Czech Chemical Society Symposium Series

3

CMST COST Action CM1304

Conference SysChem 2016

Valtice May 5-12 2016

Book of Abstracts

Ročník 14 - Czech Chemical Society Symposium Series 14 (3) 99 - 126 (2016)
ISSN 2336-7202 http://www.ccsss.cz

SysChem 2016

8.-12. 5. 2016

Valtice Chateau (CZ)

Abstract Book edited by
Radmila Řápková, Pavel Drašar

COST is supported by the EU Framework Programme Horizon 2020.

CMST COST Action CM1304
Emergence and Evolution of Complex Chemical Systems

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Complex chemical systems have a huge potential for delivering new applications in areas ranging from materials science (in the short term) to medicine (in the long term). Complex systems are also highly relevant to fundamental questions such as the origin of life. Research on complex chemical systems has developed in parallel in three poorly connected communities working on supramolecular chemistry, far-from-equilibrium systems and the origin of life, respectively. This proposal aims to establish Europe as a world-leader in the emerging area of complex chemical systems, by bringing together these research fields. Main objectives are to develop far-from-equilibrium self-assembly and self-replicating systems, self-assembling and reproducing compartments, and the use of information-rich molecules in these contexts. The approach to these subjects is inherently multidisciplinary and will only be possible by combining the expertise of different theoretical and experimental research groups around Europe.

There are twenty-three EU participating countries and one COST International Partner Country.
Action website: www.systemschemistry.com/cm1304 .

Valtice Castle 2016 Conference is its 4th official meeting (Brussels 2013, Donostia 2014, Kerkade 2015).
It is organised in collaboration with the Czech Chemical Society

1. Establish the methodology for self-assembly far from equilibrium (Working Group 1).
Traditionally, self-assembly is about obtaining the thermodynamic product of a given system. However, by operating self-assembly in far-from-equilibrium systems it should be possible to create new properties that are not achievable under thermodynamic control, such as new self-assembled states that do not correspond to the thermodynamic product and stable spatial and temporal inhomogeneity. Attaining this goal will require a joint effort from the supramolecular and far-from-equilibrium communities.

2. Develop a new class of materials that are self-synthesizing, responsive and potentially self-repairing (Working Group 2).
This should be achievable by combining the autocatalytic systems explored by the origin-of-life community with the self-assembly principles of supramolecular chemistry. This may lead to, for example, new self-assembled materials for molecular electronics and self-assembled gels for tissue culture.

3. Develop synthetic self-replicating systems capable of undergoing Darwinian evolution (Working Group 2).
The approach to such systems relies on operating the replicating molecules created by the origin-of-life researchers under far-from-equilibrium conditions. Success here constitutes an important step towards the development of synthetic life. Approach to this goal will require the input from researchers from the origin-of-life and the far-from-equilibrium communities.

4. Develop methodology for compartmentalization of chemical systems and achieve a direct coupling between chemical reactions, energy harvesting and transport and membrane dynamics (Working Group 3).
The development of chemical systems of ever increasing complexity brings with it the need to confine these in space, which protects the systems from the environment and keeps the components together. Yet, in order to be able to interface several different confined systems they need to be separated by semi-permeable barriers with controllable size, stability and permeability. This research requires the involvement of the origin-of-life and supramolecular chemistry communities.

5. Develop synthetic, information-rich molecules or assemblies that have the potential of being replicated in a purely chemical system (Working Group 4).
The incorporation of information-rich molecules is particularly relevant, since advanced functional behavior of complex chemical systems will require increasingly elaborate chemical instructions that need to be carried in the constituent molecules.

ABSTRACTS

TOWARDS EFFICIENT PREBIOTIC ACTIVATION PATHWAYS FOR α-AMINO ACIDS AND PEPTIDES

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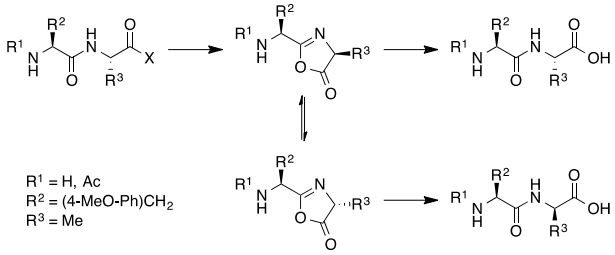
Self-organization in chemical systems must take place through the emergence of dissipative processes, requiring efficient activation pathways. *N*-Carboxyanhydrides (NCAs) or 5(4*H*)-oxazolones are essential intermediates during the activation of α-amino acids or peptides, respectively, when strong reagents are involved[1]. Under conditions compatible with that of the early Earth, pathways capable of leading to these intermediates have been identified[2–5]. However, many other reagents leading to peptide bond formation can be found in the literature though yields were usually limited. A survey of the activity of these reagents using a system capable of detecting strong activation will be presented using the epimerization associated with the conversion of free or acylated dipeptides into 5(4*H*)-oxazolones[6] to monitor activation (Scheme 1).



Scheme 1. **Dipeptide epimerization as a tool to monitor activation**

The dipeptides were thus exposed to the putative activating agents in aqueous solution as well as to photoactivation processes considered as a possibility of converting the potential energy of visible or UV light into chemical energy. The first results of this survey revealed that most of the reagents commonly considered as peptide activating agents do not yield 5(4*H*)-oxazolones.

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THE ONGOING SEARCH FOR THE SIMPLEST PEPTIDE SELF-REPLICATOR

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One of the main challenges in contemporary Systems Chemistry research is establishing how interactions and coordinated functions in molecular networks give rise to emergent properties. Recently, while looking for such complex network-dependent behavior, several groups have disclosed the self-synthesizing materials (SSMs), which promote their own formation by accelerating synthesis of their building blocks or the assembly of super-structures. The SSMs offer models for understanding how molecular assemblies and cellular machineries had emerged in the origin of life, perhaps one of the most fascinating scientific questions. In line with this research, we have recently described peptide-based SSMs, driven by fibril self-assembly and reproduction[1-4]. We now present a new research direction aiming at the design of functional SSMs and their structure-activity characterization. The following topics will accordingly be discussed: (i) Regio-selective and stereo-selective β-sheet induced replication, (ii) Coupling replication and substrate metabolism within a single network[5], and (iii) Self-assembly and self-replication of charge-transport fibrils[6].

We thank the COST CM1304 action for travel support.

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EARLY LIFE FROM THERMAL NONEQUILIBRIUM?

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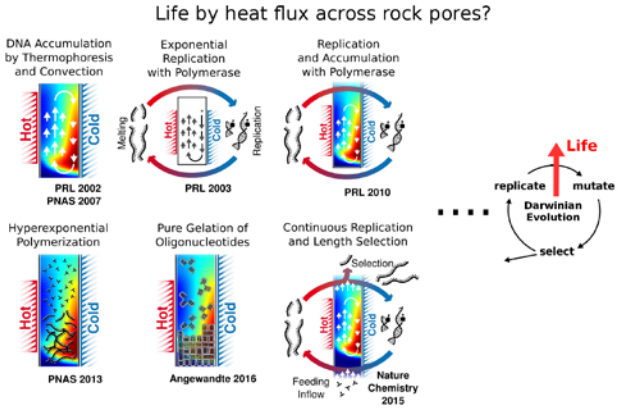
Introduction. The Origin of Life is one of the fundamental, unsolved riddles of modern science. Life as we know it is a stunningly complex non-equilibrium process, keeping its entropy low against the second law of thermodynamics. Therefore it is straightforward to argue that first living systems had to start in a natural, non-equilibrium settings. Recent experiments with non-equilibrium microsystems suggest that geological conditions should be able to drive molecular evolution, i.e. the combined replication and selection of genetic molecules towards ever increasing complexity.

Non-Equilibrium Settings. As a start, we explored the non-equilibrium setting of natural thermal gradients. Temperature differences across rock fissures accumulate small monomers more than millionfold[1] by thermophoresis and convection[2]. Longer molecules are exponentially better accumulated, hyperexponentially shifting the polymerization equilibrium towards long RNA strands[3]. The same setting implements convective temperature oscillations which overcome template poisoning and yield length-insensitive, exponential replication kinetics[4]. Accumulation and thermally driven replication was demonstrated in the same chamber, driven by the same temperature gradient[5]. Protein-free, non-ligating replication schemes can be driven by thermal convection. For example, the hairpins of tRNA can be used for reversible codon-sequence replication, bridging from replication of genes to the translation of proteins[6]. Non-templated polymerization and hybridization- dependent degradation leads to replication-like information transmission [7]. Replication and trapping of DNA persist over long time in a constant influx of monomers, closely approaching the criteria for an autonomous Darwin process.

Biotechnology Spinoff. Experiments using non-equilibrium conditions at the microscale are non-trivial. For example, molecules have to be detected selectively with the most sensitive biochemical, optical and microfluidic approaches. Advances of biotechnology in this regime are very fruitful. Our award winning NanoTemper spinoff company, with now more than 70 employees, demonstrated that basic research for the origin of life can lead to cutting edge biotechnology[8,9].

