyrin	Jean-Michel	UPMC Paris	FR	http://www.ifr83.idf.inserm.fr/fr/linstitut/groupedereflexionscientifique.html
5e	Spira	Micha	Univ. Jerusalem	Israel	http://spiralab.huji.ac.il/
5e	Villard	Caterine	CNRS Grenoble	FR	http://creta.grenoble.cnrs.fr/english/Scientific_thematics_en/Scientific_thematics_4.htm
5f	Andreasson	Joakim	Chalmers Tehchnical Univ.	SE	http://www.chalmers.se/en/staff/Pages/joakim-andreasson.aspx
5f	Benenson	Yaakov	ETH Zurich	CH	http://www.bsse.ethz.ch/synbio/people/kobibe
5f	Credi	Alberto	Univ. Bologna	Italy	http://www.unibo.it/SitoWebDocente/default.aspx?UPN=alberto.credi%40unibo.it
5f	Erokhin	Victor	Univ. Parma	Italy	http://www.fis.unipr.it/lmn/Victor/Scientific.htm
5f	Gentili	Pier-Luigi	Univ. Perugia	Italy	http://www.unipg.it/personale/007364
5f	Mann	Steve	Univ. Toronto	CAN	http://www.eecg.toronto.edu/~mann/
5f	Pischel	Uwe	Univ. Huelva	Spain	http://moodle.uhu.es/contenidos2/
5f	Remacle	Francois	Univ. Louvain	Belgium	http://perso.uclouvain.be/jean-francois.remacle/
5f	van der Boom	Milko	Weizmann	Israel	https://sites.google.com/site/milkovanderboomslab/
6a	Ces	Oscar	Imperial College London	UK	http://www.imperial.ac.uk/AP/faces/pages/read/Home.jsp?person=o.ces
6a	Lagzi	Istvan	Eötvös Univ.	Hungary	http://nimbus.elte.hu/~lagzi/
6a	Maeda	Shingo	Waseda Univ.	Japan	http://www.experts.scival.com/shibaura/expert.asp?n=Shingo+Maeda&u_id=125&oe_id=1&o_id=15
6a	Misra	Sarthak	Univ. Twente	NL	http://www.ce.utwente.nl/msa/SMisra/Home.html
6a	Reimhult	Erik	BOKU Wien	Austria	http://www.nano.boku.ac.at/bimat/
6a	Stano	Pasquale	Univ. Rome 3	Italy	http://www.plluisi.org/stano.html
6b	Cronin	Lee	Univ. Glasgow	UK	http://www.chem.gla.ac.uk/cronin/
6b	Lewis	Jennifer A.	Harvard	US	http://www.seas.harvard.edu/directory/jalewis
6b	Lipson	Hod	Univ.v. Cornell	US	http://lipson.mae.cornell.edu/
6b	Martin	Keith	Univ. Cambridge	US	http://www.neuroscience.cam.ac.uk/directory/profile.php?kmartin1
6b	McAlpine	Michael	Princeton	US	http://www.princeton.edu/mae/people/faculty/mcalpine1/
6c	Bashir	Rashid	Univ. Illlinois	US	http://www.ece.illinois.edu/directory/profile.asp?rbashir
6c	Lipomi	Darren	NanoEngineering UCSD	US	http://darrenlipomi.com/
6c	McCaskill	John S.	Univ. Bochum	DE	http://www.biomip.de
6c	Parker	Kevin Kit	Harvard	US	http://wyss.harvard.edu/viewpage/126/kevin-kit-parker
6c	Rasmussen	Steen	Univ. of Southern Denmark	DK	http://www.sdu.dk/en/Om_SDU/Institutter_centre/C_FLinT.aspx
6c	Sen	Ayusman	Univ. Penn State	US	http://www.chem.psu.edu/directory/axs20
6c	Stepánek	Frantisek	ICT Praque	CZ	http://www.chobotix.cz/
6c	Company		SHALAB, Shuji Hashimoto Laboratrory, Univ. Waseda	Japan	www.shalab.phys.waseda.ac.jp/chemical-e.html
6e	Stepanek	Frantisek	ICT Praque	CZ	http://www.chobotix.cz/
7c	Fellermann	Harold	Computing Science New Castle Univ.	UK	http://harold.teerun.de/index.html
7c	Hauser	Helmut	Univ. Graz	Austria	http://www.igi.tugraz.at/helmut/
7c	Ikegami	Takashi	Univ. Tokyo	Japan	http://sacral.c.u-tokyo.ac.jp/~ikeg/
7c	Jensen	Klavs F.	MIT	US	http://web.mit.edu/jensenlab/
7c	Lida	Fumiya	ETH Zurich	CH	http://www.birl.ethz.ch/people/iidaf
7c	McCaskill	John S.	Univ. Bochum	DE	http://www.biomip.de
7c	Pelesko	John A.	Univ. Delaware	US	http://www.math.udel.edu/MECLAB/
7c	Rasmussen	Steen	Univ. of Southern Denmark	DK	http://www.sdu.dk/en/Om_SDU/Institutter_centre/C_FLinT.aspx
7c	Reif	John H.	Univ. Duke	US	http://www.cs.duke.edu/~reif/
7c	Solé	Ricard	Pompeu, Barcelona	Spain	http://complex.upf.es/~ricard/Main/RicardSole.html
7c	Winfree	Erik	Caltech	US	http://www.dna.caltech.edu/~winfree/

These research teams are not a complete list of all teams in the different subareas, but rather those known by the panelists to be interested in the relation between the subarea and the overall goal of the roadmap. Of course the list will inevitably be far from complete, but may serve both as an indication of the range of groups involved and as a starting point for more extended compilations of relevant research groups.

