European Cooperation in the field of Scientific and Technical Research - COST -

Secretariat

Brussels, 30 November 2007

COST 248/07

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding (MoU) for the implementation of a European Concerted Research Action designated as COST Action CM0703:Systems Chemistry

Delegations will find attached the Memorandum of Understanding for COST Action CM0703 as approved by the COST Committee of Senior Officials (CSO) at its 169th meeting on 15 - 16 November 2007.

MEMORANDUM OF UNDERSTANDING
for the implementation of a European Concerted Research Action
designated as

COST Action CM0703

SYSTEMS CHEMISTRY

The Parties to this Memorandum of Understanding, declaring their common intention to participate in the concerted Action referred to above and described in the Technical Annex to the Memorandum, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 299/06 "Rules and Procedures for Implementing COST Actions" (or in any new document amending or replacing it), the contents of which the Parties are fully aware of.

2. The main objective of the Action is, through investigating autocatalytic reaction systems within supramolecular, prebiotic and other fields of chemistry, to develop methods for their integration into dynamic supersystems.

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at 72 million EUR in 2007 prices.

4. The Memorandum of Understanding will take effect on being accepted by at least five Parties.

5. The Memorandum of Understanding will remain in force for a period of four years calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of Chapter V of the document referred to in Point 1 above.

A. ABSTRACT AND KEYWORDS

Systems chemistry is the joint effort of prebiotic and supramolecular chemistry assisted by computer science from theoretical chemistry, biology, and complex systems research to tackle dynamic supersystem integration including at least one autocatalytic subsystem. It is the bottom-up pendant of systems biology towards synthetic biology. The origin of life is seen as a major stimulus to organize research but the field is open for chemistries of limited prebiotic plausibility. Subsystems may be classified as genetic, metabolic, or compartiment-building. Pairwise integration into higher organized supersystems is expected to yield the knowledge enabling later the triple integration into minimal chemical cells. The integration approach will necessarily link to the question of asymmetric autocatalysis and chiral symmetry breaking, while the key challenge is to find the roots of Darwinian evolvability in chemical systems. 5 workgroups will define a trigonal bipyramid, where the axis theory to asymmetry is surrounded by 3 areas of integration.

Keywords: Autocatalysis, self-replication, self-reproduction, supramolecular chemistry, prebiotic chemistry

B. BACKGROUND

B.1 General background

Why systems chemistry?

Autocatalysis – the catalysis of a reaction by a reaction product – belongs to those phenomena in chemistry which albeit well known, are usually considered as a curiosity in the chemical laboratory. On the other hand, autocatalysis, feedback, and control are elementary principles without which biological systems and networks could not exist. Learning the language of these networks from a systems dynamics point of view is the subject of the emergent field of “systems biology”. Reconstructing the dynamic complexity of the living is the subject of another emergent field, called “synthetic biology”. Its major goal is to create a minimal form of cellular life in the sense of a top-down approach, viz. starting at a given biological cell and then cutting down its complexity to arrive – finally – at a minimum set of genes in a network that is “just alive” under the extreme heterotrophic laboratory conditions.

This COST Action understands “systems chemistry” as a bottom-up complement of “systems biology” toward “synthetic biology”. Synthesis and design is per se a chemical endeavor – but the goal of synthesis in chemistry is usually a chemical structure. On the other hand, the design and synthesis of complex dynamic behavior in chemical systems is as much in its infant shoes as the reduction and reconstruction approach of synthetic biology. It is a challenge for the chemistry of the 21st century. Biology by itself cannot answer the questions how life originated on this planet from simpler chemical precursor systems, how life may have originated elsewhere in the universe, or, whether new forms of life-like systems can be synthesized de novo in the laboratory.

Systems chemistry seeks to combine the "classical" knowledge of chemistry, viz. the language of molecules, their structures, their reactions and interactions, together with the "classical" knowledge derived from existing forms of life. One component of this approach, acting both as a translator and abstractor between these languages comes from the fields of theoretical biology and complex systems research; the other key component comes from a chemistry that is the offspring of both supramolecular and prebiotic chemistry, and adds a new dimension that has not been sufficiently addressed so far. Over the past decades more and more chemists have learned to design and implement simple self-replicating and self-reproducing systems and today we even have the first examples on the issue of chiral symmetry breaking in autocatalytic reactions. What is missing here is a kind of generalization of "synthetic methods" based on the principles of autocatalysis, supramolecular self-organization, molecular information processing, and moreover, applicable in the range from small molecules via nano- to mesosystems.

Why a COST Action in Systems Chemistry?