Environments. Besides temperature gradients, many more non-equilibrium settings can be imagined and become increasingly accessible to experimentation. For example, geological pH gradients, geological redox potentials or the optical excitation of geological nanoparticles should drive metabolic reactions in a very peculiar way. To be successful, an effort on the origin of life has to be embedded in a strong and very active interdisciplinary background of biology, biochemistry, chemistry, astrogeology and not the least, theoretical modelling at various levels of abstraction.



Scheme 1. **A heat flow across a pore of rock offers central mechanisms for the molecular evolution of life.**

Selection for increasing complexity. The replication of long nucleic acid sequences was required for the evolution of biological complexity during the origin of life; however, short sequences are normally better replicators than long ones. Recently, we showed how a common physical environment provides a simple mechanism to reverse this trend and enables long sequences to flourish[10]. On a similar note, the trap is creating gels from oligonucleotides - and sorts them in a phase transition with equal sequence and single base pair discrimination[11].

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SELF-ASSEMBLY OF NOVEL PEPTIDE-DNA CONJUGATES

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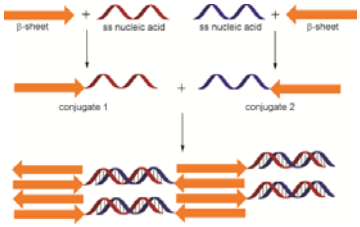
Systems chemistry attempts to mimic the biological complex networks of molecules within synthetic chemical framework. Analysis of their dynamic self-organization, as well as self-replication and catalytic properties, can help us to better understand the bottom-up organization of supramolecular architectures. Thus, we investigate self-assembly of synthetic peptide-oligonucleotide conjugates. Although peptide- and nucleic acids- based self-organizing systems have been explored in many aspects and are well documented in the literature, artificially synthesized hybrid molecules present a unique family of compounds. Studying such conjugates will offer new superior soft matter suitable for many applications and might even shed light on bottom-up scenarios related to the origin of life. Here, we present a set of self-assembling peptide-DNA hybrids that have been designed and synthesized. Short nucleic acid segments have been attached to amphiphilic replicating peptide sequences previously explored in our lab[1-4]. The basic system consists of two conjugates, for which the nucleic acid segment of one is complementary to the other (Scheme 1). We demonstrate the self-assembly of our system into different morphologies: fibers and sphere-like structures. To the best of our knowledge, this study proposes the first systematic analysis of structural and functional characteristics of small peptide-DNA assemblies.



Scheme 1. **Schematic design of the peptide-oligonucleotide self-assembly system**

We thank Dr. Rivka Cohen-Luria for her help and assistance. This research is supported by COST Action CM1304.

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PROTEIN SELF-ASSEMBLY

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Protein-based materials have great potential to advance society. As a cornerstone of bionanotechnology it is essential to develop new ways of stitching proteins together. We seek to address the fundamental question of protein self-assembly, which has applications as diverse as crystallization, the fabrication of advanced materials, and therapeutics. Here, we will present several examples of assembly, ranging from the contribution of small molecules to polymers.

The calixarenes are archetypal building blocks of supramolecular chemistry. We have made progress using calixarenes as molecular glues to drive protein assembly (Fig. 1). A combined approach based on NMR spectroscopy and X-ray crystallography has provided convincing evidence that sulfonato-calix[4]arene is a versatile ligand for protein surface recognition and assembly[1-3]. New examples of related building blocks will be presented.

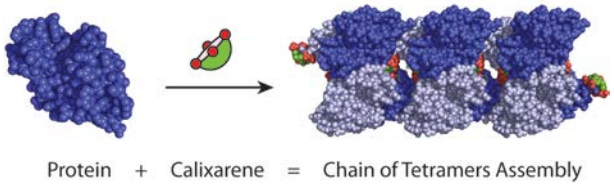

Fig. 1. **Calixarene mediated protein assembly. The crystal structure of lysozyme bound to sulfonato-calix[4]arene revealed a tetrameric protein assembly that formed linear chains[2]**

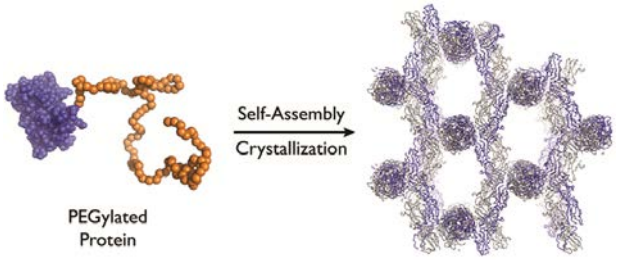

Fig. 2. **Assembly of a protein-polymer conjugate. The crystal structure of a PEGylated protein revealed an unusual double-helical protein assembly and a highly porous architecture[4]**

We are also investigating the impact of PEGylation on protein structure and assembly. Recently, we reported the crystal structure of a model protein (11.5 kDa) that was PEGylated with a single PEG 5000 (ref.[4]). The crystal structure was remarkable as the protein-polymer conjugate formed a double-helical assembly. And the helices were arranged orthogonally to yield a highly porous architecture (Fig. 2). The volume available in the pores was calculated to be sufficient to accommodate the PEG chains (based on MD volume calculations[5] of PEG 5000). This result suggests that the size of the polymer could be used to control protein

assembly. Current efforts are focused on noncovalent PEGylation. Two examples of this concept will be presented.

We gratefully acknowledge the support of NUI Galway and Science Foundation Ireland.

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POTENTIAL APPLICABILITY OF THE BRAY--LIEBHAFSKY OSCILLATORY REACTION

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The Bray-Liebhafsky (BL) reaction[1,2], is the catalytic decomposition of hydrogen peroxide into water and oxygen in presence of iodate and hydrogen ions. Although apparently simple, it has a very complex underlying mechanism involving numerous intermediate species such as I_2, I^-, HIO, HIO_2, I_2O and several radicals. With respect to self-organization, this apparently simple reaction that begins after mixing three simple ingredients, aqueous solutions of hydrogen peroxide, sulphuric acid and potassium iodate, exhibits impressive complexity[3–5]. Besides simple oscillations, complex oscillations and chaos are also obtained in this reaction system. BL system is much less investigated than Belousov Zhabotinski reaction, mostly due to common believe that it is hard to reproduce results in it because it involves mass transfer of gas components.

Nevertheless, because of their high sensitivity to any perturbations BL reaction is explored for analytical purposes[6–8] and for catalyst characterization[9–11]. Our investigation proves it to be robust and highly reproductive system, which can be controlled in batch, as well as, in CSTR conditions. Hence, the BL system has great potential in various applications.

Support from the Ministry of Education, Science and Technological Development of the Republic of Serbia, grants 172015 and 45001, is gratefully acknowledged.

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DE NOVO SYNTHESIS, GROWTH, AND REPRODUCTION OF ARTIFICIAL LIPID MEMBRANES

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We are developing catalytic coupling reactions that can drive the self-assembly and reproduction of lipid vesicle assemblies[1]. The formation of chemically driven self-reproducing vesicles has the potential to aid us in understanding how sets of reactive small molecules led to the first living cells, a problem in chemistry that is still a virtual "black-box." A major goal in the field is to achieve continual growth and synthesis of phospholipid vesicles containing embedded catalysts; however one major roadblock was that phospholipid membrane expansion will eventually lead to dilution of the catalyst and slowed growth. We recently provided one solution by coupling lipid synthesis with autocatalysis, creating the first synthetic membranes that can continually self-reproduce[2]. Simultaneously, we have expanded the chemistries available to accomplish *de novo* membrane synthesis. For instance, we have repurposed the native-chemical ligation to enable the non-enzymatic synthesis of phospholipids from thioesters, thus mimicking lipid synthesis by acyltransferases in living organisms[3]. Furthermore, we have developed methods to modify lipid membranes with proteins, either spontaneously during lipid membrane assembly or spatiotemporally using light-triggered bioconjugation reactions[4,5]. We are currently implementing our lipid synthesis schemes in living cells, where we will be able to test the effect of specific lipid formation on signaling, clustering, and membrane shape transformations.

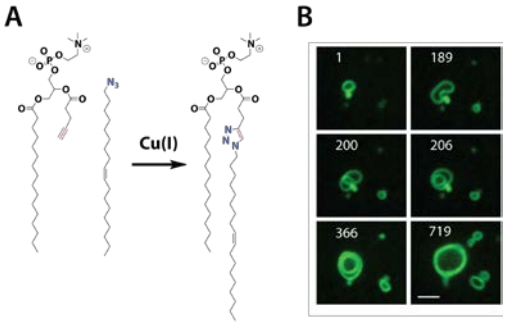

Fig. 1. **A) Copper catalyzed azide-alkyne cycloaddition** leads to the synthesis of a membrane forming phospholipid from non-membrane forming single-chain precursors. **B) Continual phospholipid synthesis** can be achieved by utilizing an oligotriazole autocatalyst. The constant production of phospholipids leads to vesicle growth. Numbers indicate elapsed time, in minutes, from start of imaging. Scale bar, 3 microns.