3. Compiled goals, expected breakthroughs, necessary achievements and useful developments

Area	Nr	5 Year Goals	10 Year Goals	Necessary achievements	Expected Breakthroughs	Developments in Other Areas	Other Area	Need
1a SysChem	1	Developing modules for robust system construction	Miniplants exhibiting integrated programmable catalysis	Chiral reactor parallel search with feedback loops.	Energy harvesting: smart technology to optimise power supply with available resources without massive storage	Physics of water : how does water structure reflect the interface, is there a far ordering beyond 5nm?	Condensed matter physics	Needed
	2	Smart chemical pills with integrated control	Programmable reactor able to make chemicals needed in trainable and programmable way	Reverse process of controlling deconstruction by voltage from chip	Basic understanding of water and interfaces	Miniaturization of NMR or other structural characterisation tools	Physics	Useful
	3			Light directed chemistry allowing dynamic microsystems controlled during operation by light, orthogonal to electrode control	Artificial cells			
	4			Combination of 3D printing of experimental apparatus and chemistry	Exploitation of quantum processing, tunneling, entanglement, collective transitions, at room temperature?			
1b DNAComp	1	Genetic production of nanostructures in vivo or in cell-like systems. Realization of autonomous molecular machines that can trasnport and assemble materials	Development of free-running (open) systems (having some primitive metabolism, external energy/materials source). Autonomous ("energy scavenging"?) molecular robots.	Realize truly modular systems, reduce/avoid chemical crosstalk Generation of ability for molecular systems to achieve autonomy Improved interfacing/control/screening methods	The applications for this field will most probably lie either in biomimetic (and hopefully sustainable, low-energy consumption, environment-friendly) assembly processes and production systems, or in the realization of autonomous agents, which can interact with their environment (for sensing, theranostics, bioremediation, food & drug safety).	Modelling and simulation	Computer Science	Needed
	2	Orchestration of multistep assembly processes by molecular programs Fully-automated molecular programming	Implementation of evolutionary schemes Artificial evolution (autonomous) Self-replicating systems	Autonomous theranostic systems, intelligent drug delivery and "molecular sentinels" Artificial ("unnatural") engineered evolution/self-replication generally, there are many, many chemical/materials challenges involved in order to implement more complicated ideas in the "test tube"	Intelligent therapeutics, autonomous theranostic systems, intelligent drug delivery and "molecular sentinels"	Artificial chemistries	Chemistry	Needed
	3	Scaling up production of nanostructures Scale-up beyond proof-of-principle Bridging length scales from nanoscopic to macroscopic	Implement learning/trainable systems Learning molecular systems/pattern recognition	Biological & sustainable production of artificial materials and devices coupling to and utilization of other chemistries (translation from DNA code to "something useful")	Biological & sustainable production of artificial materials and devices	Microfluidics	Materials/Engineering	Needed
	4	Integration with living (mammalian) cells Better standardised software tools for design Better simulation models	Reconfigurable, programmable, multi (or general) purpose systems Programming "on the fly"	Controlled materials/energy exchange & realization of "homeostasis" // utilization of external energy sources (light, chemical, etc.)	Artificial ("unnatural") engineered evolution/self-replication. Growth and reproduction of an artificial system.	Robotics	Engineering	Useful
	5	Interfacing molecular computing and conventional technology; hybrid systems; autonomous sensor/diagnostic/theranostic systems; development of robust, modular, and scalable computing/fabrication schemes; programmable control of dynamical, self-organizing processes; systems with some sort of memory	From artificial cells to artificial tissues; artificial development and differentiation; growth and self-replication Information not filled in above					
1c InorgBio	1	Establish the theory and initial proof of concept that evolution of 'inorganics' can be robustly demonstrated using 'computer assisted' robotics	Fully autonomous inorganic machinery allowing evolutionary dynamics to emerge	Researchers trained in programming and chemical synthesis	Inorganic life	New theory for self-assembling and self-organising robots	Robotics	Needed
	2			New understanding of what biology is in terms of evolutionary chemistry first Rapid prototyping of chemical robotics	New understanding of what biology is in terms of evolutionary chemistry first	Models for emergent complexity	Complexity Theory	Needed
	3			Minimal requirements for functional evolution. New sensor systems	Minimal requirements for functional evolution	Control of architecture, programming of evolutionary systems	Evolutionary Computation	Needed
	4			Developments in optimisation algorithms and molecular spectroscopy	New understanding of information and link with entropy and evolution (not Shannon or Kolmogorov)	Developments in algorithms	Computer Science	Useful
1d ArtChem	1	Inclusion of stereochemistry	Accuracy sufficient to be predictive for technological processes	Spatial organization needs to be modeled in rule based system	New approaches in heterogeneous catalysis	DNA machines Molecular modeling Quantum theory	1b Bioinformatics Computational chemistry	Useful Needed
	2	Inclusion of spatial organization/structures	Models with feedback of chemistry on complex materials	New one-pot chemical reactions as contribution to "green chemistry" derivation of rules for spatial (self) organization from simplified physical models.	New one-pot chemical reactions as contribution to "green chemistry"	Spatially organized chemistries	2b	Needed
	3	Establish further links between discrete algebraic theory and dynamical systems theory	Develop a unifying theory of molecular computing that joins discrete algebraic descriptions with dynamical systems theory and that is intuitively usable by programmers to predict the behavior of their molecular programs.	Theory, algorithms, and tools for constructing and analyzing implicitly defined chemical models including their qualitative dynamics.		Better understanding of selforg./repairing systems	2e	Useful
	4	Implement computational tools for the design and analysis of ChemBioIT.	Implement useful tools following such a theory, i.e., develop computational tools for the design and analysis as well as bio-chemical/electronical tools for the construction of the actual systems ("ChemBioIT compilers").	Most of the current tools require an explicit representation of the chemical system by a list of reactions.		Abstract interpretation, temporal logics and theorem proving, formal languages. Information and communication theory	Computer Science	Useful Needed
	5	Combine more symbolic treatments with statistical mechanics and/or quantum mechanical models of molecular structure.	Develop the theory to become more realistic, i.e., include more chemical details like thermodynamics or realistic molecular structures and energies.					
2a ReacDiff	1	Different variants of information coding, optimized for system dynamics. Self-organization of basic information processing devices from simple elements.	Long distance interactions in chemical medium. Reaction-diffusion medium with on/off property.	New variants of nonlinear media (for example BZ reaction and surrounding artificial tissue) that can proceed in a encapsulated space (like a nerve cell), but exchange substrates and products with the neighborhood, thus allowing for sustained activity. New variants of nonlinear media that can be controlled with external factors. DNA-directed chemical reactions : with rate control via sequence	Experimental demonstration of a reaction-diffusion computer that can be switched off and next turned on with an external stimulus. Formulation of general teaching strategies for compartmentalized media with different types of interactions.	Microfluidics, LOC and other hybrid chemical/physical Technologies Optical nanoparticle labelling	5a 5b	Useful
	2	Experimental demonstration of coupled phase and RD system evolution. First evolving in vitro morphogenetic system with Turing structures.	Evolutionary optimization of evolved Turing structures Evolutionary optimization of multiphase RD	Formulation of general teaching strategies for compartmentalized media with different types of interactions. Understanding the influence of surface structures on RD systems. Scale-bridging pattern formation between molecules and macroscopic structures.	Scale-bridging pattern formation between molecules and macroscopic structures. Artificial cells exploiting RD systems	Reconfigurable, self-constructing and self-repairing systems Neural computation in artificial networks. Information encoding in cellular systems.	4f 3c	Needed
	3	Sustained operation of reaction-diffusion computer with reactants delivered and products removed. Sustainable RD system with self-repair	Coupling chemistry with mechanical properties in order to produce required outputs. Self-maintaining RD system with in-built product cleanup.	Experimental demonstration of self-repair phenomena in a computing reaction-diffusion medium. Autonomous pattern forming systems that can process information.	Experimental demonstration of self-repair phenomena in a computing reaction-diffusion medium. The integration of evolution and chemical pattern formation.	All types of simulations, especially Simulation of ChemBioIT processes and subsystems. 3D-printing control of system geometries.	7, 7a 6b	Needed
	4	Discovery of new physico-chemical phenomena that can be used for external control of reaction-diffusion medium (information input). Significant computation by RD system used in directing construction	Strategies of training that can be applied to self-organized structures composed of nonlinear elements. Programmable RD computer with external interface	3D-printing control of system geometries. A "printing" technology allowing one to generate a medium with arbitrary defined non homogeneous concentrations of reactants. Efficient techniques of reconstruction and visualization of 3D droplet structures. Electrochemical and optical control of RD systems.	Experimental demonstration of a system that can self-generate multiple copies of reaction-diffusion computers. Autonomous pattern forming systems that can process information.	Autonomous smart microparticles for distributed control of RD systems Active transport control	5d, 6a 5c	Useful
	5	Investigation on new types of nonlinear media for information processing applications. Flattened RD systems in microfluidics	Self-organized 3D computing media. Hybrid RD systems showing emergent structure					
2b Multiphase	1	Robust ChemBio-ICT component self-assembled that creates new functions Examples of new programmable self-assembly structures	Molecular self-assembly engineering design principles More general programmable self-assembly	More collaborative work between experimentalists and theorists.	Assembly of an autonomous self-reproducing protocell in the test-tube (create life from scratch)	Better understood systems chemistry and supramolecular chemistry	Systems and Supramolecular chemistry	Needed
	2	Realize a minimal self-reproducing protocell Expand "standard" self-assembly modules	Vastly expand "standard" self-assembly modules	Assembly of robust functional ChemBio-ICT components that are better / can do more / than pure ICT or ChemBio components. More focused scientific activities towards the large scientific milestones. Expansion of theoretical (e.g. exact solvable) self-assembly processes.	Assembly of robust functional ChemBio-ICT components that are better / can do more / than pure ICT or ChemBio components	Better micro and nano electronics	Better micro and nano electronics	Needed
	3	Couple metabolic processes with self-assembly	Expand coupling between metabolic processes with self-assembly	ICT controlled self-assembly. ICT-molecular energy transfer.	ICT controlled self-assembly. ICT-molecular energy transfer. Novel functionalities through ICT-molecular self-assembly structures	Better materials	Engineering/Materials	Needed
	4	Robust self-assembly of ICT and ChemBio joint components. Expand ICT-molecular self-assembly processes	Programmable ICT-molecular self-assembly processes	More exploratory activities in ICT component self-assembly and coupled ICT-molecular self-assembly.	ICT-molecular information exchange			
	5	Controlled ICT component self-assembly	Programmable ICT component self-assembly					
2c Interfaces	1	Electrocatalytic layer with full biomimetic properties	Layer as reactor for multistep chemical synthesis triggered via external stimuli	Precise control of 3D layer self assembly.	Catalytic active layer with enzyme-like properties	Optogenetics	Biology/Engineering	Needed
	2	Self renewing sensing layer for continuous in vivo monitoring	Triggering self assembled layer activity via external stimuli	Concepts for Self renewing sensor for continuous in vivo monitoring Development of external stimuli triggered chemistry for activation with high 3D resolution	Concepts for Self renewing sensor for continuous in vivo monitoring	Microfluidics	Engineering/Materials	Needed
	3	Complete mimic of the photosynthetic Z-scheme in biomimetic layersection in situ	Semi-artificial photosynthetic layers	Fully automated total synthesis of proteins Simulation to predict needed functionality to achieved a precise self assembly of 3D structures	Fully automated total synthesis of proteins	Formal models of bacterial consortia	Computer Science/Mathematics	Useful
	4	Adressability of multiple functionality via specific stimuli	Non limiting Electron transfer layers in analogy to multicenter redox enzymes		Insights into the nature of biological pattern formation	Directed evolution	Biology	Needed
	5	Synthetis of biomolecules in (electro-) catalytic layer	Electrochemical energy conversion in biomimetic layers					
2d IterChem	1	Amplification and separation combined	Switchable amplification and separation	Master the surface problems of amplification and potential separation	Programmable surfaces with modules added changing its properties	Surface chemistry	Chemistry	Needed
	2			Programmable compartments with defined inside surfaces and outside behavior	Programmable compartments with defined inside surfaces and outside behavior	Multiphase	Chemistry	Needed
3a SynthBiol	1	Standardise measurements techniques Routine gene circuit synthesis	Standardise in-vivo activity Development of complex functional materials	It is needed to make governments understand that education & science cuts are bad. Promote inter-disciplinary work (mainly in mixed labs) Better DNA synthesis capabilities.	General-purpose chassis (almost-"empty" and standard bacteria to use as chassis for circuits) Personalised medicine/drugs	Software tools and libraries High throughput screening	IT Biology	Needed
	2	Expand orthogonality modules Agreed vision of scope of field	Scale up intracellular circuits Effective clinical therapies	More hosts/chassis organisms/synthetic genomes. Mammalian-cell circuits aiming at medical applications.	Mammalian-cell circuits aiming at medical applications. Water security/desalination	DNA Synthesis Systems biology	Chem BIology/CS	Needed
	3	Improve mammalian syn. bio. Stable regulatory framework	Medical apps. based on mammalian cells Tissue engineering and regenerative medicine	Accurate computational tools Promote "computational biology" in academia (University subjects, Master, ...)	Accurate computational tools Novel crops	Standard protocols Computational modelling	Bio CS	Needed
	4	Unify in-silico representation Global adoption of standards	Bacterial chassis General public acceptance of value	More extensive databases Achieve reliable tools for information sharing among labs More refined models of metabolism	Standard robust-like biological engineering Synthetic genomes	DNA synthesis/assembly	Molecular Biology	Needed
	5	Environmental apps Established routes to market	Automate protocols Movement into mammalian cells					
3b GRNCell	1	Adaptive distributed biosensors	Practical demo of bacterial metabolic "chemical plant", made up of multiple consortia	Better real-time monitoring of genetic circuit components (interfacing and screening)	Directed tissue engineering	Formal models of bacterial consortia	CS/Maths	Needed
	2	Reliable synthesis of non-trivial, distributed logic circuits	Tissue engineering demo	Programmed pattern formation Methods for incorporating stable genomic changes into "non-standard" organisms	Programmed pattern formation	Microfluidics	Engineering/Materials	Needed
	3	Multiple cellular communication schemes in wide use, including horizontal gene transfer	Practical demo of therapeutic application of engineered consortia (eg. pathogen detection and destruction in situ)	Distributed cellular "decision making" and actuation Better understanding of fundamental processes underling pattern formation, and thus more realistic models and simulations	Distributed cellular "decision making" and actuation	Optogenetics	Biology/Engineering	Useful
	4	Better interfacing with consortia (perhaps using optogenetics)	Regular demonstration of engineered inter-kingdom communication		Insights into the nature of biological pattern formation	Directed evolution	Biology	Needed
	5		Programmed bacterial population that mimics development/differentiation in multi-cellular organisms					
3c ArtNeural	1	Understand structural plasticity of the brain and develop algorithms to explain it.	Integrate symbol systems with connectionist approaches to make a unified approach	A method to produce genuine collaboration between distantly related disciplines in a manner which is more than superficial.	The ability to exhibit general artificial intelligence, creativity, and adaptivity.			
	2	Determine whether there is copying/replication of supra-synaptic information in the brain		Radical new type of programmable information processors This requires not only the standard grant funding methodology, but a physically localised group of individuals working on a long term 10 year goal with performance related bonuses.	Radical new type of programmable information processors			