COST D27 on "Prebiotic Chemistry and Early Evolution" created the fundament for cooperative European research dedicated to the question of the origin of life. It became a success story within COST which clearly helped to develop the European research area in this field. The Action had 6 workgroups focusing on RNA chemistry and in vitro evolution, metabolic chemistry connected to the generation of peptides, structural and dynamic issues of chiral symmetry breaking, self-reproduction of vesicles, functionalization of liposomes, and theoretical aspects of evolution in replicator networks. COST D27 terminated on February 27, 2007. A COST Action is needed for the development of systems chemistry because the field is in its "nascent" stage and needs exactly the instruments COST can offer: Annual meetings, WG meetings, and STSMs trigger the exchange of "nascent knowledge" and know-how better and more flexibly than alternatives in other funding areas. A COST Action is the proper tool to "seed" European scientific cooperation in a broader perspective. Once the field starts to flourish, groups of researchers may well feel invited to go for joint project-based funding. This COST Action aims at such seeding in a similar way as the preceding Action D27 did. It differs from D27 with respect to the point that systems chemistry is not limited to the origin-of-life problem. The origin and synthesis of life is more seen as a stimulus to the art of developing coupled autocatalytic reaction systems and not as a restriction to potential approaches that are not plausible in the historic context of prebiotic chemistry. Thus this Action will be both, more open towards unforeseeable approaches and at the same time more focused on the issue of autocatalytic reaction coupling than D27 was.

B.2 Current state of knowledge

At the international level it can be seen that "synthetic biology" develops to become a strong attractor. Following the announcement of Craig Venter in Nov. 2002 that he is going for the "minimal cell" after the Human Genome Project, numerous groups with a background in biology have started their own projects here. At the EU-level synthetic biology is funded within FP6's NEST initiative. Synthetic biology can be understood as a top-down approach starting from "systems biology" as a knowledge platform. "Systems chemistry" is viewed as the bottom-up pendant of systems biology towards synthetic biology. Scope and vision of systems chemistry were defined during a discussion workshop following "Chembiogenesis 2005", the midterm evaluation meeting of COST D27 in Venice (see Angew. Chem. 2005). Research into the direction of a chemical protocell was launched as an integrated project "Programmable Artificial Cell Evolution"/PACE within FP6's IST/FET programme, briefly followed by the "Los Alamos Protocell Project" funded by the US department of energy, and a third similar endeavour at the Komaba campus in Tokyo. Meanwhile, further activities are being developed

by the Chellnet team in Britain. What is common among all of these “bottom-up” activities is that they have a center in information science and dynamic modelling. Theoretical models, such as Kauffman’s “autonomous agent”, Ganti’s “chemoton theory”, and Rasmussen’s “Los Alamos bug” seek to guide experimental work in chemistry. This is a fruitful stimulus for chemistry indeed, but what is often forgotten here is that “real chemistry” very often – or even routinely – behaves not exactly as clean and “programmable” as the models want to have. Luckily, over the last years this has created some awareness among information scientists that chemistry is not just a piece of utilizable technology but a fascinating real science with real challenges. If chemists were able to “synthesize” a given complex autocatalytic information-processing reaction network, to integrate dynamic subsystems into supersystems, and to teach such systems to evolve in the Darwinian sense, chemistry were a new science. Systems chemistry is meant as the ground platform to make such things happen in the future. The broadness of possible approaches calls for a new COST Action.

B.3 Reasons for the Action

The reason for this Action is a gap of knowledge with respect to general recepies to generate chemically coupled autocatalytic systems. The main **objective** for systems chemistry is to develop the art of autocatalytic synthesis and the integration of catalytic and autocatalytic subsystems into dynamic supersystems. The "holy grail" (long term!) for systems chemistry is the creation of a chemical supersystem which for the first time shows the issue of evolvability in the Darwinian sense. There are good starting points in Europe. Research in chemical self-replicating systems has laid the ground for systems chemistry and links prebiotic with supramolecular chemistry. Research in dynamic combinatorial libraries, a field developed in the area of supramolecular chemistry, has interfaces here. Research in vesicle self-reproduction, in asymmetric autocatalysis and chiral symmetry breaking and the quest for “organo-autocatalysis” are further ingredients for systems chemistry. The interface with theoretical biology has been successfully developed in COST D27 and needs further strengthening. Research in theoretical chemistry may fruitfully contribute here as well. All of these fields are strongly connected to genuine research in Europe and many even originated here. The **expected results** from a concerted coming together of the above fields within systems chemistry are a deeper understanding of autocatalytic reaction networks in chemistry, a better insight how to “translate” the stimulus from the origin of life problem into fundamentally new pieces of chemistry, and perhaps a first chemical knowledge platform, which could allow the systematic construction of “living” chemical supersystems in the future. The **means** to achieve this goal is to start from well-established “isolated” autocatalytic systems such as self-replicating templates, self-reproducing vesicles, the Formose-reaction, the Soai-reaction etc. and to set up chemistries allowing a cross-talk with the autocatalytic core and its integration into higher organized systems. This in turn needs bringing together the expertise from various areas of chemistry.

One may speculate whether or not the Large Hadron Collider at CERN would have ever been ready to be launched without George Gamow’s “big bang hypothesis”. Regardless whether or not the quark gluon plasma will ever be much closer than today, the fascination of the public radiated by the question of the origin of the universe contributes to public awareness that physics is a grande science. It were most desirable for chemistry today if it could accept to “live” with such a big problem like physics does. Clearly, the origin of life, viz. the big bang of biology belongs to the same category of problems as the origin of the universe does. It is a challenge and a chance for European chemistry to strengthen its public appreciation as a grande science.