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A DNA-BASED SIGNAL RECORDER STUDIED *IN VITRO* AND IN SIMULATION

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DNA is the primary location for information storage in all living organisms. Yet, only little work has been carried out that uses DNA as a potential *in vivo* information storage. Here, we present the design of a DNA based signal recorder that employs DNA hybridization and strand displacement, together with its experimental *in vitro* and computational characterization.

The signal recorder implements a stack data structure that can be written to using “push” and “write” DNA strands and read out in last-in-first-out manner using “read” and “pop” DNA strands (see Fig. 1). The system has been designed to be readily transferable into an *in vivo* device.

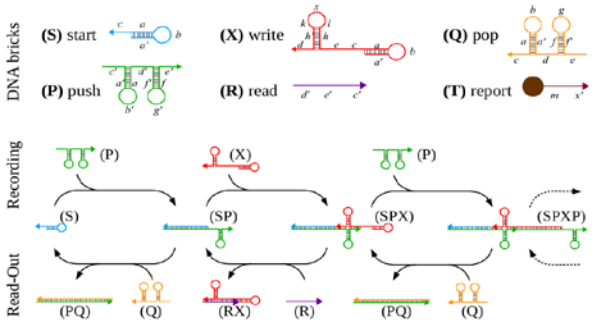

Fig. 1. **Schematic design of the stack based DNA signal recorder**

Capillary electrophoretic analysis and TEM microscopy indicate that the DNA recorder can successfully store and release at least three consecutive signals (Fig. 2 left), but also identify potential side reactions. Complementing the experimental characterization, we present computational results of coarse-grained particle-based models as well as a rule-based stochastic model (Fig. 2 right), which we currently employ to better understand the system.

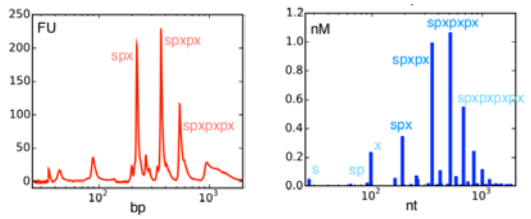

Fig. 2. **Electropherogram (left) and computer simulation (right) of a recorder with four consecutive signals (SPXPXPX)**

This work has been supported by UK EPSRC grants n° EP/J004111/1, EP/J004111/2, EP/L001489/1, EP/L001489/2.

IS THERE NON-TRIVIAL TOPOLOGICAL STRUCTURE IN BIOPOLYMERIZATION SPACES?

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The prime examples of biopolymers, proteins and nucleic acids, are both assembled iteratively *via* condensation of a small number of distinct building blocks. If different polymers of the same length and type are viewed as elements of an abstract space than Hamming distance is a natural measure of relationship between polymers, inducing a metric in sequence space. With a single operation (mutation), i.e. the exchange of one monomer unit, it is possible to transform every sequence into every other one in sequence space. The complexity of sequence space stems from the sequence composition.

In the realm of natural products, two polymer classes, polyketides and terpenes, are found, which in contrast to

proteins or nucleic acids are assembled from only a single type of building block. While this seems boring at first sight it turns out that both polymer classes show an extreme high structural diversity. This property can be attributed in part to cyclisation and rearrangement reactions interleaving polymerisation. These two chemical reaction patterns add topological complexity to the abstract space for polymers.

In this contribution we will apply a graph-grammar based approach[1,2] to explore the structure of the polymerisation spaces of polyketides and terpenes of a defined length. Furthermore, we will illustrate that the formulation of graph rewrite rules with complicated precondition constraints can be greatly simplified by using a term rewriting system on top of the graph rewriting system.

This work was supported in part by the Volkswagen Stiftung proj. No. I/82719, and the COST-Action CM1304 "Systems Chemistry", by the Danish Council for Independent Research, Natural Sciences, by the ELSI Origins Network (EON), which is supported by a grant from the John Templeton Foundation. The opinions expressed in this publication are those of the authors and do not necessarily reflect the views of the John Templeton Foundation.

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EXPLORING PHYSICAL AUTOCATALYSIS

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Life must originally have arisen through a transition from relatively simple chemical mixtures to highly complex and dynamic non-equilibrium systems. Simple chemical models of living cells can offer insight into the principles underlying biology and the emergence of life on earth[1]. Here I will describe the design of novel self-replicating micelles driven by mild bond-forming reactions which increase the molecular complexity of the components[2]. Micellar autocatalysis is driven by irreversible bond formation and offers new technology for the development of protocell models as well as sophisticated tests of 'lipid world' scenarios for the origins of life. We use an ultrasensitive label-free optical microscopy technique to visualize the spontaneous emergence of an autocatalytic system from an aqueous mixture of two chemicals[3]. Quantitative, *in situ* nanoscale imaging reveals heterogeneous self-reproducing aggregates and enables the real-time visualization of the synthesis of new aggregates at the reactive interface.

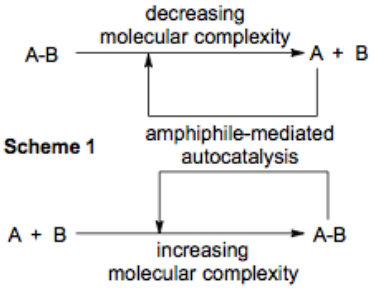

Fig. 1. **Examples of physical autocatalytsis driven by bond forming reactions to give an increase in molecular complexity**

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INTEGRATION OF MOLECULAR MOTORS IN NON-EQUILIBRIUM POLYMER NETWORKS

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Making molecular machines that can be useful in the macroscopic world is a challenging long-term goal of nanoscience. Inspired by the protein machinery found in biological systems, and based on the theoretical understanding of the physics of motion at the nanoscale, organic chemists have developed a number of molecules that can produce work when triggered by various external chemical or physical stimuli. In particular, basic molecular switches that commute between at least two thermodynamic minima and more advanced molecular motors that behave as dissipative units working far from equilibrium when fueled with external energy have been reported. However, the ultimate challenge of coordinating individual molecular motors in a continuous mechanical process that can have a measurable effect at the macroscale has remained elusive until very recently. We will discuss advances developed by our group on artificial molecular machines and involving their mechanical coupling within dynamic polymeric systems. We will show that it is now possible to amplify their individual motions to achieve macroscopic functions in materials. In particular, we will present a dual-light controlled system operating in fully non-equilibrium conditions, and in which the integrated motions of two types of mechanically active units can be tuned by the modulation of their frequencies.

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SUPRAMOLECULAR PATHWAY SELECTION AND DISSIPATIVE SELF-ASSEMBLY USING CHEMICAL FUELS

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Bottom-up approaches to spontaneously self-assemble molecules have resulted in well-ordered and sophisticated architectures, many of which are able to exert specific functions[1]. Whereas traditionally the equilibrium properties of the assemblies were studied, in more recent years the focus has shifted to kinetical studies of the assembly process. The latter studies have provided new mechanistic insights (e.g., nucleation effects and multiple couple equilibria), and have shown that the sequence and rate of experimental procedures (e.g., dilution, heating/cooling, stirring/shaking) determines the "pathway selection" of the assembly process[2–4]. Recently, we have demonstrated an approach where redox reactions are used to achieve pathway selection, which will be one of the topics of my presentation[5].

In addition, we demonstrate that chemical fuels can be used to obtain so-called dissipative self-assembly. Specifically, I will show a self-assembling system that is controlled by phosphorylation and dephosphorylation cycles powered by adenosine-5'-triphosphate (ATP) as a chemical fuel. Using dissipative self-assembly approaches we hope to go beyond the current switchable (and stimuli-responsive) supramolecular systems, and make structures that resemble natural microtubules both in structure as well as in function.

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SPATIO-TEMPORAL PATTERN FORMATION IN AN AUTOCATALYTIC HYDROGENASE REACTION

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HynSL hydrogenase from *Thiocapsa roseopersicina* is applied to catalyse the oxidation of molecular hydrogen

$$H_2 = 2H^+ + 2e^-$$

in a thin-layer reaction chamber. The experimental study reveals the unique autocatalytic nature of the reaction. In spatially distributed systems the reaction produces propagating fronts in which a selected substrate, the electron acceptor benzyl viologen, is reduced. The dependence of the reaction front velocity on the enzyme concentration is a power function with a positive enzyme concentration threshold, with an exponent of 0.45 ± 0.05. This indicates that the autocatalyst is an enzyme form. The front velocity decreases on increasing the electron acceptor concentration, as a sign that the autocatalyst interacts directly with the final electron acceptor[1].

A minimal model is then constructed on the experimental findings. The quadratic autocatalysis is placed within the enzymatic cycle, where all steps are reversible. Rate laws are selected to obey microreversibility. Since the rate of oxidation/reduction depends on the pH, fast protonation and deprotonation of the various enzyme forms are assumed.

At constant hydrogen activity and pH, one unstable and on stable steady state exist, revealed by linear stability analysis. The reduction of benzyl viologen only takes place in the vicinity of the stable steady state. This leads to a reduction front following the autocatalytic conversion of the enzyme into its active form. The minimal model is able to reproduce the experimental observations at constant pH. It also supports that a prion-type autocatalysis is responsible for the behavior of the system.