	3	Programmable R-D demonstrator	Robust, evolvable chemically controlled robot.	Development of hybrid 'hardware'/chemical information processing systems					
	4	Physically realised volume signalling systems	Robust, reconfigurable processor networks with electrical and chemical signalling	Suitable sustainable R-D systems capable of rapid pattern formation					
3d TissEng	1	Design and construction of functional sinussoidal structures	The scientific community working in this area is highly focusing on the creating functional tissue islands with that can maintain their function for reasonable time.	Surface driven control on the cellular adhesion of different cell types	Organ like models	Better theoretical models for the geometric and molecular interaction of evolving cellular networks	Theoretical Biology		Needed
	2		Common bioprinted tracheas	Constructive cell experiments, which solve biological questions like Cue for the self-organization of cellular material	Constructive cell experiments, which solve biological questions				
	3		Functional liver lobula	cell cell interaction or neuronal cell communication producing devices like Perfect scaffolding technique for multipurpose applications	Cell cell interaction or neuronal cell communication producing devices				
	4			Structuring of porous material, multilayer technology	3D multicellular, multifunctional devices implementing partial brain functions				
3e CellInfEnc	1	Understanding of genetic algorithms.	(Re)Engineering of genetic functionality.	Increased knowledge of fundamental biology (e.g. ongoing sequencing efforts)	Ability to reprogram the genome.	Experimental techniques.			Needed
	2	Understanding of proteomic signal processing.	(Re)Engineering of proteomic functionality.	A theory of proteomic circuits akin in power to the theory of electronic circuits. Developments in the theory of computation by molecular assemblies, in addition to experimental progress.	A theory of proteomic circuits akin in power to the theory of electronic circuits.	Nanotechnology.	DNA		Needed
	3	Understanding of membrane algorithms.	(Re)Engineering of membrane-driven fabrication.	Flexible, programmable, highly gain, multi-channel tagging techniques for subcellular structure, such as via DNA computing. Increased biological knowledge, including dynamical imaging techniques for subcellular structures.	Flexible, programmable, highly gain, multi-channel tagging techniques for subcellular structure, such as via DNA computing.				
4a GenCode	1	Demonstrate, in silico, the co-emergence of a general system of constructive computation and the 'genetic' programme needed by the system to construct itself.	Demonstrate, in silico, a co-emergent system that continues to generate more refined descriptions and self-constructive computations.	Achievement of the 5-year goal 1 and 10-year goal 1	Construction of a type II von Neumann machine				
	2	Demonstrate the existence of a minimal autocatalytic system that has all of the essential features of co-emergent genetics and self-construction.	Build a complex autocatalytic co-emergent genetically programmed self-constructive system capable of transitioning to dynamic states reflecting self-definitions that are increasingly information-rich.	Evolution of type II von Neumann machines Achievement of the 5-year goal 2 and 10-year goal 2	Evolution of type II von Neumann machines				
	3			Construction of general purpose type II von Neumann machines	Construction of general purpose type II von Neumann machines				
4b IVMolEvol	1	Incorporation of evolution into ongoing construction process	Evolution of a metabolic system with self-sustaining properties	Effective coupling of in vitro evolution with high throughput sequencing	First enzyme free high fidelity evolution system	Printable environments	3D printing & electronic microsystems		Needed
	2	Evolution of polymerase ribozymes	Evolution of a high fidelity DNAzyme polymerase	Better understanding got the origin of life and artificial life Integration of programmable separation technologies with evolution on chip	Better understanding got the origin of life and artificial life	Evolutionary encoding design	Evolution theory/ Biomathematics		Useful
	3	Integration of genetic and container evolution	Evolution of an artificial cell	Rapid pre-clinical production and screening of pharmaceuticals for function Integration of real-time parallel selection control (e.g. electrochemical)	Rapid pre-clinical production and screening of pharmaceuticals for function	Click chemistry of ligation	Organic synthesis		Useful
	4	Coupled reaction-diffusion controlled evolution	Spatially evolving in vitro systems	Autonomous micro scale chemical evolution processors for 10 year goal	Extension of chemical evolution to physical processes	Sensitive compositional label-free detection	Spectroscopy		Useful
	5	Evolution of information encoding	Artificial integrated evolution and translation						
4c ComInfrMat	1	Combining supramolecular hybrid systems that exhibit several of the functionalities of replication, compartmentalization, and information transfer.	Fully artificial cell that is composed of one or several hybrid materials and self-sustained	Prediction of assembly of biohybrid systems	Novel sensor technologies because of better interfacing of electronics with receptors	Prediction of body immunological response to artificial materials	Immunology		Useful
	2	DNA materials that act as drug delivery vehicle	Several artificial cell types communicating with each other and performing joint functionalities.	Stabilize and reduce immunogenicity of biohybrid structures in the body	Accelerated and improved gene synthesis for synthetic biology	Integration of polymer characterization on biomaterial synthesis chip including e.g. DLS, fluorescence & mass spectroscopy, AFM	Engineering		Useful
	3			Creating enzymes or electronic synthesis systems that can fabricate biohybrid structures	Catalytic nano-reactors for multistep catalysis				
	4			Electronic integration of synthesis and other sensing functions of bioorganic hybrids	Biodegradable electronics				
4d DevelSys	1	Quantitative insight (experimental/theoretical) concerning factors influencing the performances of evo-devo	Directed evo-devo demonstration in (synthetic) biology	Benchmark problems for evo-devo.	A creative evo-devo system exploiting unknown functions of a given bio/chem/mechano/electronic substrate.	Molecular and cellular computing for instantiation at molecular level	Roadmap 1-3		Needed
	2		Quantitative theory of evo-devo performance	Standardized experimental computing platforms for evo-devo studies: virtual environments, electronics, program evolution.		Virtual world simulation	Roadmap 7, Computer Science		Needed
	3			Standardized experimental platforms of physical artefacts for evo-devo studies: molecular systems, robotic systems, orgnic systems.		Synthetic biology	Roadmap 1, Biology / Computer Science		Useful
	4					Bioelectronics	Roadmap 8, Engineering		Needed
4e EvDesExp	1	Small molecule drug discovery campaign driven subtaintially by EDoE	All small molecule drug discovery campaigns driven substantially by EDoE	Integration of several models (binding, toxicity, ADME), into multiobjective optimization.	New level of productivity for preclinical pharmaceutical research.	Effective encoding of small molecules, databases of binding results	Chemo-informatics		needed
	2	Use of EDoE to discover effective chemistry-container combinations for protocell research	Use of EDoE to produce a fully evolvable protocell	Identification of appropriate structures and variables to be explored, encoding of this information into a genome for EDoE.	A Protocell	Set up experimental protocols to be explored via high throughput experiments, and to be genetically encoded for EDoE	MEMS		needed
	3	One significant scientific result for evolving systems, driven by EDoE	Dissemination of EDoE techniques to all evolutionary experimental contexts	Interface built for the particular evolutionary experiment (whether peptides, proteins, or DNA) to a genomic representation for EDoE	Chemical evolutionary engineering	High throughput infrastructure for chemical evolution	MEMS		needed
4f SelfRepair	1	Self-repair of silicon-chips will become a major research area	Self-repair of silicon chips will be deployed in space applications	New concepts on self-repair must be developed, especially the routing-problem of the signal-pathways	It could be learned in principle how nature managed to solve the problem of repair systems smaller and simpler than the machines to be repaired.	Surface coating	Chemistry		Needed
	2	Reconfigurability will be used to help managing complexity	Reconfigurability will become a common sub-feature of high-end electronic devices	Better insight into parallel decision making and parallel conflict management the dichotomy between programmable and autonomous must be settled, perhaps by inventing semi-programmability	Better insight into parallel decision making and parallel conflict management	Parallel computing	Computer sciences		Useful
	3	Autonomy of sensor-networks will become a major issue in research	Sensor-networks will become semi-autonomous	Perhaps some parts of the computation can already be implemented in chemistry intrinisic fault detection is a difficult task.	Perhaps some parts of the computation can already be implemented in chemistry	logic reasoning	Philosophy and mathematics		Useful
	4	Adjustable and reconfigurable sensors will become an research issue	Reconfigurable biochemical sensors will become mainstream research	The machinery to detect and repair faults should not be orders of magn. larger than the normal device					
5a LOC&Hybrid	1	Manipulate individual liquid volumes of scale 10cm and 50nm on the same device. Very small volumes to manipulate single cell/element manipulation Very large volumes to store everything necessary. (Multiscale Fine Grained)	Dedicated software translating needs into droplet manipulation on matrix (resilient, fault recovery, ...) System usable without the knowledge of the technology. (Evolvable)	Nanoliter scale fluidic handling 5 yr: Manipulate individual liquid volumes of 10cm and 50nm on the same device. Transition in size of liquid droplets. Manage the voltage locally	3D nano printing technology with combined(hybrid materials	power management	9c-e		Needed
	2	Use a 10 MPixels matrix for electrowetting (pixel size ca 200µm). Become design agnostic. (Evolvable Flexible) Use of electrochemical display technology with active CMOS-Faradaic pixels less than 10µm on cm-sized chips.	Have a feedback on the liquid volumes for parameters such as position, content, activity. Increase resilience Allow system to react when sensing. (Evolvable, Self-Constructing)	Newly autonomous, parallel MEMS/NEMS fabrication technologies nanoscale positioning tools based on self-assembly 5 yr: Use a 10 MPixels matrix for electrowetting (pixel size ca 200µm). Materials. Adaptation of current TFT technology	newly autonomous, parallel MEMS/NEMS fabrication technologies	Autonomous chemical sensor and actuator networks	5d		Needed
	3	3D ink jet printing of complex LOCs Fabrication of BioNEMS Self-powered MEMS-robots	Supramolecular self-assembling nanorobots Digestable sensors Programmable nanosensors	"active nanoparticles" "intelligent energy harvesting" 10 yr: Dedicated software translating needs into droplets manipulation on matrix (resilient, fault recovery, ...). Computer Aided Design of protocols and droplets manipulation	"active nanoparticles"	Evolutionary Processing		4	Useful
	4	Programmable nano-containers	Use a living system to generate charges for electrowetting with on-chip supply chain management. Manage resources such as energy, food, nutrients, waste, ... (Autonomous)	10 yr: Have a feedback on the liquid volumes for parameters such as position, content, activity, etc... Sensors (physical, chemical, biological) compatible with electrowetting and materials	Computation, microelectronics, materials science, biology (synthetic biology to change/add functionalities in cells/bacteria)	Programmability and programming autonomous systems	8c		Needed
	5	Removing dependencies on complex external connections (pipes, wires, …) to generate true LoC, not chip in a lab (Autonomy, compare 5d)	Electrowetting system capable of handling all kind of solvents. Full versatility towards the nature of liquids that can be handled (access to all kind of chemical processes). (Creativity, Complexity)						
5b JL&NPs	1	Use DNA & NPs to assemble electronic circuitry	Deployment of NP-self-assembly in nanoelectronics fabrication	In solution synthesis of NPs with defined properties	Novel self-assembly paradigms	Parallel particle manipulators	Physics		Useful
	2	NP based iterative chemical processing	Ongoing fabrication and deployment including NPs	Ultimate detection limit in customized molecular sensing Further developments of NP internal structure beyond Janus NPs	Ultimate detection limit in customized molecular sensing	Characterisation of NP-solution interface	Surface Science		Needed
	3	Construction of combinatorial NP-polymers	Evolution of NP polymers	Extension of robotics to the sub-micrometer domain Separation of raw NP synthesis and in situ decoration/ customisation	Extension of robotics to the sub-micrometer domain	Novel multiphase synthetic	Physical organic synthesis		Needed
	4	Rich repertoire of amplifying NP molecular sensors	Single molecule autonomous sensing with NPs	Establishment of end-user programmable NPs	Novel paradigms for artificial living systems and living technology	Quantum NP programming	Quantum physics		Useful
	5	Autonomously powered NPs	Smart NPs acting as MICREAgents						
5c Elec-kin/chem	1	Hybrid electronic chemical cell	Fully autonomous nanomorphic cell	Detailed molecular theory (involving water structure) of electrokinetic/electrochemical phenomena	Nanoionic based information processing in adaptive devices	Evolutionary optimisation	Directed evolution		Useful
	2	Nanopore directed synthesis	Nanopore integrated chemical construction systems	Programmed control of cell interactions by autonomous particles Demonstration of efficient electrochemical molecular amplification processes e.g. DNA	Programmed control of cell interactions by autonomous particles	DNA machines to modulate nanoionics	Biophysics, DNA		Useful
	3	Microscale electronic chemical agents	Medical diagnostics and drug release with MICREAgents	Fundamental understanding of nonlinear surface chemistry and phase effects Progress in system integration in nanofluidics, surface coatings and NP structuring	Fundamental understanding of nonlinear surface chemistry and phase effects	Nanoparticle design	Nanoscience		Useful
	4	Ambient powered autonomous micro scale chemical hybrids	Autonomously moving micro scale electrochemical robots	Development of bootstrapping information encoding between electrical and chemical signals	High density and improved interface to neural systems and the human brain	Multiscale simulation tools	Theory and simulation		Needed
	5	Programmable complex electrochemical coatings	Complex electrochemical construction control involving NPs						
5d AutoSenAct	1	To develop a self-reproducing autonomous lablet technology at the 100 µm scale	To establish an autonomous electronic artificial cell at the scale of 10µm	Autonomous electrical power and intermediate storage to particles without cables from chemical, photo, electrical or other sources.	Novel artificial life form and general platform for artificial life	Progress in DNA machines and DNA based self-assembly	DNA Computing		Useful
	2	To achieve electronically controlled translation of nanoscale objects on the 10µm scale	To demonstrate its electronic programmability via (a) pre-programming (b) programming during operation	New understanding of biological systems (in particular the information flows and translations in biological systems) through a second translation system (electronic-chemical). Reversible control of particle docking and undocking by means of self-assembly.	New understanding of biological systems (in particular the information flows and translations in biological systems) through a second translation system (electronic-chemical)	Progress in modeling and understanding of nanoelectrochemistry and nanoionics	Nanoionics		Needed
	3	To complete an electronic chemical cell combining simple metabolism, containment and a genetic component on an electronic active surface	To demonstrate self-assembly and self-reproduction of such a cell, in an environment containing the raw electronic component substrates	A nanoscale solution of von Neumann's universal construction automata Efficient local communication between particles via electrical signals.	A nanoscale solution of von Neumann's universal construction automata	Progress in chemical amplification and systems chemistry	Systems Chemistry		Needed
	4	To develop an optical interface to hybrid electronic artificial cells	To demonstrate useful applications of ongoing construction and environmental sensitivity in such an HECC population	Control of interactions between smart particles and bio-objects such as cells.	The basis for a new kind of neuromorphic-electronic computation combining the best of both worlds	Architectures for noisy low power circuitry and advances in low power electronics AND The achievement of protocell closure with a complex metabolism AND Progress in the evolutionary design of experiments	Low power electronics and Applied evolution		Useful
	5	To establish an interface between lablet technology and biological cells AND To develop a theory of information bootstrapping in such hybrid systems, building on evolution theory	To open up a route to sustainable personal fabrication of such entities						
5e	1	Sensors for neuropharma screening	Brain implants	Better interfacing of cellular components with electronic components	Perfect bidirectional communication	Microfluidics	Material Science		Needed