It is presumably too early to speculate about possible economic benefits of systems chemistry, but its value for the future of industrial synthesis may be enormous. For example, the formose reaction, discovered 1.5 centuries ago by Butlerow, is both discussed as highly relevant for the origin of life and a potential way to produce complex sugars from simple formaldehyde on the industrial scale. It is an autocatalytic reaction that usually leads to a whole diversity of sugars – a rich mixture of tetroses to heptuloses including all possible stereoisomers. If this reaction could be steered to make alpha-D-glucose or any other sugar selectively, "reprogrammed" to make alpha-L-glucose and D-glyceraldehyde tomorrow, and D-talose the next day, nobody will deny that such a supersystem would have a bright economic future. All that is needed could be just a piece of systems chemistry waiting to be discovered.

B.4 Complementarity with other research programmes

Interest in systems chemistry at the European level is documented by the abovementioned research activities funded by FP6-IST/FET's project on "Programmable Artificial Cell Evolution", the newly founded "European Center for Living Technology"/ECLT in Venice, FP7-IST/FET call on "Bio-ICT-convergence", and FP6's NEST call on "synthetic biology". While in the former three structures the research focus is in information science, the latter primarily addresses molecular biology as its focus. This COST Action aims to join and to link prebiotic and supramolecular research with the abovementioned activities while setting the focus in chemistry.

C. OBJECTIVES AND BENEFITS

C.1 Main/primary objectives

The main objective of the Action is through investigating autocatalytic reaction systems within supramolecular, prebiotic, and other fields of chemistry to develop methods for their integration into dynamic supersystems.

C.2 Secondary objectives

It is important to see the main objective in the context of three long-term scientific goals:

1. To understand the transition from the non-living to the living state of matter as the chemical roots leading to the evolvability of matter in the Darwinian sense.

2. To find the chemical roots leading to the complex dynamic interplay of subsystems in a living cell.

3. To understand, at which level of the transition from the non-living to the living the generation of homochirality could be an issue.

The rationale behind these goals is:

(1) Origin of life research today is in the situation that there is no other scientific alternative to the Darwinian way of explaining how complex forms of life emerged from simpler ones. Methods for directed evolution of proteins and RNA molecules work so well, because they are based on the products of biological evolution: Polymerases in the case of RNA-molecules and a whole translation machinery in the case of proteins. The fact, that directed evolution can be employed to breed RNA-molecules and proteins with almost any desired property does not give any clues how molecular evolution came into existence. There is a huge gap of knowledge to fill in the future. For example, enzyme free self-replication of nucleic acids works only with short templates. Short templates have neither sufficient geno- nor phenotype that evolution could tinker with to create something interesting. What is the minimal complexity in a reaction network embedding self-replication to demonstrate the chemical evolution of biological evolvability – at least in principle? How can one teach longer strands having sufficient geno- and phenotypic capacity to self-replicate as easily as shorter ones? What are the fundamental recipes to overcome product inhibition causing a limitation of evolvability of such systems? How can one deal with the zoo of side-reactions that are knocked out in the design of present-day self-replicating systems? The gap of knowledge is not only at the level of experimentation but also at the level of evolutionary theory for such systems.

(2) The origin of Darwinian evolvability is one of the central challenges. The other, equally challenging frontier is the origin of a sufficiently complex chemically organized system embodying a minimal living, viz. self-containing, self-sustaining and self-reproducing entity. All natural life forms are based on cells as the unit of life. The distinction between a unit of life and a unit of evolution may be made for present-day life, it is however questionable whether any reasonable definition on the origin of life can be made without equating the living state of matter with an evolvable state of matter. If so, the task is to find answers what sets of molecular structures, reactions and interactions are required to arrive, finally, at a system that fulfills both, the criterion of minimal life and minimal evolvability. The transition from limited to unlimited heredity may however be a later issue of research dealing with life's origin.

(3) Some researchers see biomolecular homochirality as the result of biological evolution. Others have stressed that the existence of racemates in the beginning even kills the start of evolution in its chemical roots due to what is described as "enantiomeric cross-inhibition" in the literature. With the reaction discovered by Soai we have now firm experimental evidence that chemical self-replication can proceed with chiral symmetry breaking, viz. the spontaneous generation and amplification of molecular homochirality. A generalization of the Soai reaction and the translation of its principle (2nd order autocatalysis) into other classes of (potentially prebiotic) reactions is awaited and a huge challenge.