Since not only the redox potential but also the reaction rates strongly depend on the pH, transient oscillations are anticipated in unbuffered systems, a feature observed in specific experimental conditions[2].

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AUTOCATALYTIC SETS AND THE ORGANIZATION OF LIFE

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Life is a self-sustaining chemical reaction network. In other words, living systems produce their own components, in such a way as to maintain and regulate the chemical reaction network that produced them.

This view of life was expressed more formally already several decades ago in the concept of an autocatalytic set[1,2]. An *autocatalytic set* is a reaction network in which each molecule can be produced from an appropriate food source by using only reactions from the network itself, and where all reactions in the network are catalyzed by at least one of the molecules in the network itself. Autocatalytic sets are assumed to be a necessary condition for life, and also to have played an important role in the origin of life.

We have developed a mathematical framework, known as RAF theory, to characterize, detect, and analyze autocatalytic sets in arbitrary chemical reaction systems[3]. This framework has been applied to simple polymer models, showing that autocatalytic sets are highly likely to exist in random chemistries (even for very moderate levels of catalysis), and that they often contain an entire hierarchy of smaller and smaller autocatalytic subsets[4]. Furthermore, the framework has also been used successfully to analyze real chemical and biological reaction networks, such as a system of catalytic RNA molecules created in the lab[5], and the metabolic network of *E. coli*[6].

In this talk I will give a brief overview of the main concepts and results of RAF theory, including suggestions for further research.

This work is an ongoing collaboration with Mike Steel, Stuart Kauffman, Niles Lehman, and others.

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EXTERNAL TEMPLATE-TRIGGERED SELF-REPLICATION IN A DYNAMIC COMBINATORIAL LIBRARY

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Self-replication is one of the most prominent features of biological systems. In the recent years however, fully synthetic chemical systems capable of self-replication have been discovered as well[1-3]. A substantial part of these studies were conducted in the context of dynamic combinatorial libraries (DCLs), i.e. dynamic mixtures constructed from small building blocks which are capable of reversible bond formation. Due to their dynamic nature, the product distribution of DCLs can be shifted by external (host-guest chemistry) or internal (self-replication) template effects. However, only a few systems are known in which self-replication can be controlled by external chemical stimuli[4].

In this talk, we present a DCL in which self-replication can be triggered by addition of a template molecule. Upon oxidation in aqueous buffer, the recently developed dithiol building block ***1*** forms a diverse DCL of cyclic disulfide oligomers among which the cyclic hexamer (***1***$_6$) can emerge as a self-replicator, forming self-assembled nanosheets. When ***2*** is combined with dithiol ***2***, a DCL of more than 30 mixed members is formed. It is well known that the tetramer of ***2*** (***2***$_4$) is a strong binder of spermine (***3***). Addition of ***3*** to the mixed DCL thus results in the formation of ***2***$_4$ as the only ***2***-containing species and a ***1***-rich DCL, from which ***1***$_6$ can emerge, resulting in the self-sorting of the DCL to the two homo-oligomers ***2***$_4$ and ***1***$_6$. The work represents an important step towards the embedding self-replicators into signaling cascades.

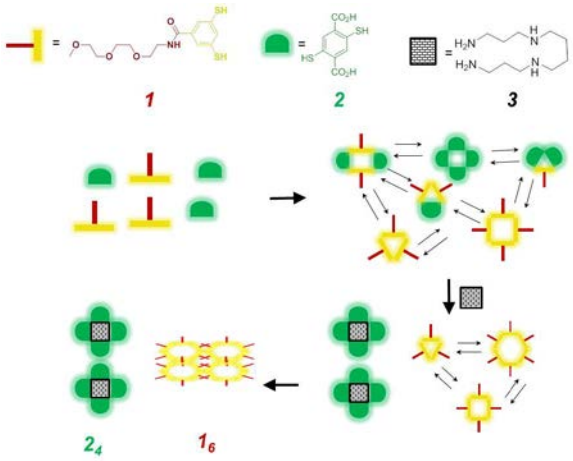

Fig. 1. **Spermine-induced self-replication of *1*$_6$ from a DCL prepared from building blocks *1* and *2*.**

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IN SILCO RIBOZYME EVOLUTION IN METABOLICALLY COUPLED RNA POPULATION

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The RNA World hypothesis offers a plausible bridge from no-life to life on prebiotic Earth, by assuming that RNA, the only known molecule type capable of playing genetic and catalytic roles at the same time, could have been the first evolvable entity on the evolutionary path to the first living cell. We have developed the Metabolically Coupled Replicator System (MCRS), a spatially explicit simulation modelling approach to prebiotic RNA-World evolution on mineral surfaces, in which we incorporate the most important experimental facts and theoretical considerations to comply with recent knowledge on RNA and prebiotic evolution. The MCRS model framework has been extended in order to investigate the dynamical and evolutionary consequences of adding an important physico-chemical detail, namely explicit replicator structure – nucleotide sequence and 2D folding calculated from thermodynamic criteria – and their possible mutational changes, to the assumptions of a previously less detailed toy model.

For each mutable nucleotide sequence the corresponding 2D folded structure with minimum free energy is calculated, which in turn is used to determine the fitness components (degradation rate, replicability and metabolic enzyme activity) of the replicator. We show that the community of such replicators providing the monomer supply for their own replication by evolving metabolic enzyme activities features an improved propensity for stable coexistence and structural adaptation. These evolutionary advantages are due to the emergent uniformity of metabolic replicator fitnesses imposed on the community by local group selection and attained through replicator trait convergence, i.e., the tendency of replicator lengths, ribozyme activities and population sizes to become similar between the coevolving replicator species that are otherwise both structurally and functionally different.

In the most general terms it is the surprisingly high extra viability of the metabolic replicator system that the present model adds to the MCRS concept of the origin of life. Surface-bound, metabolically coupled RNA replicators tend to evolve different, enzymatically active sites within thermodynamically stable secondary structures, and the system as a whole evolves towards the robust coexistence of a complete set of such ribozymes driving the metabolism producing monomers for their own replication.

SYSTEMS CHEMISTRY: BEFORE AND AFTER RNA

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The appearance of RNA is considered an important phase in the origins of life studies as exemplified by the RNA-world hypothesis[1-3]. The prebiological pathways by which RNA formed are a matter of continuing interest and debate[1-4]. While there are efforts to have RNA available as early as possible through primordial prebiotic chemistry[5], other considerations lead to a scenario where RNA could have appeared later, at a stage where both the chemical processes and the environment would have been more conducive for RNA's sustained origination and function[2,4,6].

In our approach for understanding the emergence of RNA, we synthesized, and investigated the base-pairing properties of, potentially natural alternatives of RNA. By comparing them to RNA, we have gained not only a greater understanding of the structure-function relationship of RNA, but also the realization that RNA is likely a product of chemical evolution[7]. This is evidenced by the mutual interdependence of ribofuranose, phosphodiester backbone and purine-pyrimidine base-pairing in a given environment – necessary for the functioning of RNA. That is, the *selection* of each components of RNA could have occurred, not at the level of prebiotic chemistry, but at the level of an oligomer[7]. This necessitates a systems-chemistry approach to the formation and selection of RNA[6].

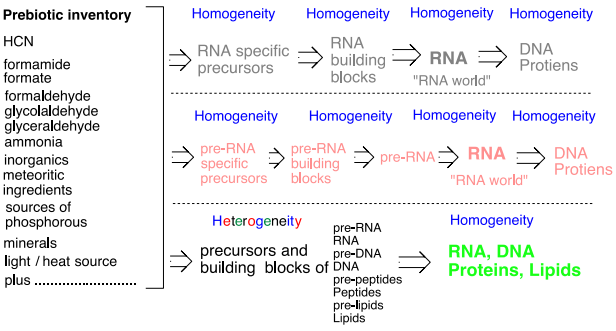

Fig. 1. **A systems chemistry approach (bottom) juxtaposed with previous approaches (top two)**

Based on the possibility of selections at the level of oligomer, we are working on a scenario wherein the

combinatorial interactions of diverse prebiotic systems chemistry lead first to heterogeneous systems from which a homogeneous informational/functional system can emerge that is capable of further evolution[6]. In this scenario not only RNA, but also DNA/proteins/lipids would be end-products of an incremental, constitutional replacement of the preceding chimeric and heterogeneous systems. This systems chemistry approach does not end with the emergence of an informational/functioning system, but becomes more relevant for further evolution towards a functioning cellular system[6].

The lecture will present the results of our systems chemistry approach towards the emergence of RNA and beyond.

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FITNESS LANDSCAPES OF FUNCTIONAL RNAs

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The notion of fitness landscapes, a map between genotype and fitness, was proposed more than 80 years ago. For most of this time data was only available for a few alleles, and thus we had only a restricted view of the whole fitness landscape.