HybCellRab	2	Controlled neuronal communication between individual cells	Controlled neuronal communication between cell populations	Neuronal diodes Controlling cellular processing	Neuronal diodes	Microelectronics	Material Science	Needed
	3	Better interfacing with neuronal cells and tissue	Longterm functionality of BCI systems	Neuronal tissue engineering Designing cellular function	Neuronal tissue engineering	Optogenetics	Synthetic Biology/Engineering	Useful
	4			Improved nanoelectronic devices	Simple information processing based on neuronal circuitries	Neuroscience	Biology	Needed
5f HybInfProc	1	Development of generic platform for integration/concatenation of various molecular-scale devices	Fabrication of VLSI devices containing molecular/biosystem components	Concatenation of molecular-scale logic devices	Understanding of multiscale operation of nervous system	Development of synthetic/biomimetic neurotransmitters for interogation of neurons at the molecular level	1d	Needed
	2	Implementation of different computing approaches within molecular systems (e.g. combination of reservoir computing with molecular switches)	Development of all-molecular computing systems of high complexity	Interrogation with neurons/synapses at molecular level construction of biocompatible neurointerface operating at moleuclar level	Interrogation with neurons/synapses at molecular level	nanofluidics at single cell level	5e	Needed
	3	Development of molecular-scale interfaces with neurons and other types of cells	Molecular interfacing of animal brains with molecular electronic systems					
	4	Interfacing of molecular logic/informaton processing systems with semiconducting electronics	Integration of molecular devices with all-optical processing devices					
6a ChemRobot	1	increase range of applications	commercialisation	chemically robust vesicles with sharp phase transition	control of (bio)chemical reactions in "inaccessible" environments	3D printing with sub-micron resolution	engineering	Useful
	2	implement principles of artificial chemotaxis	autonomous locomotion	direct control over biochemical pathways in tissues and biofilms efficient chemo-mechanical coupling for locomotion	direct control over biochemical pathways in tissues and biofilms	chemical oscillator with bio-compatible components	chemistry	Needed
	3	develop reversible particle aggregation	reconfigurable swarming behaviour	self-assembly of multicellular materials switchable surfaces robust in chemically complex environments	self-assembly of multicellular materials	stimuli-responsive polymers with a sharp phase transition	chemistry	Needed
	4	implement basic programmability	fully flexible chemical programmability	embedding of complex reaction networks including excitable and oscillatory ones		massively parallel microfluidic fabrication	engineering	Useful
6b AddMenuf	1	Manufacturing of convincing combined top-down bottom-up hybrid materials (not "just" printing organs with stem cells)	Self-reproducing and self-assembling 3D printers	Basic science and technology activities closely collaborate with (marked driven) industrial development of additive manufacturing activities	Self-replicating 3D printer, initially "just" printing all its parts	Material functionalities from large scale (long range) self-assembling materials	Material science	Needed
	2	Printing with multiple materials	More universal construction - or closer to that ultimate goal	Self-replicating and self-assembling 3D printers	Self-replicating and self-assembling 3D printers	More intuitive interfaces (virtual reality) for programming additive manufacturing	Computer science / virtual reality	Needed
	3	Printing semiconductors / transistors	Printing organic electronics and structures			Novel biomaterials and organs	Synthetic biology	
	4	Printing self-assembling material	Integration of 3D printing and self-assembly					
	5	Printing structures capable of ongoing reactive structuring	3D printing as reproducible programming system for setting up self-sustaining construction systems					
6c MultiSclRob	1	Physical refill of energy, e.g. via radiation	Energy metabolism with refill from the environment	Creating autonomous, self-supporting, self-replicating, sustainable systems is a great challenge. To some extent, understanding life means not only being able to create it from scratch, but also improving, supporting, saving it, or even making it even more advanced. This can be thought of as a long-term goal of hybrid autonomous systems: connection of ICT and bio-/chemo- developments, embodied artificial evolution of soft and wet"robots, integration of material science into developmental robotics, and potentially, addressing the self-replication in autonomous systems.	Self-controlling chemical networks	Formation of vesicular/micellar/droplet structures	2b	Needed
	2	Selective take up of material from the environment	Programmable selective take up of material from the environment.	Selective transport into agent. Transport into agent must depend on agent's content (feedback). Artificial membrane channels	Artificial membrane channels	Scaffolds for efficient formation of chem. robots	3d	Useful
	3	signal transduction from environment into agent	Processing of signal, e.g. via susceptible chemical networks.	Steps towards an artificial immune system Repeatable signal transduction, real chemical sensing (not by using up some component that cannot be refilled)	Steps towards an artificial immune system	functionalized nano particles	5b	Useful
	4			Self-surveying chemical networks with susceptible sub-network		Self surveying reaction networks	6d	Needed
6d	1				high-performance bio-inspired materials for engineering applications (medical implants, prosthetic limbs, military armors, aerospace and navel technologies, machine parts, structural and civil engineering...etc)			
6e EmbodyRob	1	Making such systems more programmable	Information/control exchange between chembio and ICT	Robust programmable microscopic motility	Better programmablility of funcionalities at the microlevel			
	2	More ChemBio-ICT integration	Power exchange between ChemBio and ICT	Advances in both ICT hardware, chembio self-assembly and metabolic (power providing) processes self-replicating micro-robots	Advances in both ICT hardware, chembio self-assembly and metabolic (power providing) processes			
	3	Self-replication		Programmable chembio-ICT micro-robots				
	4	Onboard complex computing	Swarming collective intelligence and problem solving with micro chembio-ICT robots	Artificial mucles / medical repair / environmental remidiation				
	5	Initial sustainable recycling of materials	Sustainable recycling of materials					
7a SimSubSys	1	A verified simulation toolbox for subsystem engineering relevant to ongoing integrated fabrication.	Extension of toolbox to embrace all candidate including quantum technologies.	Modular interface development for multiphase simulation of subprocesses	Understanding how life channels physical information processing power to explore self-construction	Computer directed and autonomous experimentation	Extensions to Lab on a Chip Technology	Needed
	2	First simulations of ongoing fabrication systems.	A verified simulation model of evolving ongoing fabrication.	Fundamental theory of efficient stochastic simulation Autonomous identification of emergent dynamical quantities	Fundamental theory of efficient stochastic simulation	Evolutionary Design of Experiments	Experimental design	Useful
	3	Full integration of SBML-style reaction kinetics with physical multiphase equilibria.	Extension of multiphase-integration with SBML to non-equilibrium phases.	General framework for modelling emergent phenomena Automated model refinement mechanism as hierarchy : especially w.r.t. combinatorial chemical reactions	General framework for modelling emergent phenomena	World wide web database of models and simulations	Internet	Useful
	4	Computer language for the evolution of coding in ongoing fabrication systems.	Programming environment for simulation of ongoing fabrication systems.	Combination of multi-scale deterministic and event driven stochastic simulation	New ChemBioIT processes and subsystems, found and/or understood by simulation	Ground-breaking implementations of novel living technology concepts	Artificial Life	Useful
	5	Computer design of functional subsystems for ongoing fabrication	Multi-scale simulation of integrated ongoing fabrication.					
7c SymINTEvol	1	Generation of a list of industrially relevant applications beyond search for key - lock structures in pharmacology	Implementation of some show cases	Construction of a support system which does only interact with chemical system in a manner that is understood quantitatively	Artificial immune system	support system for chemical networks	2b, 3ab, 0, 4cde, 6de, 8	Needed
	2	Description and simulation of a self - surveying chemical network	Simulation supported programming of such networks	Self - surveying chemical networks Identification of chemical primitives	Self - surveying chemical networks	Chemical primitives which can used for evolved networks	1a, 1c, 3abe, 0, 4cde, 6de, 8	Needed
	3	A more lab oriented investigation of the P=BPP question with respect to real chemistry		Toolbox for the implementation of customizable chemcial networks Clarification of role/vision of ChembioIT in economical context, we need compatibility with present research schemes.	Toolbox for the implementation of customizable chemcial networks			
	4	Design of a set of chemical primitives for the construction of reaction networks	Simulation supported demonstration of programmability	Realistic picture of relation of chemical networks to abstract problems in complexity theory				
	5	Proper analysis of how simulation integrated CBT can be embedded in industrial processes	Embedding in industrial processes					
8a ITConstr	1	Design/evolve "transducers" through which coded information corresponding to elementary physical processes/operations can be communicated	Build operational transducers	5 yr: For information transfer between each pair of modes, construct means of information transfer and find modes of generality (coding)	Coded transfer of information between any two of the specified modes of controlled processing/operation (electronic, chemical, micro-fluidic)			
	2	Demonstrate controlled transfer of (coded) information between electronic, chemical and mico-fluidic modes	Build a single system able to perform a simple nano-detailed construction task and deliver the product to the environment	10 yr: [experts will have to define the necessary achievements]				
8b NatComp	1	Outline theory	Full theory	Development of theory				
	2	Diverse demonstrators designed using theory	Routinely used design and analysis approach	Validation of theory in multiple combinations of multiple substrates				
8c ProgAutonom	1	Design theory	Scalability to suitably macroscopic artefacts	Theory of "emergent programming" -- how to convert the desired properties of emergent artefacts into the required properties of micro-components	"Emergent engineering" would be a massive breakthrough			
	2			Theory of "embodied programming" -- how to incorporate physical processes/properties of the substrate in the design and analysis				
8d ArchComCon	1	Theory applied to embedded construction problem	General theory of embedded information processing and construction	Advances in stochastic computation and modelling : efficient multi-purpose platforms	New adaptive computer architectures	Intelligence foundation in adaptive neural processing	Cognitive science	Useful
	2	Optimal encoding theory for construction in specific contexts : e.g. self-assembly	Construction encoding language for general purpose encoded construction	Nanoscale computation in embedded systems Full understanding of evolutionary stability in cooperative structures	Nanoscale computation in embedded systems	Embedded computation architecture	Robotics	Useful
	3	Results on optimal architectures for programming construction	Design toolbox for construction systems	Proof of principle for technological open-ended evolution of architecture Robust implementations of real world instant ions as testable model systems	Proof of principle for technological open-ended evolution of architecture	Evolving genetic encoding	Evolution and language	Useful
	4	Evaluation of tradeoff between autonomy and programming precision ion construction	Omega machine deployment as general purpose bootstrapping tool for construction systems	Integration of conventional (e.g. 3D printing, lithographic) construction with autonomous processes	Better understanding of guiding principles in brain architecture	Biological morphogenesis theory	Biological Development	Useful
	5	Efficient implementations of a family of construction models for exploration	Results on optimal architectures for construction systems					