Secondary objectives include:

- to discover new autocatalytic reaction systems within supramolecular, prebiotic, organic, inorganic, biomolecular chemistry (at least one in the first year, two in the second, four in the third, and eight in the last year)
- to develop organic replicators, viz. supramolecular reaction systems in which templates instruct the synthesis of autocatalytic copies (at least one per year)

- to develop organoautocatalysts based on the screening of Aldol, Mannich, and other CC and CX-bond formation reactions [at least one per year]
- to arrive at asymmetric autocatalysis and chiral symmetry breaking involving organic replicators and organoautocatalysts [at least one new class till the Action ends]
- to screen conditions allowing autocatalytic reactions based on "small" starting materials such as formaldehyde, hydrogen cyanide, cyanoacetylene, and formamide [till midterm]
- to arrive at experimental and theoretical energy profiles for organic replicators and organoautocatalysts by the conjunction of temperature-dependant kinetic studies, dynamic modelling, model testing, and parameter extraction on one side and high level QM and QD computation on the other [at least two full profiles till midterm evaluation]
- to develop new methods for kinetic data mining of complex autocatalytic reaction systems monitored by high-field NMR combining kinetic NMR titration with diffusion ordered spectroscopy [till midterm evaluation]
- to study autocatalytic networks of biomolecular replicators based on oligonucleotides and/or peptides seeking their integration into dynamic supersystems [1st supersystem till midterm]
- to investigate minimal models of translation and encoded synthesis by a suitable coupling of autocatalytic pathways between self-replicating peptides and oligonucleotides [till the end of the Action]
- to investigate oligonucleotide self-replication at the surface of minerals aiming to implement the chromatographized replicator model [to be achieved between midterm evaluation till the end of the Action]
- to arrive at the first demonstration of minimal Darwinian selection in a network of oligonucleotides and/or peptides with competes for common resources [to be achieved from midterm evaluation till the Action’s end]
- to investigate the coupling of the formose reaction to a phase transfer autocatalysis employing suitable precursor lipids [midterm till end]
- to couple the self-reproduction of micelles and liposomes to the generation of peptides and oligonucleotides at the surface of compartments [midterm till end]
- to investigate spatiotemporal self-organization in the Soai reaction [to be achieved till midterm evaluation]
- to arrive at new theoretical models and new potential schemes for dynamic supersystem construction [till midterm]
- to arrive at new theoretical models for chiral symmetry breaking [till midterm]

C.3 How will the objectives be achieved?

Achieving the objectives needs a conjunction of prebiotic and supramolecular chemistry in Europe. There is a delicate but scientifically unfruitful gap between the communities one has to be aware about. This gap is expressed by two opinions that calls for a new policy.

Opinion A: Research in the origin-of-life within the field of prebiotic chemistry has so far suffered from an over-estimation of plausibility considerations, e.g. geochemical constraints, in the definition of its topic. This self-restriction and self-limitation is today even enforced, when prebiotic chemistry becomes embedded into astrobiological research. The conditions on the early earth are far from being known with certainty. Even more, the historical dimension of the problem is out of the scope of chemical reasoning.

Opinion B: Research in supramolecular chemistry interested in the origin of live has so far suffered from a frequent misplacement of terms that have a distinct meaning in biology and were later found to be at the wrong level of language.

Policy: Systems Chemistry should benefit from the stimulation arising from the origin-of-life problem but not restrict its scope to the latter. Considerations of “prebiotic plausibility” should not allow to limit the development of chemistry that is new and interesting from a chemical perspective. Aqueous and non-aqueous organic, inorganic, and biomolecular chemistry is within its scope. Theoretical biology is seen as a necessary ingredient to develop a better understanding of phenomena discovered in autocatalytic systems with respect to their meaning in biology. Complex systems research is seen as helpful to support the Action by the development of proper simulation tools for the treatment of spatiotemporal phenomena and phenomena involving compartimentation, nucleation and growth of nano- to mesoscale compartments. Computational chemistry is expected to be helpful for the better design of chemical self-replicating systems and organo-autocatalysts including asymmetric ones.

C.4 Benefits of the Action

A successful conjunction of the two abovementioned communities from supramolecular and prebiotic chemistry together with theoretical sciences within a COST Action on Systems Chemistry is expected to bring at least a widening and cross-appreciation of horizons, a methodological complementation, and a fruitful joint understanding of leading targets for future chemistry. In the best case, research concerted by the stimulation from the origin-of-life problem could lead to new paradigms for industrial production. The vision of production plants, which are chemically reprogrammable to synthesize a given set of target compounds by harvesting second-order autocatalytic networks look remote today indeed. The vision will become closer however once chemistry begins to understand that selection means iterated selectivity, Darwinian chemistry builds upon exponential dynamics, while frozen accidents building up from second or higher order autocatalytic dynamics enables to synthesize homochiral compounds from prochiral precursors and more generally "programmable" targets from a network that has the targets in its repertoire, even if there is no difference between the free energy of alternatives at the kinetic or thermodynamic level. Autocatalytic reaction systems are slow explosions in solution. Learning to tame, to control, and finally to design such supersystems will enable a similar transition in chemistry as physics underwent in the process of converting the nuclear bomb into a nuclear power plant. Unlike physics in the latter process, systems chemistry will deal with a subject that is much more innocent and harmless than nuclear energy. Nevertheless, ethical considerations should not be excluded here. If seeded properly via a COST Action, the field which has more roots in

Europe than elsewhere (most of the pioneering contributions came from European researchers) has excellent chances to grow as an entity which is clearly identifiable with European research.