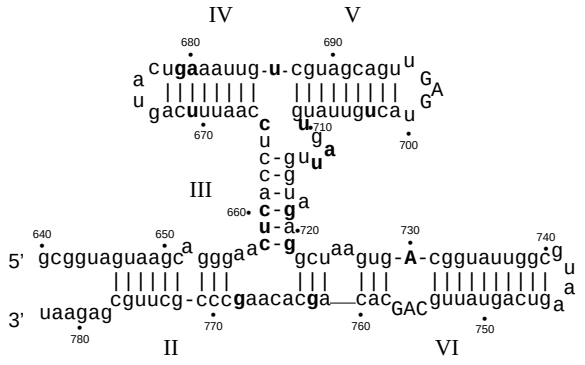

Fig. 1. **Secondary structure of the Neurospora VS ribozyme (**Numbering is according to convention[4]. Positions in bold represent structural critical sites. Capitalized positions represent functional critical sites. (A730 is both))

Recently, advances in genetics and molecular biology allow a more detailed view of them. Here we review experimental and theoretical studies of fitness landscapes of functional RNAs, especially aptamers and ribozymes. We find that RNA structures can be divided into (1) critical structures, (2) connecting structures, (3) neutral structures and (4) forbidden structures[1].

Such characterisation, coupled with theoretical sequence-to-structure predictions, allows us to construct the whole fitness landscape[2,3]. Fitness landscapes then can be used to study evolution, and in our case the development of the RNA world.

Financial support has been provided by the European Research Council under the European Community's Seventh Framework Programme (FP7/2007–2013)/ERC grant agreement no (294332).

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EVAPORATION OF LIQUIDS IN NANO-SCALE. COMPUTER SIMULATIONS

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Large scale molecular dynamics simulations of Lennard-Jones fluids are used to investigate evaporation of liquids for two cases: evaporation of droplets into gas[1,2] and evaporation of liquid slab into vacuum[3].

We found in simulations of droplet evaporation that the temperature was continuous at the liquid-vapor interface only if the vapor density ratio was not small[1]. If not, the temperature jump appeared. The discontinuity, which disagrees with the hydrodynamic model, was discovered experimentally by Feng and Ward[4]. According to the simulations, the jump appeared if the mean free path in the gas phase was too long considering temperature gradient. The temperature jump reduces the energy flux and decreases the evaporation rate. Basing on quasi-stationarity of the evaporation process and analyzing the simulation results we found the relation that, for the ideal gas, strictly relates the temperature jump with the mean free path of the gas[2]. As a consequence, we propose the formula for the evaporation rate that is valid for the ideal gas and has no adjustable parameter. The formula excellently fitted the simulation data even if the temperature jump was very high[2].

The simulations of evaporation into vacuum[3] gave surprising results. We found that the momentum flux in the vapor is equal to the liquid pressure in the evaporating slab. Thus conservation of momentum determines the number of evaporating molecules per unit time. We also found that the kinetic temperature of the gas flux is approximately equal to the gas liquid equilibrium temperature for the pressure inside the liquid. Basing on the properties we have derived new relation for the mass evaporation flux in order to replace commonly used, yet highly inaccurate, the Hertz-Knudsen relation[5].

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FORMATION OF MIXED ANHYDRIDES IN THE REACTION OF 5-(4*H*)-OXAZOLONES WITH PHOSPHATE ESTERS AND NUCLEOTIDES

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Nowadays, the origin of life is considered to have occurred through a co-evolutionary process involving different subsystems rather than through self-organization in a system made of a single biopolymer[1]. The combination of peptides and nucleotides subsystems should not only be considered regarding the possible benefits it could induce in prebiotic chemistry[2], but also because such a combination has been responsible for the development of translation in living organisms[3]. Our group has proposed scenarios through which the evolutionary process leading to translation could have unfolded by using *N*-carboxyanhydrides (NCA) or 5-(4*H*)-oxazolones as substrates, consisting of reasonable activated forms of amino acids under prebiotic conditions[4] capable of yielding mixed anhydrides by reaction with phosphate ester. These mixed anhydrides are high-energy intermediates that easily give back amino acids[5]. From adenylates and even in the presence of low CO_2 concentrations, NCA are readily formed and undergo polymerization so that mixtures involving oligomer products can be obtained. On the contrary, the amino acid moiety of 5-(4*H*)-oxazolones adducts with RNA are not susceptible of undergoing these kinds of intramolecular pathways and, therefore, provide a new approach to study the behaviour of mixed anhydrides with other kinds of reagents. Here we investigate the reaction of 5-(4*H*)-oxazolones with models of RNA monomers to analyse the scope of the formation of phosphate esters mixed anhydrides (PEMAs) and the specific reactivity that arises as a prerequisite to the analysis of possible scenarios for the development of translation.

This work was supported by grants from the Simons Foundation (Grant Number 293065 to Z.L.), and from the Agence Nationale de la Recherche to the PeptiSystems project (Grant Number ANR-14-CE33-0020). The authors thank the COST action CM1304 Emergence and Evolution of Complex Chemical Systems.

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TOWARDS SYNTHETIC CELLULARITY VIA PROTOCELL DESIGN AND CONSTRUCTION

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The design and construction of compartmentalized materials ensembles for modelling complex biological systems, exploring the origin of life, and advancing future living technologies is attracting considerable interest in a wide range of research communities. In this talk, I will review some recent experiments undertaken in my laboratory that provide steps towards synthetic cellularity using bioinspired materials chemistry principles and techniques. I will discuss four new protocell models based on; (i) nanoparticle self-assembly (colloidosomes)[1], (ii) interfacial assembly of protein-polymer nanoconjugates (proteinosomes)[2], (iii) micro-droplet formation (coacervation)[3,4], and hybrids of the above[5]. I will use these new model systems to discuss pathways towards chemical cognition, modulated reactivity, basic signalling pathways and non-equilibrium activation in compartmentalized artificial micro-ensembles.

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PHOTOCONVERSION OF LIGHT INTO CHEMICAL ENERGY BY GIANT LIPID VESICLES

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The reaction centre is a transmembrane pigment-protein complex that plays a major role in the photochemical conversion of light into chemical energy in plants, algae and photosynthetic bacteria[1,2]. It couples light-induced electron transfer to the generation of a proton concentration gradient across a lipid membrane, via reactions involving a quinone molecule that binds two electrons and two protons at its active site. The so-obtained electrochemical gradient can be harnessed to synthesize ATP[2]. In a previous work[3] it has been shown that the reconstitution of functional, but randomly oriented, RC is possible in conventional (diameter 50-100 nm) lipid vesicles typically obtained by the detergent depletion method[4]. Following a bottom-up approach, here we show that synthetic protocells, based on giant lipid vesicles embedding a highly oriented reaction centre, are capable of generating a photo-induced proton gradient across the membrane. Under constant illumination, protocells generate 0.06 pH gradient units in one minute, contributing to a proton motive force of 3.4 mV per minute.

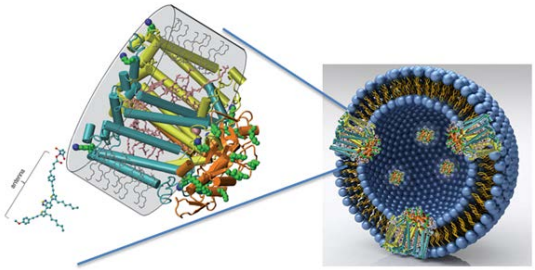

Fig. 1. **Highly oriented photosynthetic RCs within the GV membrane**

Remarkably, the facile assembly of the sophisticated reaction centre into the synthetic lipid membrane, as obtained by the droplet transfer method[5], paves the way to the construction of novel and more functional protocells for synthetic biology.

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INFERRING CASCADES OF AUTOCATALYTIC CYCLES WITH PETRI NETS

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We model chemical reaction networks as directed hypergraphs that are generated in rule-based manner[1], using graph grammars as models of given sets of reaction mechanisms. Graphs serve as abstractions of molecules. This provides a level of chemical realism sufficient to ensure conservation of mass, atom type and charge. Atom maps, for instance, are thus consistently defined within the model. The generative approach pursued here goes beyond the necessarily static network models that need to be specified *a priori* and allows, in particular, application to network design problems. Chemical pathways are represented by integer hyperflows[2]. In contrast to more traditional approaches of flux balance analysis or elementary mode analysis we insist on integer-valued flows. Although this choice makes it necessary to solve possibly hard integer linear programs it conveys the advantage that more detailed mechanistic questions can be formulated and computed directly. An integer hyperflow subsequently will be analysed with Petri nets[3] in order to get information on the temporal realizability of pathways wrt. their necessity of catalysts.

Here, we demonstrate the applicability of the mathematical frameworks using a very general model of sugar chemistry to investigate the flows in the autocatalytic formose reaction and its relatives. We ask how autocatalytic cycles are related to each other in functional cascades and how these intricate structures "communicate" to the embedding background network of potentially "destructive" side reactions. The ability to answer this question is essential for the characterization and classification of large-scale chemical reaction networks. Networks involving distributed autocatalysis and their properties are the core objects to understand the transition from prebiotic chemical processes to the emergence of life. In addition to classification of chemical pathways and the automatic inference of the relation of pathways, Petri nets can furthermore be employed for atom tracing predictions, as well as automatic depiction of pathways. Fig. 1 depicts a cascade of autocatalytic cycles that was found by i.) enumeration of a large set of "autocatalytic"

integer hyperflows, ii.) inferring the necessity of catalysts, and iii.) automatic inference of the relation of the autocatalytic pathways.