4. Compiled Strengths-Unknowns-Weaknesses Analysis

Area	Nr	Strengths	Unknowns	Weaknesses
1a	1	Plasticity, adaptability, changeability needs interfacial systems chemistry : not possible with Si machining	The structure of water and interfacial chemistry	Weakness is that of chemistry: a piece of novel chemistry requires long work to take next step
SysChem	2	Enabling technology for the roadmap	Attaining atomically detailed structures beyond the 5 nm scale	Lack of modularity of chemistry : each new molecule is different, with certain unpredictable properties
	3	Systematic scientific development		Chemical space harbours its own surprises (lack of programmability), although much can be done with serious simulation.
1b	1	DNA origami i) works relatively well, ii) it is amenable to automation/computational design, iii) has inspired many researchers. Essentially, one can achieve almost arbitrary shapes, and diverse dynamics with DNA or DNA devices, but not arbitrary "function".	The usage/development of synthetic DNA analogues may be required in the future or some sort of "chemical translation".	The drawback is that DNA/RNA may not be the best molecule from a "materials" point of view, Chemical functionalization is still difficult, and not everything can be done that might be desirable. Also the aqueous/salty environment is not ideal for many applications.
DNAComp	2	Demonstrable control over nano-scale self-assembly. DNA Nanomachines have an impressive array of achievements ranging from stepped movement to fabrication control and even self-replication.	"Killer applications". Scalability to large structures, and complex processes.	Another issue is "scale". It is currently not clear how one would generate large quantities of DNA devices, or very large structures, or operate DNA computing circuits very fast and without leakage/crosstalk (i.e., precision).
	3	Impressive computational performance with "seesaw gates" and strand displacement. Modular systems combining DNA processing with DNA synthesis. Proof of principle of integration with living cells/organisms. Integration with microfluidics.	Potential health/ethical/environmental implications	Still relatively few "real world" applications. Continued emphasis (in some quarters) on trying to solve computationally hard problems. Relative lack of automation
1c InorgBio	1	The special strength of this is that it potentially defines a new route to view evolution outside of biology placing emphasis on functional complexity with minimum 'templated' bit content.	The idea of using non-organic polymers for evolutionary molecular dynamics is both risky and innovative.	
2a	1	RD is a general mechanism used ubiquitously in biology. Good information processing applications of reaction-diffusion medium are highly parallel. They are an inspiration for algorithms running on classical computers.	What are the miniaturization limits of reaction-diffusion information processing? Can one have reliable information processing with hundreds of molecules? Are there efficient programming methodologies in the light of non-linear interactions?	Diffusion is a local process and thus provides interactions with nearest neighbors. For complex operations long distance interactions between active centers are required. Time and space scales are limited by molecular diffusion.
ReacDiff	2	Self-organization phenomena can be used to assembly processing devices from droplets containing active medium. RD systems allow combination with signal amplification for general computation. RD systems allow combination with signal amplification for general computation.	How to optimize information coding and relate it with chemical kinetics? How to best combine with more permanent multi-phase structure formation in artificial systems. Stability of complex structures to external perturbations.	RD computing with a typical nonlinear chemical medium is slow. For practical applications we need a faster (smaller?) medium. Isotropy in space means that information is broadcast in all directions.
	3	It is relatively easy to make 3D structures of active elements (e.g. droplets). Allows combination with genetic molecules to allow evolution. Allows combination with genetic molecules to allow evolution.	What is the optimum applications of reaction-diffusion medium for information processing? Can we build universal computer with reaction diffusion medium without Boolean coding and logic gates?	There is no on/off switch in reaction diffusion computer. At the moment it operates up to the moment all reagents are consumed.
2b	1	Bottom up approach. DNA computing & membrane computing can be implemented directly based on self-assembly.	No direct engineering approach seems available to create desired higher level functionalities	Very difficult to impose direct control - only indirect control possible via environment Labor intensive - costly
Multiphase	2	Flexibility and scalability. Directed self-assembly is down-hill theomodynamically ($\Delta G < 0$).	An emergent - or self-organized - engineering approach is necessary	Usually the systems(chemistry) becomes messy very quickly once more components are mixed
	3	Specificity (ability to target) We can make molecular programmed nanoscale to mesoscale structures/ functionalities.	Unknown how to predict general self-assembled mesoscale structures	Difficult - often impossible - to design top down -need to design bottom up. Trial and error method often necessary in design - lack of theory
2c	1	Production of chemically well defined building blocks	Precise structure of the self assembled layers	Reproducibility of the self assembly process
Interfaces	2	Construction of complex assemblies in a single or few steps	Mechanism of multiple parallel and orthogonal process in 3D layers	Impact of stochastic gene expression
	3	Possibility to introduce multiple and invidually adressable functions via specific stimuli	Ability of engineered consortia to maintain long-term homeostasis	Difficult to eliminate cross-talk between components
2d	1	controlled environment	interaction and crosstalk between parts of the system	difficult interfacing to outside world
IterChem	2	relatively easy to be integrated in small form factors	contamination of surfaces	Loss of material without amplification
3a	1	Brings together scientists from many disciplines in a strong and vibrant community	What about ethics? As the discipline evolves, the ethics issues will emerge. Future public response to potentially controversial developments.	Fashion-victim discipline. What is science? and what is not? (i.e. iGEM) Relative lack of "real world" applications
SythBiol	2	Brings standards to biology, thus turns it into a "technical science" Integration of "design thinking" into biology.	Fundamental understanding of gene circuit operation. Standards arise. But, who is to say which standard is more standard than which?	"Fast" development impedes "good" development (i.e. publish FAST, a LOT and NOW). As a basic science (hard to build apps now) the funding cuts is killing entire research systems.
	3	Endless source for biotech applications. Needs have driven significant technological developments (assembly, analysis, etc.).	Definition of what synthetic biology actually IS! Is this a boom? Or a here-to-stay approach? Introducing Syn Bio in univeristy degrees may help to regulate it.	Difficulty of mammalian synthetic biology. Lack of fundamental biological understanding
3b	1	Ability to decouple modules (encapsulation and reuse)	Degree to which mammalian cells can be engineered in populations	Narrow bandwidth of most existing communication schemes
GRNCell	2	Flexibility and scalability (different messages, with different content types)	Inter- and intra-kingdom consortia engineering? Possibilities and capabilities?	Impact of stochastic gene expression
	3	Specificity (ability to target messages at certain cells in a mixed population)	Ability of engineered consortia to maintain long-term homeostasis	Difficult to eliminate cross-talk between components
3c	1	evolvable	scalability	how to exploit higher dimensional systems
ArtNeural	2	potential for highly reconfigurable systems	practical processing speeds realisable	programmability
	3	simultaneous processing on several different spatial and temporal scales.	long-term stability	development of more complex architectures
3d	1	Creating artificial living systems is having great scope for the future biotechnology, system biology, pharmaceuticals and tissue engineering.	Molecules which guide and switch cells in a reproducible way under the control of the human constructor	Still the lack of biocompatibility of polymer material
TissEng	2	The cellular manipulation through the above mentioned approach is the only feasibility for achieving such a complexity.	Maintainance of tissue function made by artificial means	Universal scaffold and material for controlling multi cell culture
	3	Steps towards a tool box in designing 3D hybrid structures and first clinical trials		Limitation of primary human cell culture
3e CellInfEnc	1	Mathematically sound.	Applicability/feasibility.	Sometimes far from experimental realization.
4a	1	Biological paradigm is understood	Whether effective emulation of biology is possible	Biological example is very chemically restrictive and may not be easily transferable
GenCode	2	Proteins are demonstrably able to cover a huge catalytic space	Whether strictly collinear information processing is a advantage	How to set up the possibility of increasing functional complexity is not well understood
	3		Not obvious what to choose as "general mechanisms"	
4b	1	Ability to evolve solutions without detailed chemical knowledge of desired structure	Optimal encoding of information for evolutionary search	Distributed processes are subject to parasitic instability
IVMolEvol	2	Ability to be implemented in hours on laboratory timescales without cellular complications	Ability to constrain solutions for simplicity and modularity	Potential sensitivity to uncontrolled environmental conditions
	3	Generalizable to higher level (e.g. encoded) evolutionary processes	Population size and generation time limits for effective evolution	Difficult to accurately predict or program in advance
4c	1	Combinatorial material libraries from polymers are relatively easy to synthesize and automation has progressed in recent years.	How far can the synthetic robots be integrated into computational systems	Size of libraries of synthetic macromolecules is small compared to sequence space in biopolymers.
CombFnMat	2	Solid phase synthesis of unnatural sequence specific polymers allows perfect sequence control	Screening for functionality	Small molecular weights and limited backbone structures
	3	Synthetic biopolymer hybrids add significant functionality to informational biomolcular systems allowing their interfacing with devices.	General procedure of how to bridge the microscopic and macroscopic world unknown.	Replicability is limited compared to DNA and proteins.
4d	1	Can automatically generate structure and function of an artefact, given an objective function	There is no formal evo-devo theory suitable for using in an evo-devo design process	Expensive (in terms of computation and time needed)
DevelSys	2	Is creative, suprising resulting designs possible		Only simple functional structures (at the order of 10 logical elements) can be evolved.
	3	Adaptive; can be used as an adaptation mechanism after structural perturbation		Requires still a lot of manual fine tuning (e.g. of objective function and parameters)
4e	1	Generally applicable to a wide range of experimental contexts.	Time scale: to surmount engineering challenges, how much evolutionary time will be needed?	Challenge of including a priori knowledge in the evolutionary algorithm
EvDesExp	2	Scales well with technological increases in high throughput infrastructure and computational bandwidth.		Genetic encoding of spatial structure is difficult (e.g. for small molecule design, 3D printed structures).
4f	1	Can be used to test algorithms before they are implemented in the target hardware	is it possible to drastically reduce the power consumption of these devices?	Reconfigurable hardware has its own life, long learning curve required.
SelfRepair	2	Safe playing, all the side-reactions in the target hardware can be neglected.	what is creativity?	As a very abstract emulation machine it can not cope with all the dirty details of the target hardware.
	3	Allows a much better observability than in real hardware		Observability, still possible, is already limited.
5a	1	Parallel processing. Digital approach - just like computing	Reproducibility Still requires liquid to be entered by one way or another onto the device	Reliability Highly sensitive to materials handling
LOC&hybrid	2	Large scale integration capability High resolution capability Access to very small volumes	Positioning accuracy. Access to very small volumes: no real physical limitations have been observed but there might be some	Surface fouling
	3	EWOD: Feedback is possible through impedance measurement	Cost scaling with integration	Manipulation of any solvent for chemical reactions
5b	1	Allows modular separation of particle synthesis/properties from collective deployment	NPs with on-board electronic logic exploiting quantum principles possible in principle	Compatibility of conditions for synthesis and deployment
µ&NPs	2	Wide range of properties and coatings possible and programmable	Surface interaction effects in solution require further characterisation	Ability to program detailed internal structure currently limited : beyond Janus particles
	3	Bridging molecular and microscopic scales	Extension of biopolymers to quasi-bio-NPs with rich combinatorial repertoire of functions	Still not good toolsets for parallel control and manipulation of NPs (cf AFM)
5c	1	Direct interface between programmable electronics and chemistry	Attaining sufficient specificity of reaction control with voltage (need coatings)	Involves some hard to reproduce hardware parts
Elec-kin/chem	2	Scalable down to nano electrodes and nano pores and up to cms	Avoiding side reactions and electrode interaction side effects such as leakage	Complexities of surface and electrokinetic effects at molecular level
	3	Rich array of electrokinetic and reaction phenomena, including locomotion	Upgrading low voltages of autonomous power with potentials for reactions	Needs to be combined with self-assembly and kinetic chemical self-organisation

