



## ***Systems Chemistry***

European Center of Living Technology  
Venice International University

October 3-4, 2005

Scope & vision  
Draft Programme

Organizer:  
Günter von Kiedrowski  
RUB

## **Scope**

At the beginning of the 21st century biology has matured to become a leading science in the sense that it generates questions, frontiers and challenges to many different fields. But in spite of the formidable success of the Human Genome Project, biology itself has not been able so far to answer the most fundamental question concerning the origin of its subject. Biologists today have a wealth of information dealing with the parts making up a living system. The nature of this knowledge does however not allow to draw any good conclusion how life originated on this planet from simpler chemical precursor systems, or, how life may have originated elsewhere in the universe, or, whether new forms of life can be synthesized *de novo* in the laboratory. I feel that a new of treatment is required that needs 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 key component of this approach, acting both as a translator and abstractor between these languages should come from the fields of theoretical biology and complex systems research; the other key component should come 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 seems to be missing here is a kind of generalization of "synthetic methods" based on the principles of supramolecular self-organization, autocatalysis, molecular information processing, and moreover, ranging to be applicable from small molecules via nano- to mesosystems. Let **Systems chemistry** be the name of a field, in which chemists, theoretical biologists, and complex systems researcher interact to find the chemical roots of biological organization.

## **Vision**

***The quest is for general recipes to generate chemically coupled autocatalytic systems.*** This approach complements the emerging field of "synthetic biology". Whereas the latter aims at the utilisation of intracellular regulatory networks as biological building blocks to construct synthetic cells, the former aims to find the chemical roots of such regulation in non-evolved systems. "Protocells", "chemotons" and "minimal cells" are just different words for the same issue of research that may be biology-driven as a top-down approach or chemistry-driven as a bottom-up approach. In any case, the disassembly and reconstruction approach of synthetic biology means the existence of biological building blocks as the products of biological evolution. Even if synthetic biology will be able to generate a more primitive form of cellular life this does not necessarily

answer the question how such thing could emerge when starting from scratch. Unfortunately, the same fundamental problem underlays our current vision that directed evolution will help to reconstruct a preceding biochemistry such as the RNA world. Finding a set of self-replicating RNA molecules that cooperate in a vesicle to constitute a minimal cell will be a remarkable scientific achievement of the 21th century. Nevertheless, one will stay puzzled by the question of how such thing could have developed in the absence of evolved "tools" such as polymerases.

***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 and self-sustaining entity.*** All life as we know today is 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 fullfills 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.

***Life today is based on proteins and nucleic acids, lipids, sugars, amino acids and other molecular building blocks, where almost all molecular components are in a homochiral, viz. enantiomerically pure state.*** The creation of minimal life and evolvability is thus necessarily connected to the question at which level in the transition from small molecules to minimal living and evolving systems the amplification of homochirality took place. From today's perspective it seems very likely that this process might be deeply linked to the emergence of self-replication and was even indistinguishable from the latter in the beginning. Whether an autocatalytic transformation of racemizing building blocks, a mutual annihilation of autocatalytic products of opposite handedness, or a process in which chiral templating proceeds as a higher order autocatalytic process played a leading role, or whether the building blocks were racemic (like in the formose reaction) or prochiral is an open question to which chemistry must find more answers in the future.

***A primary problem here is that we even don't know the repertoire of organic molecules delivered from space or endogeneous sources and what was the initial set of chemical reactions that started the long transformation from space molecules to the first living systems. So long as this question is not fully answered by astrobiological research, any "primitive" organic or inorganic chemicals may be employed in the design and exploration of chemical systems that hopefully express dynamic signatures of the living.*** The good news is that research in autocatalytic systems currently gains much