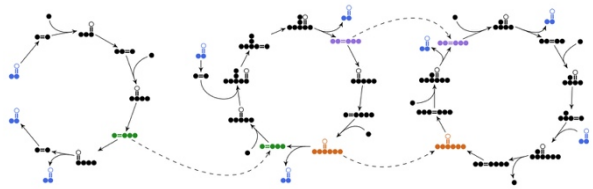

Fig. 1. **Overview of 3 autocatalytic pathways in the formose chemistry,** where carbon-carbon double bonds and carbonyl groups are shown, while hydroxyl groups and hydrogens are implicit. The first pathway can trigger the second pathway via the green molecule, and the second pathway can in turn trigger the third pathway using either the purple or orange molecules. The autocatalytic compound, glycolaldehyde, is shown in blue

This work was supported in part by the Volkswagen Stiftung proj. no. I/82719, and the COST-Action CM1304 "Systems Chemistry" and by the Danish Council for Independent Research, Natural Sciences. It is also supported by the ELSI Origins Network (EON), which is supported by a grant from the John Templeton Foundation. The opinions expressed in this publication are those of the authors and do not necessarily reflect the views of the John Templeton Foundation.

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SELF-ASSEMBLY AND DYNAMIC BEHAVIOUR OF SINGLE HYDROCARBON CHAIN AMPHIPHILES

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The ubiquity of lipid membranes in contemporary cells points to an early emergence of membranous compartments in the chemical evolution that led to the formation of protocells, the chemical systems that must have preceded ancient cells. As for many aspects of the protocell composition, the main issue about the compartment is to find out potential prebiotic building blocks[1]. Moreover, it is unlikely that the membrane formation occurred in isolation. That is, one has to envision possible interactions between all prebiotic chemicals as complex mixtures[2], or chemical systems, which participated to the formation of protocells as well as defined early membrane functions.

The composition of early membranes cannot be directly ascertained. However, various amphiphile types and related compounds are plausible as established by the analysis of the chondrite carbon content[2], or suggested by the availability of phosphorus in Fe/Ni rich meteorites[3] and the products of "prebiotic" synthesis models. Amphiphiles such as Single hydrocarbon Chain Amphiphiles (SCAs) are more likely to have constituted the bulk of the membrane building blocks than phospholipids.

While the self-assembly of a single SCA species was already reported over 40 years ago[4], the interest in complex mixtures of several amphiphile types or amphiphiles and other prebiotic molecules is only recent. Recent studies have however already underscored that mixtures of SCAs even with non-amphiphilic molecules can influence the SCA self-assembly, thereby the stability of resulting structures[5]. Two categories of non-amphiphilic molecules can be considered: molecules that are relevant for the development of precellular compartmentalization and reaction networks (e.g., pigments5, nucleobases6, sugars[6], peptides, etc.), and those that are simply "bystanders".

We will discuss several cases that highlight the significance of interactions between the molecules in chemical systems for the stabilization and dynamic behaviors of amphiphile structures. During chemical Evolution, these interactions could have delineated chemical units on which selection for the persistence of a certain protocell type could apply. Subsequent evolution could have then reinforced the interdependency of membrane and content compositions. This interdependency is consistent with the tight integration of modern cell membrane and metabolism.

We thank our colleagues of Cost Action CM1304 and TD1308 as well as M. M. Hanczyc and D. W. Deamer for fruitful scientific discussions. We thank SDU, the Danish National Research Foundation and the COST Action CM1304 for their support.

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A ROBUST BISTABLE SWITCH IN α-HELICAL THIODEPSIPEPTIDE REPLICATION

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Response to specific stimuli and short term memory storage has been a key aspect of living systems. These phenomena are manifested by, among many others aspects, bistability and feedback-regulated reaction networks. Towards mimicking such behaviour by synthetic systems, we utilize an α-helical coiled-coil based replication networks.

In this research, we used a thiol-terminated nucleophilic fragment ***N*** and a thioester based electrophilic fragment ***E*** which, upon ligation, form a longer thiodepsipeptide ***R***, which can catalyze its own formation[1,2]. ***R*** can also produce ***E*** and ***N*** when subjected to the proper thiol molecule. With this simple network configuration, we demonstrated the construction of a bistable switch by thiol dependent equilibration experiments starting from different initial composition keeping the amount of material same in each experiments[3]. The robustness of this bistable system is also tested by varying the physical and chemical parameters. We believe that this research will give us more detailed mechanistic insights into early stage memory storage regulated by external stimuli.

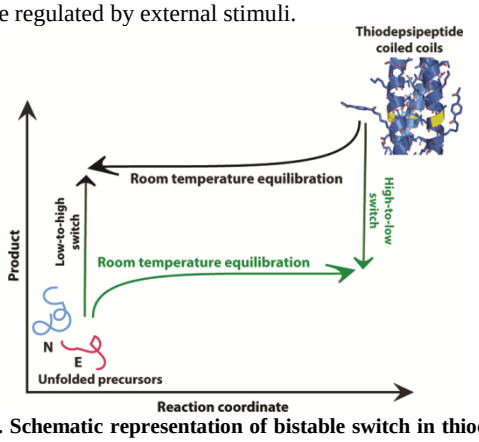

Fig. 1. **Schematic representation of bistable switch in thiodepsipeptide replication**

We acknowledge ReAD ITN for the financial support. We are thankful to Dr. Rivka Cohen-Luria for her assistance in the lab.

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EFFICIENT PASSERINI REACTIONS IN AN AQUEOUS VESICLE SYSTEMS

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The use of water as a solvent for organic transformations offers several environmental benefits[1]. Therefore, water as a reaction medium has received considerable attention in the synthetic organic chemistry, since it has been an inexpensive, non-toxic and non-flammable solvent[2]. However, one major disadvantage for the synthesis or transformation of organic compounds is that most organic molecules are insoluble in water. To circumvent this disadvantage, surfactants (amphiphiles), which can solubilize organic molecules, have been employed. The presence of surfactants not only ensures higher solubility of hydrophobic compounds in water but may also enhance reaction rates[3]. This rate-enhancing effect can be explained by at least three effects: the increased concentration of the reacting species in the area of aggregates formed from surfactants (e.g., micelles, vesicles), a different polarity of the actual locus where the reaction takes place, and possible steric hindrance so that the extent of side reactions is decreased[4]. Meanwhile, the use of aqueous surfactant systems instead of organic solvents gains importance from the view point of green chemistry[5].

During our studies, we investigated the influence of various aqueous surfactant systems on the Passerini multicomponent reaction. Based on the obtained results, we developed a new, green protocol. This protocol allows to synthesize α-acyloxy carboxamides in aqueous solution in the presence of the vesicle-forming surfactant DODAB at room temperature[6].

In order to extend the above mentioned protocol we combined Passerini multicomponent reaction with enzymatic oxidation step in a one-pot procedure. This protocol comprises enzymatic aerobic transition-metal-free oxidation of alcohol, followed by multicomponent Passerini reaction to afford α-acyloxy carboxamides with high yields, up to 86 %. The results of our studies will be discussed and possible applications to the synthesis of more complex molecules will be provided.

We gratefully acknowledge the financial support of NCN project Harmonia No 2014/14/M/ST5/00030 for financial assistance. This work is the outcome of ideas discussed at a Systems Chemistry meeting of the COST action CM1304.

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SELF-REPLICATING MOLECULES: EFFECTS OF CHIRALITY AND DEATH

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How did life start? Can we make life? These are among the most fundamental questions in contemporary science.

In this talk I will show how, starting from a mixture of relatively simple interconverting organic molecules, a set of self-replicating molecules can emerge spontaneously following the mechanism shown in Figure 1 (ref.[1,2]).

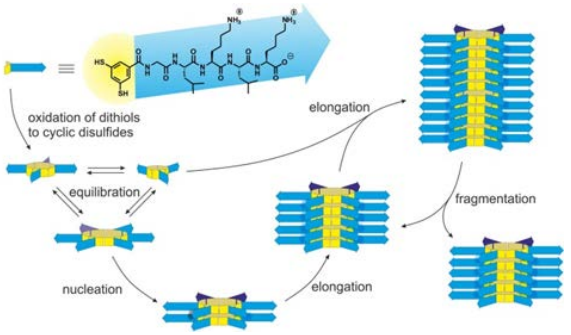

Fig. 1. **Mechanism of self-replication:** the building blocks form an exchanging mixture of macrocycles of different sizes via oxidation of thiols to disulfide bonds and subsequent disulfide exchange. The hexamer macrocycles self-assemble into fibres as the peptide chains (arrows) form beta sheets through a nucleation-elongation mechanism. The fibres grow from their ends and break upon mechanical agitation doubling the number of fibre ends that further promote the formation of self-replicating hexamer.