5d	1	The ability to bootstrap on top of the progress in traditional electronics and MEMS/NEMS (e.g. 3D integration)	There are some problems with the first aspect, because electronics is primarily geared to high frequency operation and parasitic currents are getting larger with increased integration, not smaller	The fact that the electronics substrate is not itself amenable to ready self-construction, although more strongly integrated organic electronics may change this
AutoSensAct	2	The ability to harness electronic computers in developing the electronic side of the artificial cell.	Most power sources only deliver low voltage, that needs to be scaled up for electrochemical control.	The complications of gaining control of electrokinetic and electrochemical processes at the microscale and the sensitivity of microelectronics to chemical interference.
	3	No need to do "chip in a lab" heavy-weight interconnections for power, control and communications	New tools for the parallel selective manipulation of labelled smart particles are required. Autonomous locomotion is possible but its efficiency and controllability in complex fluid environments unknown.	
5e	1	Progress in Neuroscience	Control over cellular function	Weak signal transfer
HybCellFab	2	Progress in Micro- & Nanotechnology	Maintain longterm neuro-electronic communication	Reliability of neuronal systems
	3			Design of neuronal signal processing
5f	1	Molecular-level miniaturization of devices	Interfacing with other devices may be difficult	Low stability and reliability, molecular-scale cross talk between devices
HybInfProc	2	Simple fabrication (synthesis instead of assembly)	Reproducibility of synthesis/assembly	Low speed
	3	Possible interfacing with neural systems on molecular level	Selectivity towards data encoded as chemical/molecular signals	Rapid degradation of complex molecular systems, neurotoxicity of molecualr/polymeric interface
6a	1	Based on principle proven by evolution -- swarming.	Technical feasibility of manufacturing scale-up.	Difficult to achieve the programmability offered by electronic devices.
ChemRobot	2	Offers functionality not achievable by silicon-based electronic and mechatronic devices.	Economics of larger-scale application.	Based on chemistry, thus may cause negative public perception.
	3	Large number of application areas (pharmaceuticals, agro, food, consumer goods, cosmetics...)	Treatment of regulatory authorities such as FDA (Food and Drugs Administration).	Unfavourable ratio between payload and capsule material.
6b	1	Open-ended design possibilities which can be shared by everybody: democratizing material production	How to combine top-down and bottom up design - huge engineering challenges	Additive manufacturing is difficult to parallelize in contrast to self-assembly and self-organization
AddManuf	2	Combine bottom up and top down manufacturing of macroscopic hybrid chembio-ICT objects/artifact with the low-level complexity of living systems	Design such that all parts can be recycled (as the parts in biological systems)	Many additive manufacturing techniques are serial, directed by a limited number of heads. As structures become more fine-grained, this must give way to less information-intense programming including self-assembly.
	3	Steps towards a tool box in designing 3D hybrid structures for tissue engineering and first clinical trials	Maintainance of tissue function made by artificial means	Still the lack of biocompatibility of polymer material. Universal scaffold and material for controlling multi cell culture
6c	1	Many agents can be produced in parallel	Range of functions that can be implemented is unknown (though cells prove a fundamentally rich range)	Engineering such systems may require evolution -> reproduction with inheritance has not yet been demonstrated on a general base
MultiScRob	2	Most systems are robust to mechanical damage		There are major concerns with respect to safety. These concerns are not only politcal but shared by insurance companies
	3	Cheap		A real metabolism (means one that takes up simple energy and material sources from the environment is not yet implemented.
6d	1	On-going development of powerful optimization algorithms such as CPPN-NEAT		Computationally expensive simulations and reality gap problems
EvoRobotics	2	Advanced and emerging fabrication technologies, especially in the area of additive manufacturing		
6e	1	Bringing the robotics concept to the micro and nanoscale.		Small scale makes it difficult to program/control functionalities
EmbodyRob	2	Programmable ChemBio-ICT robots for movement, construction and production		All weakness and problems associated with self-assemby as robots in part are self-assembled
7a	1	Can be universally applied to any process or subsystem, based on current understanding of physics and chemistry	The extent to which simulation can be simplified without loss of predictive power	Certain key processes such as predicting reaction rates are computationally often prohibitively expensive
SimSubSys	2	Strong sets of tools for analysis of modelling consistency with theoretical frameworks	Evolutionary process capitalise on initially rare events, how mach overhead is needed	Methodologies for embedding accurate simulations in larger extended systems are not yet complete
	3	Ability to integrate empirical information in coarse-grained models	Techniques for extracting emergent quantities (such as membrane enclosures) to be used in further computation.	Input information is often missing about detailed composition or boundary conditions
7b	1	Simulation can replace (or suggest) experiments, when experiments are expensive or impossible.	It is usually unknown a priori how much detail is needed to model a given phenomenon	Difficult to incorporate all relevant parameters, and fit them, without building results into the simulation.
SimDesProg	2	Approach gains momentum with ongoing decrease in computational cost.	How to manage incremental simulation model refinement most efficiently.	The inverse problem of designing system performance by simulation is hard.
7c	1	Dynamic aspects can be emulated	Interactions between parallel processes	Implementation is hard
SymINtEvol	2	Evolutionary processes can be studied over numbers of generation not always feasible in the lab	Chemistry (e.g. reaction constants) only known for homogeneous settings.	"Killer applications" such as artificial immune support systems are far away
	3	Focus on evolutionary dynamics without too much bothering about problems of implementation -> Before a technology is implemented, its potential can be explored.		In industry: Laboratory chemists have often a certain idea of what a simulation is; "chemistry as IT" - aspects are hard to convey.
8a	1	Biological paradigm can serve as a model when it is better understood	Whether effective general (coded) control of information can be achieved across different modes of constructive material processing	Understanding of the overall integration of biological paradigm of this aspect of cells is very very piecemeal; only just being looked at in Systems Biology
ITConstr	2			We do not have an example of this being done successfully at the nano-scale
8c ProgAutonom	1		Scalability	No good "design" process
8d	1	Addresses major weakness of computer science : non-robust processors	Optimal designs for encoding information in complex physical contexts	Absence of universal architectural framework for integrating construction and information processing
ArchComCon	2	Large family of material frameworks and formalisms	Efficiency considerations in stochastic contexts: e.g. next reaction inefficiencies	Lack of robustness in many models based on formal architectures like von Neumann's
	3	Able to bootstrap complexity in principle	Conditions for open-ended evolution of architectural complexity	Computational complexity of calculations in the context of massively parallel detail