attention in various areas of chemistry and that the acceptance to work with "complex mixtures" of molecules has increased since the advent of combinatorial chemistry. What is still a challenge for present day chemistry is to filter out the signal of self-organisation in the noise of lots of side reactions. Gaining chemical control to a whole network of reactions having an autocatalytic "core" at a low level of information content but otherwise just producing "diversity", viz. a rich mixture of constitutional and stereoisomers, is clearly a challenge. Being able, for example, to "steer" the formose reaction to produce ribose selectively instead of a diversity of other sugars could be a major breakthrough, because it would change our picture about the plausibility of the RNA world hypothesis almost instantaneously. All what is needed could be a selective consumption of ribose by a coupled (autocatalytic) process that does not anymore allow the breakdown of the ribose skeleton once it is "protected" at the level of the autocatalytic product. Lipid chemistry has a rich potential for establishing such "secondary" autocatalytic reactions due to the rich supramolecular chemistry induced by phase transitions at the nano- and mesoscale. Coupling lipid and self-replicating template chemistry could be another field of research here.

***Generally, the art of synthesizing coupled autocatalytic systems points to the future of chemical research inspired by the origin-of-life problem. Coupling will necessarily involve not only one class of molecules but at least two.*** So not only nucleotides or peptides or sugars or lipids but nucleotides AND peptides, nucleotides AND lipids, sugars AND peptides, peptides AND lipids, to name only a few possible combinations here. The exploration of couplings between an autocatalytic core like the formose-reaction, a self-reproducing micelle, or, a self-replicating template does not necessarily require that the set of reactions "talking with the core" are autocatalytic by themselves, viz. constituting an independently running autocatalytic cycle. Theory gives the insight that any reaction triggered by the core autocatalyst e.g. in the sense of heterocatalysis will also cause multiplication and growth of those compounds generated due to the presence of the autocatalyst. Thus the outcome of such coupling manifests in a stoichiometric relationship between the number of "core autocatalyst's" and the number of molecules coming up in the "periphery" of the reaction network. If the whole process is now selectively generating a specific set of molecules, different from the mixture in the absence of coupling, informational "harvesting" takes place. As self-replication can be defined as autocatalysis PLUS information transfer, selecting specific products from an autocatalytic network means self-replication. Of course, templating is one of the best proven ways for establishing a mechanism for information transfer but the term "template" may have a much broader meaning in the future than it had in the past. The same extrapolation may be foreseeable to the issues of evolvability and "cellular compartmentation".

## **Goals**

Goal (1) of the workshop is to conjunct a selection of leading researchers addressing the problems described above. The workshop will benefit from the fact that the European Action COST D27 "Prebiotic Chemistry and Early Evolution" will have its midterm evaluation conference ("Chembio-genesis 2005") prior to the workshop in Venice. Systems Chemistry is partly addressed by activities within the European Integrated Project "Programmable Artificial Cell Evolution" (PACE), the US Department of Energy funded "Los Alamos Protocell Assembly Project" (PA), and the Japanese Project on Complex Systems located at the Komaba campus in Tokyo. The workshop aims to create a link between COST, PACE, PA and Komaba-activities while adding the important issue of chiral symmetry breaking.

Goal (2) of the workshop is to arrive by discussion and brainstorming at a jointly agreeable definition for a field, which deals with the problems sketched in the scope & vision, has its focus in experimental studies between chemistry, biology, and physics and includes adjacent theoretical disciplines, such as theoretical biology, to benefit from valuable ideas, concepts, theories, and methods developed here and to stimulate theoretical studies more closely connected to experimental research.

Goal (3) of the workshop is to break down the vision into a number of implementable pieces of chemistry that may lead to new lines of research, carried out either individually or collaboratively.

Goal (4) of the workshop is to distill a general line of ideas that may later enable to explore funding opportunities at the EU or international level. The action COST D27 is expected to terminate in February 2007 and "Systems Chemistry" may be the direction of an offspring action. Other opportunities are foreseen either at the level of the seventh framework programme or at the level of international programmes. A possible overlap with activities in the context of "astrobiology" need also to be discussed.

Goal (5) of the workshop is to set the base for a later compilation of articles to be published as a book. It is understood that no writing obligation exists.