Importantly, the process of self-replication was found to be exponential[3], which is an important characteristic in the context of Darwinian evolution.

The nature of the replicator that emerges from the complex mixtures was found to depend on agitation conditions[1] and the solvent environment[4].

Mutation of the replicators was enabled by providing the system with different building blocks. When mixed, these systems gave rise to the emergence of two different replicator sets (that bear resemblance to quasi-species), of which one is the ancestor of the other[5]. Molecular-level insight into this diversification process showed that outliers in the mutant distribution of the first quasi-species induced the formation of the second quasi-species.

We also explored the influence of chirality on the replication process. We found that replication is most efficient when using only homochiral building blocks. However, when using a racemic building block mixture heterochiral replication occurred, demonstrating for the first time that replication is also possible in a heterochiral environment.

The next step is now to achieve replication far from equilibrium, by allowing concurrent replication and destruction processes to take place. The first results of replication in such replication/destruction regime will be presented.

We are grateful to support from the European Research Council (ERC), The Netherlands Organization for Scientific Research (NWO), European Cooperation in Science and Technology COST CM1005 and CM1304, and the Dutch Ministry of Education, Culture and Science (Gravitation Program 024.001.035).

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ROLE OF CONFINEMENT IN SYMMETRY BREAKING

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The origin of biomolecular homochirality is still an open problem, and many scenarios have been suggested[1,2]. Following our previous theoretical work on the plausible role of lipids in promoting chiral enrichment[3,4], we consider the role of aluminium-silicate phases in governing the chirality of amino acid polymerization. In fact, aluminium-silicate phases have often pores or channels that can accommodate amino acids but small enough to prohibit the formation of helices with random chirality.

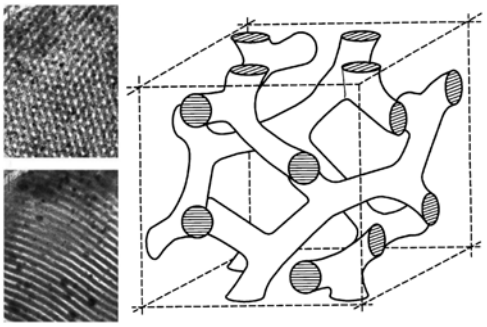

Fig. 1 **Aluminium-silicate non crystalline phase MCM-48 (adapted from [5])**

The physical-chemical features of the local confinement can control the formation of a peptide.

The role of the confinement is investigated via mesoscopic simulation techniques, mainly based on dynamic mean field density functional theory (DDFT), and by assisted peptide synthesis.

We want to suggest a prebiotic mechanism to induce symmetry breaking in peptide synthesis and we want to advocate a role of spatial confinement in the research on origin of life.

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THE PERSISTENCE PRINCIPLE: SEEKING TO RECONCILE BOLTZMANN AND DARWIN

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The Second Law of Thermodynamics, particularly in its statistical mechanical formulation, and Darwin's theory of evolution, could together be considered the two profound scientific advances of the 19th century. These two theories offered fundamental insights into the basis for material change in the world, the former primarily in the physicochemical world, the latter in the biological world. Yet, despite their revolutionary impact on scientific thinking, these two theories have not cohabited comfortably. The Second Law, though necessarily encompassing all material change, both within the living and non-living worlds, seems strangely detached from Darwinian thinking. Typical biological images, so readily explained in Darwinian terms, are incongruent when viewed through the lens of thermodynamics.

In this talk a logical connection between the physical and biological worlds, resting on a broader understanding of the stability concept[1-3], is described. The proposal rests on the idea that stability manifests two facets - time and energy - where stability's time facet is expressed through a system's persistence. So given that a system's stability can express itself through either time or energy, how do the two facets relate to one another? Can one be considered more fundamental? Surprisingly, it turns out that stability's time facet is more general than its energy facet and this is illustrated by the Venn diagram in Fig. 1. From the diagram it can be seen that thermodynamic stability is just a subset of the more general group of persistent/time stable systems. Whereas thermodynamically stable systems are necessarily persistent (having reached the equilibrium state), persistent systems are not necessarily thermodynamically stable, as exemplified by dynamic kinetic stability (DKS)[1]. But the realization that stability's more general expression is through its time facet (persistence), means that both thermodynamic stability and DKS can be linked, as *both* stability kinds manifest the drive toward increasingly persistent forms. Stability as persistence allows the two seemingly distinct stability kinds to be viewed in the same terms and allows the formulation of a general principle, the Persistence Principle, governing change in both 'regular' physicochemical world and replicative worlds. The principle may be formulated as follows: *systems will tend from less stable (persistent) to more stable (persistent)* or, more simply: *nature seeks persistent forms.*

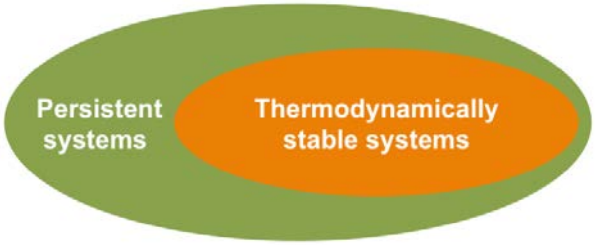

Fig. 1. **Schematic diagram illustrating the set of thermodynamically stable systems as a sub-set of the more general set of persistent systems**

That principle, logical in its formulation, and expressed qualitatively, has explicit mathematical underpinnings, as in practice persistence can manifest in two mathematically distinct ways: in the replicative world through Malthusian exponential growth, and in the 'regular' physical/chemical world through Boltzmann's probabilistic considerations[1-3], thereby possibly explaining why there are just two distinct material forms in nature, living and non-living. Finally, by encompassing both 'regular' and replicative worlds, the principle appears to be able to reconcile the Second Law of Thermodynamics and Darwin's theory of evolution within a single conceptual framework, thereby hopefully reducing, if not eliminating, the long-standing incongruence between these two central scientific theories.

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ABIOTIC EMERGENCE OF BIOLOGICAL HOMOCHIRALITY

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The dynamics of chiral replicators was simulated by deterministic kinetics in abiotic thermodynamic scenarios. A summary of recent results of the group in respect to conditions to achieve spontaneous mirror symmetry breaking (SMSB) is presented. The results lead to reasonable speculations on SMSB during the formation of the first replicators and suggest that experimental work on the topic is possible.

INTEGRATING PREBIOTIC PEPTIDE CHEMISTRY AND FATTY ACID SELF-ASSEMBLY DYNAMICS: A CRUDE BUT REALISTIC 'BOTTOM-UP' SYSTEMS APPROACH TO BIOGENESIS

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The plan for this contribution would be to address a central question for systems chemistry, if the field is to fulfill its original promise of illuminating the problem of origins of life: how do molecular mixtures lead to individualized systems with a dynamic organization based on diverse functional couplings among their components. I will pose the question in general terms[1,2] and then focus on a more specific case: compartmentalized chemistries with potential to become 'self-productive' in a simplified but biologically relevant sense[3,4]. Recent advances on these lines, both in silico and *in vitro*[5,6] will be described.

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SELF-ASSEMBLED BACTERIAL BIOFILM PROTEINS AS FUNCTIONAL BIOMATERIALS

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Bacterial biofilms are complex ordered structures. They are containing many different molecules including, proteins, carbohydrates, nucleic acids and living cells. Among those materials bacterial biofilm proteins are forming the backbone of the complex structure. Bacterial biofilm proteins from *Escherichia coli* are called functional amyloids, and their synthesis was found to be under control of an operon called curli operon. This operon codes for major (CsgA) and minor biofilm (CsgB) and other accessory proteins. CsgB and CsgA protein are interacting each other while they are forming biofilm structures. After both of the proteins were secreted to the extracellular medium, CsgB protein attached receptor protein on the E. coli cell. Following the initial attachment of CsgB on cell surface, CsgA docks to CsgB and they start to form the growin biofilm fibers. This biofilm fiber keeps growing while additional CsgA and CsgB proteins being synthesized[1,2].

We aimed to use CSgA and CsgB proteins to build up innovative biomaterial systems. To control the assembly, we have investigated the polymerizaiton of the purified biofilm proteins using quartz crystal microbalance system. We focused on understanding the mechanism behind the formation of the complex protein structures. Using the CsgA, CsgB and CsgAB monomers as the starting monomers we observed the formation of highly ordered biomaterials.