C.5 Target groups/end users

Disseminated results from the Action are expected to reach the following groups of scientists:

- supramolecular chemists
- prebiotic chemists
- chemists involved in organocatalysis research
- theoretical biologists and chemists interested in the origin of life
- computer scientists involved in the simulation of complex systems
- researchers in astrobiology
- chemical engineers interested in taming autocatalytic processes

It is foreseeable that the press and the general public will become interested in systems chemistry. It is hoped that European policy makers will become informed of the chance which comes with systems chemistry for the development of the European Research Area.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The following line of reasoning is seen as a general recipe for dynamic supersystem construction based on autocatalytic subsystems:

(1) Small organic molecules such as formaldehyde, hydrogen cyanide, cyanoacetylence and others but also sugars, lipids, nucleotides, amino acids, and even the polymers from the latter are seen as starting materials.

(2) Known "biorelevant/biomimetic" autocatalytic reactions are conceived as starting processes to develop chemistry around:

- minimal self replicating systems based on oligonucleotide, peptides and organic templates
- self reproducing vesicles from lipid precursors
- the formose reaction
- the Soai-reaction
- an asymmetric organoautocatalyst very recently discovered by Tsogoeva in Germany

(3) Chemoton theory teaches the importance of cycle stoichiometry for any kind of complex dynamically coupled machinery up to the cell. Its general idea is viewed as a starting concept.

(4) Coupling needs to be encoded both structurally and dynamically. Structural coupling means conjugation. Possible cases are:

- Conjugates of oligo/nucleotides and amino acids/peptides
- Conjugates of sugars and amino acids/peptides
- Conjugates of sugars and lipids
- Conjugates of amino acids/peptides and lipids
- Conjugates of oligo/nucleotides and lipids

(5) Dynamic coupling means reactive conjugates where one entity is acting e.g. as a leaving or a scavanging group enabling:

- to make peptides in translation models
- to screen for a minimal replicase in a peptide library
- to polymerize amino acids or nucleotides at the surface of liposomes
- to liberate as many lipids as there are bonds between residuals in the product
- potentially to solve translocation problems across a bilayer using a chemical gradient.
- potentially to "harvest" the formose reaction

(6) The level one goal for systems chemistry is any kind of two-subsystem integration.

- metabolic and genetic
- metabolic and containment
- genetic and containment

Note that the term "genetic" may just be information and function in one class of molecules or a "generalized hypercycle" in the sense that there is some means to split "genetic" into information and function creating a 2-subsystem integration on its own.

Integration is achieved by finding ways of:

- making lipids and peptides in one process
- making lipids and oligonucleotides in one process
- making oligonucleotides and peptides (e.g. by self-replication coupled to translation in the sense of metathesis reaction)

including:

- making lipids from sugars and lipid precursors
- making lipids from nucleotides and lipid precursors

- making lipids from amino acids and lipid precursors

and furthermore including:

- advice from theoretical biology
- tools from complex systems research
- much chemical experimentation that is not foreseeable here.

(7) The level two goal is a broadening of the understanding of the importance of microscopic heterogeneity expressed in lipid phases and their transition or natural phases and their transition such as

- surfaces and minerals
- aqueous phases including ice
- phases modulated by chemstate variables such as temerature. and pressure

on the functioning and integration of subsystems.

(8) The level three goal is an application of "general rules" for coupled systems construction.

The Action will recognize its roots in COST D27, but will give special emphasis that the overarching theme are autocatalytic reaction systems and their integration into coupled supersystems.

D.2 Scientific work plan – methods and means

Based on the outline of the scientific programme described above, an Action with 5 workgroup seems desirable.

Workgroup 1: Integration of genetic and metabolic subsystems. A genetic subsystem may be based on a replicatable biomolecular template or anything that can store and express chemical information and is suitable for amplification by feedback. Chemical information is meant in a broader sense and may be based on constitution (such as a template sequence), configuration, or even long living conformation. Lateral information systems, the utilization of linear, cyclic, or branched template molecules, self-replicating systems, primitive translation systems, template directed reactions, informational nanosystems and even compositional information systems are all within the scope here. A metabolic subsystem delivers suitable building blocks and energy driving the process of interest such as template self-replication or template translation. Energy may be provided by chemical, electrochemical or photochemical sources. The transformation of chemicals leading to the building blocks may be simple or complex. The formose reaction is prototypic for a metabolic subsystem – it is an autocatalytic version of a dynamic combinatorial library in modern language. Other dynamic libraries coupled to templating are within the scope here – but it is clearly desirable to work out how at least one subsystem becomes autocatalytic, either in an autonomous or in an iterative-stepwise fashion. The integration quest should keep in mind that the origin of Darwinian evolvability is the key challenge.