5. Compiled Main Achievements by Area

Area	Nr	Main Achievements	Year	By	DS
1a SysChem	1	Self-replicating molecules	1986	v. Kiedrowski	c
	2	Chiral symmetry breaking	1994	Soai	c
	3	Partial integration of subsystems towards protocell	2008-10	J. Szostak, L. Luigi, v. Kiedrowski,	c
	4	Models of plasticity wrt to polymerization	2011-13	Wolf, Willner	d
	5	Metabolic networks	~ 2005	S. Benner	c
1b DNAComp	1	Combinatorial problem solution	1994	Adleman	d
	2	Molecular automaton	2004	Benenson	b
	3	Software packages	2003	Pierce lab	b
	4	DNA self-assembly & origami	2006	Rothemund	c
	5	DNA nanomachines	2010	Stojanovic, Winfree, Yan	c
	6	Strand displacement	2011	Yurke, Qian	b
	7	DNA computing/molecular programming	2011	Lulu Qian & E. Winfree	c
	8	DNA origami in living organism	2014	Amir	d
1c InorgBio	1	Self-assembling inorganic molecules in seconds from a state space >10120	2010	Cronin	d
	2	Inorganic replicator systems	2014	Cronin (in press)	d
	3	Flow system search engine	2012	Cronin (Nature Chemistry)	c
	4	Algorithmic programming of chemical systems	2014	Cronin (Nature Commu-unications, Nature Chem.)	c
1d ArtChem	1	Abstraction of essential processes like pattern formation and self-replication in the early days of computer science	1953	Turing, von Neumann	f
	2	Theory of chemical organization	2010	Dittrich group	b
	3	Graph based simulation system	2013	Merkle	c
	4	The idea that molecules can compute and molecular computational machines	1970s	M. Conrad and R. Laing	f
	5	Developing abstract formal calculi capturing features of chemistry	1989	e.g. Berry/Boudol	f
	6	Artificial chemistries allowing to simulate large combinatorial systems (e.g., Kauffman 1986, Fontana/Buss 1994) and to develop novel theoretical concepts like chemical organizations (Fontana/Buss 1994; Dittrich/Speroni d.F. 2007).	1994-2007	Kauffman 1986, Fontana/Buss, Dittrich/Speroni	e
	7	Development of more realistic rule-based descriptions of chemical systems (e.g., BNGL, Kapa, graph-chemistry) with the potential of automatic course-graining, e.g., through abstract interpretation	###########	J. Feret/ V. Danos (last part)	e
2a ReacDiff	1	Optical control of nonlinear chemical medium Chemical morphogenesis	1989 1953	Kuhnert,Agladze,Krinsky Turing	b f
	2	Concepts of information processing in compartmentalized excitable chemical media Evolving RD systems	1995 1991-3	Showalter,Steinbock,Toth, Yoshikawa Hogeweg, McCaskill	d d
	3	Belousov-Zhabotinsky reaction in droplets separated by organic phase with lipids or surfactants	2000	Epstein, Vanag	c
		Turing patterns experimental	1994	de Kepper	c
	4	Application of microfluidic devices in reaction-diffusion computing RD computation	2005 1995	Epstein, Herminghaus Showalter,Yoshikawa, Gorecki	c d
	5	Strategies of teaching for a medium composed of active droplets Evolving RD in multiphase systems	2012 2008	Dittrich, Gruenert, Gizynski, Gorecki McCaskill, Packard, Bedau, Rasmussen	e d
2b Multiphase	1	Passive aggregates (e.g. membranes, droplets, microemulsions). Self-replicating micelles and vesicles	<1990 1989	many groups P. Luisi, P. Walde	a d
	2	Active components (e.g. microtubules, actin, etc)	<2000	many groups	b
	3	Membrane computing	<2010	Paun, + many groups	c
	4	ChemBio-ICT component self-assembled new functions	2008-2015	e.g. projects: ECCell, MATCHIT, MICREAgents	d
	5	autonomous self-replicating protocells	current	e.g. groups of Szostak, Rasmussen, Cronin, Chen ...	e
2c Interfaces	1	Programmed pattern generator	2005	Basu	c
	2	Synchronised genetic clocks	2010	Danino	c
	3	Edge detector	2009	Tabor	c
	4	Circuit evaluation	2011	Regot	c
	5	DNA messaging	2012	Ortiz	c
2d IterChem	1	Separation compatible with reaction	2013	Tangen et al.	d
	2	Isothermal amplification compatible with separation	2014	Von Kiedrowski, Plasson, McCaskill	d
	3	Iterative amplification	2013	Minero, McCaskill	f
	4	Integrate iterative amplification and cleanup	2013	Wagler, McCaskill	f
3a SythBiol	1	Minimal cell	1999	Hutchison	c
	2	The repressilator	2000	Michael Elowitz	b
	3	Engineered gene circuits	2002	James J. Collins	b
	4	Registries of parts	2003	MIT/others	a
	5	Multicellular pattern formation	2005	Ron Weiss	b
	6	MAGE	2009	Wang	a
	7	Distributed Logic Gates	2011	Ricard Sole	b
	8	CRISPR	2013	Gaj	b
	9	Amplifying Genetic Logic Gates	2013	Drew Endy	b
	10	Synthetic yeast chromosome	2014	Boeke	d
3b GRNCell	1	Programmed pattern generator	2005	Basu	c
	2	Synchronised genetic clocks	2010	Danino	c
	3	Edge detector	2009	Tabor	c
	4	Circuit evaluation	2011	Regot	c
	5	DNA messaging	2012	Ortiz	c
3c ArtNeural	1	R-D systems for minimally cognitive tasks	2010	Husbands	e
	2	R-D systems for robot control	2003	Adamatzky	d
	3	cellular hardware implementation of R-D type dyamics	1999	P. Arena	c
	4	efficiency of volume sigbnalling for robot control	1998	Husbands	d
	5	establishment of importance of chemical signalling in neural modulation in natural systems	2004	Marder	c
3d	1	organ printing	2003	Mironov	b
	2	step towards vascularisation	2012	Bhatia	d

TissEng	3	stem cells reprogramming	2008	Yamamaka	b
	4	Clinical transplantation of a tissue-engineered airway	2008	Macchiarini	a
	5	Laser processing of advanced biomaterials	2005	Chichkov	b
	6	Fusion of methods	2013	Schober	c
4a	1	Coding self-organisation	1993	P.R. Wills	e
GenCode	2	Evolution of genetic representation	2001	Füchslin/McCaskill	e
	3	Stepwise improvement of coding	2004	Wills	e
4b	1	Evolution in vitro	1967	Sol Spiegelmann	c
IVMolEvol	2	Quasispecies	1971	Manfred Eigen	c
	3	Selex : directed evolution	1990	L. Gold, A. Ellington	b
	4	Cooperative evolution	1997	Ellinger, Ehricht and McCaskill	d
	5	Recipe encoded genes	2000	S. Brenner, Affymetrix	c
4c	1	Screening of superconducting alloys	1970	J. J. Hanak	c
	2	Screening of fluorescent properties of conjugated polymers	2002	P. H. Dixneuf	b
CombFnMat	3	Screening molecular weights of PE from catalyst library	2000	A. Herrmann	c
	4	Screening block copolymer morphologies	2001	A. Karim	b
	5	Synthesis of block copolymers by controlled radical polymerization	1997	K. Matyjaszewski	b
	6	Incorporation of single monomer in polymer chain	2012	J. F. Lutz	c
	7	Fabrication of DNA block copolymers	2006	A. Herrmann	c
	8	Enzymatic amplification of highly functionalized DNA	2004	M. Famulok	c
4d	1	Mechanisms of morphogenesis (no evo)	1952	A. Turing	e
	2	Evo-devo simulation	1986	R. Dawkins	c
DevelSys	3	Virtual evo-devo in realstic 3D virtual physical world	1991	K. Sims	d
	4	Evo-devo of function (electronics and computer programs)	2000	D. Mange /C. Ferreira	d
	5	Physical instantiation of virtually evolved artefacts by evo-devo	2000	J. Pollack / H. Lipson	d
4e	1	Algorithm formulation	2007	Poli, Packard, et.al.	e
	2	Vesicle optimization	2010	Hanczyc, Poli, Packard et. al.	d
EvDesExp	3	Protein expression protocol	2011	Caschera, Hanczyc, et. al.	b
	4	Protein design	2012	DeLucrezia, Poli, et. al.	d
	5	Molecule design	2014	Borrotti, Poli, et. al.	d
4f	1	Analog evolution in digital hardware	1996	Adrian Thompson	b
	2	Embryonics	1996	Daniel Mange	c
SelfRepair	3	Multiplexer-based cells	1998	Daniel Mange	c
	4	Computing with attractors	1988	B. A. Huberman	e
	5	Evolutionary fault repair in space applications	2001	Vigander	e
5a	1	Microfluidic large scale integration (LSI)	2002	Quake	a
	2	Continuous-Flow PCR on a Chip	1998	de Mello, Manz	c
LOC&hybrid	3	Foldable Printed Circuit Boards on Paper Substrates	2010	Whitesides	c
	4	"Lab-on-a-Foil"	2010	Zengerle	b
	5	Digital electric fields controlling LOC systems	2006	McCaskill, Tangen, Wagler	b
	1a.	First paper by B. Berge on EWOD principle	1993	B. Berge	c-d
	2a.	Demonstration of Digital Microfluidics and unit operations (UCLA, Duke, CEA) both in open and closed configuration (water/air or water/oil)	1999-2000	UCLA, Duke, CEA	c
EWOD	3a.	Understanding the phenomena and expanding the range of applications (immunoassays, PCR, enzymatic reactions, cell culture, sample preparation, magnetic beads manipulation, all-terrain droplet manipulation,...)	2000-2009	U. Toronto	b
	4a.	Display based on Electrowetting (Liquavista) / Hermetically sealed and ready-to-use lab-on- chip based on EW for PCR	2010	Liquavista, CEA	b
	5a.	Lab-on-Chip based on EW (PCB technology to be cost effective) available through NUGEN + Clinical study on NBS in the US	2011	Adv. Liquid Logic	a-b
5b	1	Use of DNA-encoded beads in protein evolution	1992	Brenner S., Affymetrix	b
	2	Magnetic beads	1976+	John Ugelstad	a
µ&NPs	3	Colloidal quantum dots	1982+	Louis Brus	a
	4	Janus NPs allowing programmable NP colloids	1985,1988+	Woo Lee, C. Casagrande	d
	5	Dynamical self-assembly, reversible release NPs	2002	Grzybowski, Whitesides	b
5c	1	Electronic DNA immobilization	1997	Heller, Herlne	a
	2	Nonlinear electrokinetics	2004	Bazant	e
Elec-kin/chem	3	Single molecule sensitive nanopores for DNA sequencing	2009	Bayley	c
	4	Electronic chemical cells	2011	McCaskill et.al.	d
	5	Microscale electronic chemical autonomous agents	2013	McCaskill et.al.	d
5d	1	Coupled active CMOS chips with natural neural cells were pioneered by Peter Fromherz as a hybrid system on an electronic dock.	1991	Peter Fromherz	c
	2	A MEMS support system for future artificial cells was first developed in the PACE project (initiated by McCaskill, Packard, Rasmussen and Bedau). Since then there has been considerable MEMS lab on a chip activity to support artificial cells – mostly along the liposome direction, e.g. vesicle guns.	2004-2008	PACE Project (coord. McCaskill, 15 groups)	d
	3	Electrochemically activated DNAzyme sensors	2009-12	I. Willner	c
AutoSensAct	4	Electronic artificial chemical cells were first researched by McCaskill's team and colleagues from other institutions in the ECCell project. There the concept of an electronic genome was developed, and electrochemically directed replication and compartmentation processes were established. The active electronic component was remote and the microelectrodes all interconnected on a macroscopic surface.	2008-2012	ECCell Project (coord. McCaskill, 6 groups)	d
	5	Imprinted surface reservoirs for uptake and release of chosen metabolites in sufficient quantities for bulk reaction control.	2010	I. Willner	c
	6	A feasibility theoretical analysis for a nanomorphic cell at the 10µm scale.	2011	Zhirnov and Calvin.	f