## **Style**

We will have an average of 30 minutes for each participant, so the optimal style of the workshop is to have 20 minutes for the "bulleting" of major results or the presentation of findings not covered at Chembio-genesis and 10 minutes for discussion and brainstorming. Those who didn't talk at

Chemiogenesis may choose to have a 25 + 5 min combo instead. While Chemiogenesis 2005 has a conventional agenda, Systems Chemistry should be more flexible to adopt to the development of the discussion. Thus participants may decide to split their time into smaller units presenting their work not as one large chunk but as several smaller pieces. With respect to the freedom of speech we should agree to have a Gordon style meeting – but we may all benefit from the workshop later if we put the two days on video, burn it onto DVDs, and give access to this material to all participants. Any material that may come out from the workshop will have the status of confidential information.

To enable a “dynamic agenda” all participants are expected to bring their notebook to Systems Chemistry.

## ***Themes***

### ***Day 1:***

Templating  
Self-Replication  
Chiral Symmetry Breaking

### ***Day 2:***

Theory  
Subsystem Integration  
The Los Alamos Bug  
Chemotons

Due to the fact that some participants have to leave earlier, a strict separation of thematic issues will not be possible.

## ***Participants***

Mark Bedeau, Venice  
Donna Blackmond, London  
Timoteo Carletti, Venice  
Albert Eschenmoser, La Jolla (to be confirmed)  
Ben Feringa, Groningen  
Reza Ghadiri, La Jolla  
Martin Hanczyc, Venice

Ludovic Jullien, Paris  
Günter von Kiedrowski, Bochum  
Meir Lahav, Rehovot  
Doron Lancet, Rehovot  
Pier-Luigi Luisi, Rome (to be confirmed)  
Peter Nielsen, Copenhagen  
Norman Packard, Venice  
Irene Poli, Venice  
Steen Rasmussen, Los Alamos  
Mauro Santos, Barcelona  
Peter Schuster, Vienna  
Kenso Soai, Tokyo  
Peter Strazewski, Lyon  
Tadashi Sugawara, Tokyo  
Eors Szathmáry, Budapest  
Peter Walde, Zürich  
Some unforeseeable guests

## ***Draft Programme***

MONDAY, OCTOBER 3

Morning session: Self-replication & systems chemistry  
chaired by Irene Poli, ECLT Venice

- 09:00 Irene Poli, Venice: Opening of the workshop
- 09:05 Günter von Kiedrowski, Bochum:  
Introduction and agenda refinement
- 09:30 Albert Eschenmoser, La Jolla/Zurich
- 10:00 Reza Ghadiri, La Jolla
- 10:30 Coffee break
- 11:00 Peter Nielsen, Copenhagen
- 11:30 Peter Strazewski, Lyon
- 12:00 General discussion
- 12:30-15:00 Lunch

Afternoon session: Chirality & systems chemistry  
chaired by Norman Packard, ECLT Venice

- 15:00 Kenso Soai, Tokyo
- 15:30 Donna Blackmond, London
- 16:00 Meir Lahav, Rehovot
- 16:30 Coffee break
- 17:00 Ben Feringa, Groningen
- 17:30 Tadashi Sugawara, Tokyo
- 18:00 General discussion

**TUESDAY, OCTOBER 4**

Morning session: Protocell theory & systems chemistry  
chaired by Mark Bedeau, Venice

09:00 Steen Rasmussen, Los Alamos

09:30 Eors Szathmary, Budapest

10:00 Doron Lancet, Rehovot

10:30 Coffee break

11:00 Peter Schuster, Vienna

11:30 Mauro Santos, Barcelona

12:00 General discussion

12:30-15:00 Lunch

Afternoon session: Protocell experiments & systems chemistry  
chaired by Günter von Kiedrowski, Bochum

15:00 Pier Luigi Luisi, Rome

15:30 Ludovic Jullien, Paris

16:00 Peter Walde, Zürich

16:30 Coffee break

17:00 Martin Hanczyc, Venice

17:30 Timoteo Carletti, Venice

18:00 General discussion

Participants are kindly asked to provide (a) preliminary title/s of their contribution/s for "systems chemistry" in the course of Chembiogenesis 2005. Deadline is Friday, 30.09.2005, after the end of the sessions.