Workgroup 2: Integration of genetic and compartimentization subsystems. Again, compartments may be organic or inorganic, based on lipid micelles and vesicles, inorganic membranes or just surfaces of inorganic or organic matter such as nanoparticles. The prototype of such an integration is a self-replicating template which in the course of template formation generates its own growing compartment – a concept that waits to become reality. The growth of the compartment may be due to the liberation of a lipid leaving group, a leaving group catalyzing the transformation of a lipid precursor to a lipid, a pH change causing precipitation of a suitable material, or, a simple spreading on the surface of minerals defining a quasispecies of self-replicating templates as a surface clone. Coupling self-replication to a chromatographic process would also be in the scope here.

Workgroup 3: Integration of metabolic and compartimentalization subsystems. The prototype for such integration was the coupling of an prebiotic reaction network such as the formose reaction, or the polymerization of HCN to the precipitation of a mineral which catalyzes the reaction network. Another suitable chemistry was the reaction of one or more products from such networks with a precursor lipid to create lipids exhibiting micellar catalysis to these networks. Very sharp – explosion like – autocatalytic growth profiles are expected for such couplings as the formose reaction itself is an autocatalytic process and many precipitation and micellization reactions are known to proceed as nucleation-growth or autocatalytic reactions. If such systems proceed indeed with hyperbolic growth dynamics there is the prospect of "harvesting" the formose reaction, viz by seeding and growing a narrower set of sugars than generated otherwise. What should come in here as well is flow and microflow technology developed in chemical engineering. The screening of suitable systems may be batchwise – but the detailed kinetic analysis will benefit from flow setups.

Workgroup 4: Chiral symmetry breaking and the quest for asymmetric autocatalysis in various reaction systems. Work included here could be devoted to a deeper understanding of the Soai reaction and its spatiotemporal aspects. It is particularly challenging to search for cases of asymmetric autocatalysis and chiral symmetry breaking in the emerging field of organocatalysis but research on supramolecular self-replicating systems may also find a home here. Work on structural aspects of chiral symmetry breaking processes based on crystallisation and other phase transitions should also come in here. A special interest could be the issue of asymmetric autocatalysis in any of the before mentioned subsystems. Chiral symmetry breaking in self-replicating systems, self-reproducing vesicles or in metabolic networks is in any case an indication of a "strong autocatalytic" component and may even be used as a tool-like dynamic signature for the screening process.

Workgroup 5: Integration of theoretical chemistry, theoretical biology and complex systems (physics) research towards systems chemistry. All groups of researchers have a background in computer science but so far have no interface for a crosstalk in Europe. Theoretical chemistry and in particular QM and QD methods can significantly help in the design of organic replicators, metabolic key steps, and many other aspects of systems design at the chemistry side. At the biology side dynamic modelling based on ODE solving and stochastic simulations may significantly help to identify networks with interesting dynamic signatures. Care should be taken for a good connection with experimental research. Another important direction is the development of theoretical tools for experimental data analysis giving selectively a narrower mixture of sugars.

E. ORGANISATION

E.1 Coordination and organisation

Action Constitution Stage

The Action management and organisation will follow the following lines:

1. Given the fact that the design of autocatalytic reaction systems and their integration into dynamic supersystems are true challenges for today's chemistry, the Action will need, both, a maximum of creative input from European scientists calling for sufficient openness in the beginning, and a maximum of concertedness and focus on leading implementation schemes in the course of the Action. To account for this balance a part of the Action's members will result from a specific call to individual research groups while another part will result from an open call targeted at younger researchers in Europe interested in the theme of the Action.

2. The constitutional MC meeting will take place as early as possible (month 1) and will appoint the Action's chair-persons and the Working Group leaders. Action Chair, Action Vice and WG leaders will form a Steering Group which will jointly decide on applications for WG participation. Decisions will be based on meritocratic principles and research excellence while taking care for thematic complementarity, focus of the application, the issue of participation of early-stage researchers, and gender issues. Decisions will be on behalf of the MC. The Steering Group will aim to arrive at an Action where the majority of MC members are participating in WGs.

3. Following the recruitment phase (6 months), the Action will have its kickoff meeting. The MC will expand the Steering Group and elect a STSM manager who will be in charge for the processing of STSM applications, a dissemination manager who will be in charge for the Action's website, the communication of the Action's major results to the COST website in Brussels and the contact to the press, and an younger Action member which will represent the voice of the early-stage researcher in the Action. The local organizer for the first annual meeting will be elected. Action members will introduce their background and their prospected work. In addition, opportunities will be given for talks on "new ideas". The Steering Group will organize a final round table discussion whose results will be documented and later allow to refine the scope, vision, and scientific programme of the Action and its WGs. This refinement is expected to contribute to the best scientific success in the case of a "nascent" field that is far from having developed an established perspective and thus strongly depends on creative input.

4. The WGs will have their constitutional meetings up to 3 months after the kickoff meeting.

At the end of the constitution phase the Action will have the following management structure:

(A) A Management Committee in accordance with the COST rules and in good relationship with the COST Science Officer and the Domain Committee.