	7	Autonomous electronic "lablets" are being developed in the MICREAgents project. There the target is 100µm sized devices integrating electronics and chemistry (see Unconventional Computation article) and website. The distinguishing feature is autonomous control of pairwise lablet-lablet association with chemical and electronic communication that self-assembles an inner chemical space, that can function like the contents of a cell. An electronic docking surface will serve as a communication interface	2012-2015	MICREAgents Project (coord. McCaskill, 10 groups)	e
5e HybCellFab	1	Bidirectional signal transfer	1991,5	Fromherz	c
	2	Closed loop signal processing	2002	Fromherz	d
	3	Multisite recordings and stimulations	2013	Hierlemann	c
	4	Brain computing interface	2008	Pittsburg	b
	5	open loop BCI	2000	Nicolelis	d
5f HybInfProc	1	first molecular logic gate	1993	AP de Silva	b
	2	advanced molecular scale Boolean devices	2000	AP de Silva	b
	3	16-bit chemical processor	2004	K Szacilowski	c
	4	polymeric memristors/synaptic systems		E Erokhin	c
6a ChemRob	1	Autonomous movement of gel by chemical oscillations	2007	Maeda et al.	c
	2	Chemical communication between coupled cells	1980s	Marek and Dolnik	c
	3	Fabrication of multi-compartment liposomes (vesosomes)	2011	Ces	c
	4	Remote control of reaction-diffusion processes in chemical robots	2013	Stepanek et al.	c
6b AddManuf	1	Stereolithography of photocurable polymers	1984	Chuck Hull	b
	2	Metal sintering technology	1985-7	Deckard and Beamer	a
	3	Plastic extrusion technology	19,901,995	Stratsys, IMB	a
	4	Laser processing of advanced biomaterials	2005	Chichkov	c
	5	3D printing of chemicals into structures	2012	Cronin	c
6c MultiScRob	1	Self assembled multivesicles	2012	Hadorn et al.	b
	2	Moving droples based on Marangoni effect	2008	Hanczyc et al	b
	3	Catalytic Nanomotors	2010	Sen et al	
	4	Heart disease on a chip	2014	Kevin Kit Parker	
6e EmbodyRob	1	Motility in oil droplets	2007	Martin Hanczyc	b
	2	Drug delivery vehicles	1990s	many groups	b
7a SimSubSys	1	Simulation of quasi species of computed molecular evolution with RNA folding	1985-8	Fontana, McCaskill	c
	2	Simulation of spatial molecular evolution with CAs	1989	Boerljist & Hogeweg	d
	3	Simulation of cellular biochemistry : SBML	2000	CalTech	b
	4	Simulation of genetic self-assembly	2007	Füchslin, Maeke, McCaskill	e
	5	Simulations linking lipid self-organisation and chemical kinetics of protocell life-cycle evolution	2008	McCaskill, Maeke, Serra, Packard, Rasmussen	e
7b SimDesProg	1	Molecular Dynamics simulations (up to large molecular aggregates)	>1950s	Wide spread	a
	2	Density functional theory. Car-Parrinello MD (quantum) extending Born-Oppenheimer MD	1985 2000 2012	Car & Parrinello D. Marx IBM CPMD	b
	3	(Molecular) lattice gases (up to mesoscale) & lattice Boltzmann	1990s	Many groups	b
	4	DPD simulations (up to mesoscale) Bonded and multipolar DPD	Early 2000s	Many groups	b
	5	Mass-action reaction kinetics Stochastic kinetics Gillespie simulations	Classic 1966, 1977	Wide spread Darvey et.al., Gillespie Many groups	a
	6	Multiphase kinetics and Protocell simulations	2000s	Rasmussen,FellermannSole, Jiang et al.	e
	7	Whole cell simulation (Mycoplasma Genetalium)	2012	Covert et. al.	e
	8	Automatic extraction of dynamical invariants from kinetics	2013	H. Lipson	d
7c SymINtEvol	1	DoE using GA	2007	Poli et al	b
	2	Computational power of compliant systems	2012	Hauser, Helmut	c
	3	MATCHIT calculus	2013	Fellermann, Harold	e
	4	Chemical networks and the P = BPP question	2013	Doty David (based on eg. Nisam and Widgerson 1994)	f
	5	MEMS/NEMS simulations	several	John A. Pelesko	a
8a ITConstr	1	Unravelling the genetic code and protein translation	1961	Nirenberg et al	a
	2	Proof of principle of evolution of genetic coding	2001	Wills, Füchslin, McCaskill	c
	3	Evolution of language in simple artefacts	1997	Steels	d
	4	MICREAgents	2013	McCaskill et. al.	f
	5	EVINCE proposal on nanochains	2013	McCaskill et.al.	f
8b Nat Comp	1	Position paper on heterotic computing	2012	S. Stepney et.al.	f
8c Prog Auton	1	DNA tiling	1998	Winfree, Jonoska, etc	c
	2	In materio computing	2002	J. Miller, downing	e
8d ArchComCo	1	Self-reproducing automata	1949	von Neumann	e
	2	Physical molecular evolution	1971	M. Eigen	b
	3	Cellular morphogenesis	2002	P. Hogeweg	d
	4	Genetic Self-assembly	2006	J. McCaskill	e
	5	Evolutionary emergence of translation	2003	Füchslin, Wills, McCaskill	e

*DS : Development Status. See P 29 for definitions of levels a-f.

6. History and development of the C^{hem}B^{io}IT Roadmap

Although we stand at the beginning of this road-mapping endeavor, completed in draft form in June 2014, it has grown from a number of related initiatives in Europe. It has roots in the seminal works of John von Neumann on universal construction and Alan Turing on chemical morphogenesis (1948-1953), Evolutionary Algorithms dating back to the work of John Holland, Ingo Rechenberg and others, Evolutionary Molecular Biotechnology (1980-1995), the Natural, DNA & Membrane Computing initiatives of MOLCONET (1995-2002), the EU FET Complex Systems proactive initiative in FP6 (2004-2008, especially the PACE project), the COST initiative in Systems Chemistry (2006-2011), and more directly the contributions of several of us to an EU FET Consultation Workshop (2008), on the subject of "Designing alternative bio-inspired ICTs". We quote below from this report[2], in which the emergence of C^{hem}B^{io}IT is described as a "significant and sustainable field". C^{hem}B^{io}IT expands radically on existing proactive challenges such as Nano-scale ICT devices and systems, Pervasive adaptation, Bio-ICT convergence and Embodied Intelligence.

Following these developments, the focus sharpened to be on gaining generic programmable control of evolvable chemical synthetic processes across scales. Areas such as organic computing and self-organizing systems, as well as areas such as molecular computing have already been identified and challenges formulated, for example in the FET Complex Systems and Bio-ICT convergence pro-active initiatives. The particular focus on self- assembly and evolvability of novel chemical components has not been covered by these calls and will bring together more technically oriented scientists with their more theoretical counterparts to allow a technological breakthrough towards a mainstream evolvable and self-repairing technology for ICT. In this regard, there is an increasing community of scientists and companies involved.

As uncovered in the 2008 report, some of the possible disciplines that could contribute to such an effort were: "...Existing communities in evolutionary and genetic algorithms and programming, evolvable hardware, reconfigurable computing, nano-bionics, DNA and Membrane computing and self-organizing systems need to be brought together with materials scientists developing simpler self-assembling materials for increased information density and with molecular biologists who understand natural processes of assembling complex information processing structures." Topics that we then considered to be within the scope of C^{hem}B^{io}IT included:

- Programmable information chemistry
- Molecular, membrane and reaction-diffusion computing
- Molecular machines
- Protocells and synthetic cells
- Synthetic biology
- Artificial neurons
- Nano-bio-info interfaces
- Evolvable hardware
- Hybrid systems (incl. microfluidics, MEMS, 3D printing)
- Energy and material sustainability

These and other areas can potentially contribute to the overarching roadmap objective listed above, which places the main focus on the two areas

- Integration of information processing with (bio-)chemical production
- Unconventional computing and construction substrates and associated computational and/or mathematical studies.

The roadmap leadership team then derived a more structured list of 10 areas for initial consideration in the roadmap. These areas were also subject to review by the proposed panel of experts. A panel workshop held at the Ruhr Universität Bochum on 31st January 2013 finalized this structure of the roadmap and determined the remaining structure of the panel of experts. Some additional experts were consulted on topics not otherwise well covered. Finally a template for contributions was drafted and set up on Adobe Forms Central for input and the roadmap compiled in 2014, with time for an iteration with panelists with their valuable feedback.

7. Survey on ChemBioIT Summary

The data from the survey on C^hem^B^io^IT is available in summary form on the COBRA website at
http://www.cobra-project.eu/uploads/2/0/8/9/20895162/d1_4_website.pdf

While the survey represented a broad intellectual coverage of research interests in the C^hem^B^io^IT area, the roadmap is a specifically focused study of the main initiative towards the common roadmap goal of integrating computation and construction at multiple scales. The figure illustrates the more eclectic and academic range of interests uncovered by the survey.

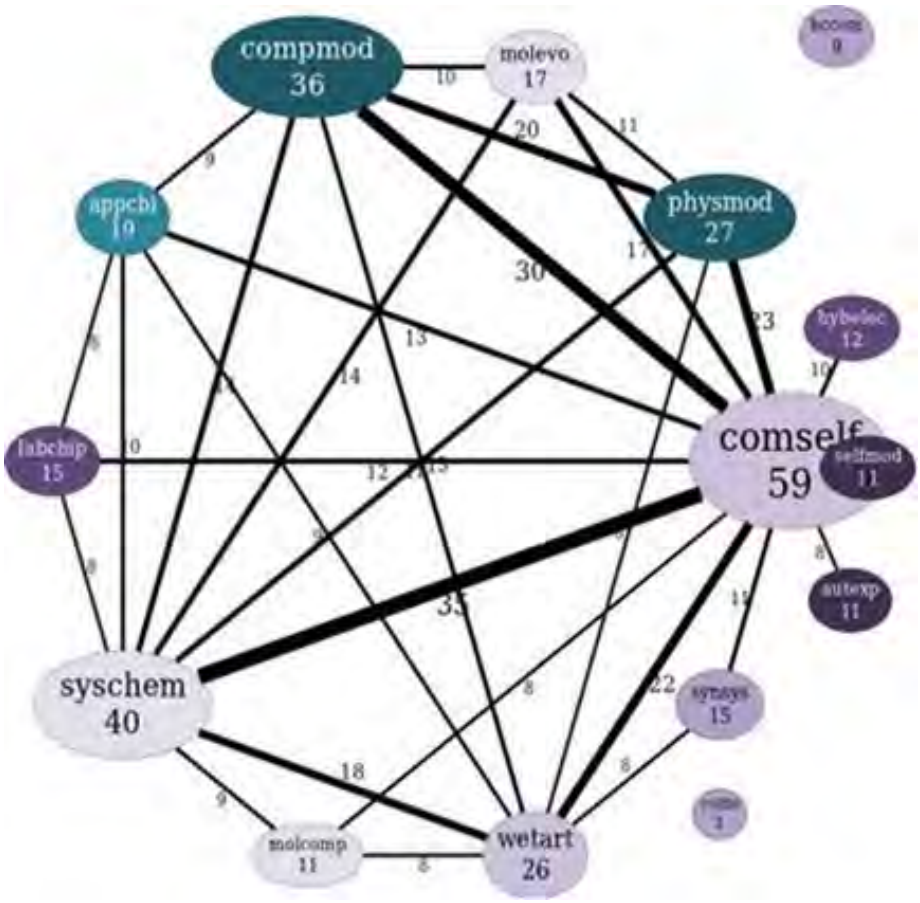


Fig. A7.1 Cross-correlations between the expertise of all 85 respondents to the C^hem^B^io^IT survey in 2012.