(B) A Steering Group elected from the MC including:

- Action Chair
- Action Vice
- Head of WG1
- Head of WG2
- Head of WG3
- Head of WG4
- Head of WG5
- STSM Manager
- Dissemination Manager
- Speaker for the early-stage researchers of the Action

Note that it is possible that less than 10 persons will constitute the Steering Group due to the pooling of coordination functions.

Action Operation Stage

1. The first regular annual meeting is scheduled for month 16 after Action start. It will open with an introductory talk of the Action Chair summarizing the results of the refinement process and introducing the refined scope, vision, and objectives of the Action. The WG leaders will then introduce the structure, objectives, and the refined scientific workplan. Details on the workplan will be introduced by WG members. Slots will be reserved for a number of external experts whose vision is seen as a stimulus for the development of the Action. Organizational issues will be addressed by a brief meeting of the Steering Group before the scientific programme, while the MC meeting will be scheduled after the scientific programme.

2. The Steering Group will jointly identify topics where an exchange of expertise is crucial for the scientific development of the Action. These topics may be found, both, on an intra-WG level, and on an inter-WG level. As a result of this process, specific recommendations for STSM applications will be communicated by the STSM manager.

3. Topics identified to be relevant to a larger number of Action members will be selected for Training Schools. Such topics are likely to include either methodological ones (e.g. on kinetic data extraction by simulation and fitting) or conceptual ones (e.g. on theories of dynamic supersystem construction such as the Chemoton theory). Both, theoretical, and targeted

experimental Training Schools (e.g. on liposome techniques) are foreseeable and will be organized for year 1 and year 2 of the Action.

4. The Steering Group will jointly work out the annual budgeting. On the average, 40% of the funds will be assigned for the annual meetings of the Action, 30% for the meetings of the Working Groups, and 30% for STSMs and Training Schools.

5. The Steering Group will be also in charge of the reports to be written before the midterm and the final evaluation meetings.

6. The dissemination manager will update the webpage on a routine base - at least every month.

7. The speaker of early-stage researchers will set up a web-based discussion forum, open to all who are involved in the Action but devoted to scientific problem solving and mutual help in the Action. Part of the discussion will be openly available on the web after solicitation by the dissemination manager.

8. The Action will promote and support the launch of National and Europe-wide research activities in the field of systems chemistry. The Action understands itself as a seeding structure aiming both, to involve and to assist individual Action members as well as external experts in the issue of fundraising.

9. A major deliverable will be a book on systems chemistry to be published till the midterm evaluation report.

10. Expected milestones include:

    - A number of high-level (Nature/Science) papers from members of the Action on the issue of systems chemistry till the Action's midterm evaluation.

    - The creation of Europe-wide public awareness that systems chemistry is a new frontier for chemical research interfacing with biology and physics (till the midterm evaluation).

    - The launch of a number of research funding programmes till the end of the Action.

E.2 Working Groups

Each Working Group of the Action will consist of six to eight research groups. Activities will be coordinated by the WG head who will be in charge of the following:

1. Shaping the Working Group and its interactions so that the focus of research stays bound to the general perspective of systems chemistry and the theme of collaborative research distilled in the constitution phase of the Action.

2. Setting and monitoring the milestones of the Working Group.

3. Dissemination of the Working Group's structure and achievements on a Working Group webpage linked to the Action's webpage. Notification of the Action's Dissemination Manager when papers in leading journals have been published.

4. Organisation of Working Group meetings: Each Working Group is expected to meet at least once a year.

5. Organisation of intra- and inter-WG STSMs in cooperation with the Action's STSM Manager.

6. Writing a meeting report after each Working Group meeting and disseminating it on the Worging Group webpage.

7. Writing the WG part of the midterm and final evaluation report.

8. Active and proactive participation in the steering group.

E.3 Liaison and interaction with other research programmes

The Action will include topics which might be interesting for research undergoing in COST Action D40 (Innovative Catalysis - New Processes and Selectivities) and COST Action D31 (Organizing Non-Covalent Chemical Systems with Selected Functions). Communication with D31 and D40 will be established as soon as the Action becomes operative. Suitable forms of exchange include the invitation of members of these Actions for "Inter-Action" lectures or the organization of a joint workshop, e.g. in the issue of organocatalysis and organo-autocatalysis, or on dynamic combinatorial libraries linking with autocatalytic reactions.

Research funded in FP6's IST-FET programme include the Integrated Project PACE ("Programmable Artificial Cell Evolution"). Members of PACE will be invited to participate in upcoming meetings of this Action. The same holds for a number of projects funded within FP6's NEST programme in "Synthetic Biology". FP7's programme on "Bio-ICT" may include research on protocells. The Action will proactively contact the groups of researchers involved as soon as details and projects are announced by the European Commission.

The Action will strengthen its interaction with the newly founded European Center for Living Technology (ECLT) in Venice which hosted the "systems chemistry workshop" following the midterm evaluation meeting of COST D27.

E.4 Gender balance and involvement of early-stage researchers

This COST Action will respect an appropriate gender balance in all its activities and the Management Committee will place this as a standard item on all its MC agendas. The Action will also be committed to considerably involve early-stage researchers. This item will also be placed as a standard item on all MC agendas. The creation of the function of a speaker for early-stage researcher within the Steering Group reflects this issue on the organizational layer.

F. TIMETABLE

The timescale of the Action will be 4 years and 3 months.

Year 1: Kickoff meeting bundled with Steering Group meeting and MC meeting (M7), Training School 1 (M8), WG meetings (M8-M9), STSMs (M8-M12).

Year 2: Annual meeting bundled with Steering Group meeting and MC meeting (M4), Training School 2 (M5), WG meetings(M8-M9), STSMs (M1-M12).

Year 3: Midterm evaluation meeting bundled with Steering Group meeting and MC meeting (M4), WG meetings (M8-M9), STSMs (M1-M12)

Year4: Annual meeting bundled with Steering Group meeting and MC meeting (M4), WG meetings (M8-M9), STSMs (M1-M12). Final evaluation meeting and final MC meeting in the first quarter of year 5.

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: AT,BE,DK,FR,DE,GR,HU,IL,IT,NL,ES,CH,UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 72 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

H. DISSEMINATION PLAN

H.1 Who?

Target A: Researchers in chemistry, biology, physics, and information science interested in autocatalysis, nonlinear processes, self-organizing networks, and the origin of life. In particular, researchers from:

- supramolecular chemistry
- prebiotic chemistry
- organocatalysis and green chemistry
- synthetic biology and systems biology
- theoretical biology
- astrobiology
- robotics and artificial life

- nanotechnology
- chemical industy interested to tame and utilize autocatalytic processes

Target B: European level policy makers and Government policy makers in charge of organizing

- the foresighting of research
- the profiling and thematic issue finding within the EU framework programmes and National research and technology programmes
- the development of new research and technology programmes

Target C: The general public

H.2 What?

(1) All target audiences will find an Action webpage which is routinely updated by the Action's dissemination manager. It will contain information on:

- "What is systems chemistry?". It is planned to utilize video clips from a workshop on systems chemistry which defined the scope and vision of the field.
- "Why do we need systems chemistry?". A vision of a future chemical industry which is based on the harvesting of autocatalytic processes that are conceived as relevant for the origin of life.
- "Where are we heading for?". A description of the Action’s objectives in non-technical language.
- "Research". A graphical and brief non-technical description of ongoing work with links to the WG homepages describing the work in more details.
- "Recent highlites/News". A Blog-type dissemination of the Action’s achievements (leading papers on systems chemistry in high level journals, start of activities funded by other sources but seeded by the Action’s spirit, highlights from meetings, highly successful STSMs).
- "Calendar". A routinely updated schedule of meetings and STSMs linked to the meeting homepage and the lab in which the STSM will take place.
- "Forum". An open discussion forum on systems chemistry.
- "Member Login". Non public information such as unpublished manuscripts, white papers, draft reports, and other interim working materials.

(2) Target A will be addressed by the standard means of scientific communication:

- Articles in peer-reviewed journals
- Invited or contributed overview and review articles
- Book chapters

- Plenary, keynote, invited or contributed lectures on international, European or national conferences, symposia and workshops
- Talks given at institute seminars
- Reports disseminated via the Action's or Working Group webpages

(3) Target B will be addressed by proposals:

- Individual research grant applications
- Joint proposals aiming to establish new lines of research funding for projects in systems chemistry at the European level

(4) Target C will be addressed via the public media:

- Articles in science magazines
- Newspaper articles
- TV science shows
- Radio interviews

H.3 How?

1. Each Action member will be obliged to acknowledge COST funding, if a peer-reviewed paper is published in the broader context of systems chemistry.
2. Each Action member will mention and briefly describe the Action if he gives a lecture or talk anywhere outside the Action.
3. The COST and Action's logo and URL will routinely appear on the acknowledgement slide or on any poster shown.
4. Scientists belonging to Target A will be informed about the Action's Annual and Working Group meetings via roundmail and dissemination of posters announcing the event.
5. A number of leading scientists from outside the Action will be invited to present keynote or invited lectures.
6. Each Action member who is invited to contribute to a TV science show, or a TV or radio interview, or to write a general overview article in a journal addressing the general public interested in science will announce that his or her work is embedded in a COST Action on Systems Chemistry.
7. The Action will proactively contact the press, once a breakthrough result has been achieved that is freshly published in a high-level journal.

8. The Action aims to "shoot goals" in top-level journals such as Nature and Science, whenever possible. This is seen as the most efficient way to promote a nascent field like Systems Chemistry.

9. Action's achievements of the latter category will be understood as a signal for a proactive contact of the Steering Group to Target B.

10. The refinement of the Action’s objectives as a result of self-evaluation and external evaluation (midterm) will be published on the Action’s website.