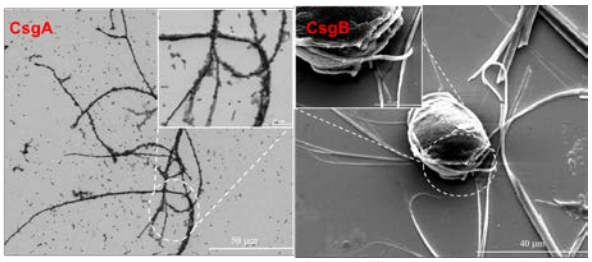

Fig. 1. **CsgA polymerization results in forming long nanowire formation while CsgB forms micron sized particles**

Later we have analysed the secondary structure changes in three cases with CsgA, CsgB and CsgAB. We observed that CsgB polymers are containing more sheet structures whereas CsgA contains less ordered structures such a random coil. In the last part of our work we probed the intrinsic fluorescence in polymerized bacterial biofilm proteins. This was the first

indication of how the fluorescence can be controlled. Additional our analysis for dissolving the biofilm protein polymers in apolar solutions, and protease treatment revealed that the biopolymers are building up a fluorophore like assembly with enhanced fluorescence.

We can conclude that biofilm are well ordered materials and their assembly can be tuned using protein engineering and genetic engineering approaches for biomedical and nanotechnology applications.

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PREBIOTIC AMPHIPHILES AND PEPTIDES: SYNTHESIS AND ASSEMBLY

MICHELE FIORE, WARREN MADANAMOOTHOO, GHINWA AJRAM, PETER STRAZEWSKI*

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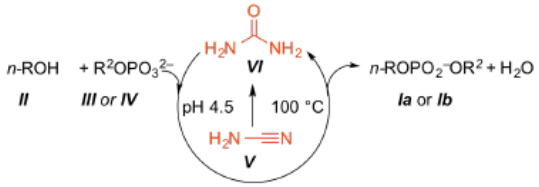
The formation of the earliest membrane-forming amphiphiles in the Eoarchean era 4.0–3.6 Gya could have coincided with the first appearance of prebiotic amino acids, peptides and N-heterocycles, all produced from then available geochemical sources including extra-terrestrial material[1]. Over decades a number of studies have demonstrated how amphiphilic molecules can be synthesized under plausibly prebiotic conditions. ¨

We investigated the formation of random sequence peptides from mixtures of lipophilic and hydrophilic amino acids on the one hand, and of racemic phosphatidic acid (PA) and phosphatidyl ethanolamine (PE), ***Ia*** and ***Ib***, one the other. For instance, heating racemic long-chain diacyl glycerol ***II*** with inorganic or organic orthophosphate (***III*** or ***IV***) and cyanamide or urea (***V*** or ***VI***) resulted in mixtures containing racemic ***Ia*** or ***Ib*** and other amphiphilic compounds. The analysis of these crude products was carried out by ESI-MS, ^{1}H NMR and IR spectroscopy through their comparison with synthesized reference compounds. After hydration of the crude extracts at different pH, giant vesicles were observed by fluorescence microscopy.



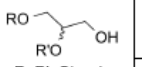
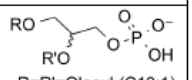
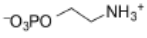
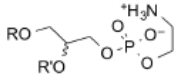
n-ROH	Phosphates	CA	Racemic Phospholipids ***Ia*** ***Ib***
 R=R'=Oleoyl (C18:1) ***II***	$NH_4[H_2PO_4]$ ***III***	***V***	 R=R'=Oleoyl (C18:1)
		VI	
	 ***IV***	***V***	 R=R'=Oleoyl (C18:1)
		VI	

Fig. 1. **Simulated prebiotic formation of PA (*Ia*) and PE (*Ib*)**

COST Action CM1304 is gratefully acknowledged.

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DESIGN AND EXPLOITATION OF AUTOCATALYSIS IN pH-TRIGGERED MATERIAL SYNTHESIS

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Autocatalytic chemical reactions display a number of useful features including a time-delay before rapid reaction and an amplified response to a weak chemical signal. Acid or base autocatalysis can be coupled to other pH-dependent processes providing a convenient method for their temporal control. For example, pH autocatalytic reactions may be used as inbuilt switches in pH-triggered material synthesis. Many materials applications require initial slow reaction followed by rapid curing such as adhesives, sealants and injectable bio-medical formulations.

Most of the known pH autocatalytic systems to date involve harsh inorganic redox chemistry limiting their use. Here we will discuss our efforts in the design of pH autocatalysis using acid or base-catalysed dehydration and hydrolysis[1,2]. We will show how these autocatalytic systems can be used to drive polymer particle formation, precipitation and for the temporal control of gelation[3]. In the latter case, programmable, transient, gelation was achieved by coupling a base catalyzed thiol-Michael addition with the enzyme-catalyzed hydrolysis of urea[4]. This systems chemistry approach has numerous attractive features for bio-inspired, bio-compatible materials applications.

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MULTIVALENCE COOPERATIVITY IN SUPRAMOLECULAR POLYMERIZATION

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All-or-nothing molecular assembly events are emerging properties of complex chemical systems largely attributed to the cooperativity of the weak interactions[1]. Here we show how the chelate effect (multivalence cooperativity) can play a central role in the regulation of the all-or-nothing assembly of structures (supramolecular polymers here) [2]. We have studied the formation of double-stranded supramolecular polymers formed of Co-metalloporhyrin and bi-pyridine building blocks. Their cooperative nucleation-elongation assembly can be summarized as a thermodynamic cycle, where the monomer weakly oligomerizes linearly or weakly dimerizes laterally. But thanks to the chelate effect, the lateral dimer readily oligomerizes linearly and the oligomer readily dimerizes laterally, leading to long double stranded polymers (Fig. 1). A model based on this simple thermodynamic cycle can be applied to the assembly of polymers with any number of strands, and allows determining the length of the polymer and the all-or-nothing switching concentration, from the pairwise binding constants. The model is consistent with the behaviour of supramolecular polymers such as microtubules and gelators[2,3]. We believe this model is applicable to many molecular assembly processes, ranging from the formation of cell-cell focal adhesion points to crystallization

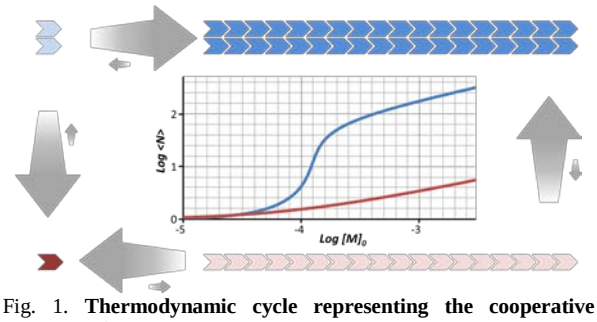

Fig. 1. **Thermodynamic cycle representing the cooperative assembly of a double-stranded polymer.** The inset shows the sudden growth of number of repeats <*N*> during the nucleation phase as the concentration of monomer increases

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HETEROGENEITY AND TURNOVER OF INTERMEDIATES DURING AMYLOID-β (Aβ) PEPTIDE AGGREGATION

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Self-assembly of amyloid β (Aβ) peptide molecules into large aggregates is a naturally occurring process that proceeds at appreciable rates under favourable kinetic conditions, yielding Aβ aggregates of different sizes and structures. Despite the great relevance and extensive research efforts, detailed kinetic mechanisms underlying Aβ aggregation remain only partially understood. We have recently developed a novel method, where fluorescence correlation spectroscopy (FCS) and Thioflavin T (ThT) were used to monitor the time dependent growth of structured amyloid aggregates and characterize the changing distribution of amyloid aggregate sizes throughout the aggregation process in a heterogeneous aqueous solution. We identified structured amyloid aggregates of different sizes with molecular weight from 260 to more than 1×10^6 kDa, and revealed the hitherto unobserved kinetic turnover of intermediates during Aβ aggregation.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by aggregation of amyloid β (Aβ) peptides, 39-42 amino acids long peptides derived from the amyloid precursor protein *via* proteolytic processing, and their accumulation in amyloid plaques. The Aβ aggregation mechanism is complex and still not fully understood despite of extensive investigations using a variety of analytical techniques. The present study adds a new dimension to the understanding of the kinetic formation of the aggregates – that of time dependent growth of amyloid aggregates and turnover of intermediates during the time course of the aggregation revealed using Thioflavin T (ThT) and florescence correlation spectroscopy (FCS)[1].

To monitor changes in the distribution of aggregate sizes during the course of Aβ42 aggregation, series of 30 consecutive FCS measurements lasting 10 s each, were

performed with about 5–7 min intervals in-between (Figure 1). Florescence intensity fluctuations over time were analyzed by temporal autocorrelation analysis to derive an autocorrelation curve (ACC). If fluorescence intensity fluctuations arise due to molecular diffusion, the decay time of the ACC indicates the average time that a molecule spends in the observation volume element (OVE), *i.e.* it reflects the diffusion of the fluorescent molecule, and hence its size. The amplitude of the ACC (A) is inversely related to the average number of molecules (N) in the OVE, and thus is representative of their concentration.

FCS analysis showed that already at time point $t = 0$ min, the reaction mixture contains ThT fluorescence active entities of different sizes that can be distinguished by differences in relative abundance (ACC amplitude, A), diffusion time (τ_D) and molecular brightness (counts per molecule and second, CPMS) as can be seen in Fig. 1A-C. The smallest aggregate that was detected was characterized by a diffusion time of $\tau_D \sim 200$ µs, which was estimated to be ~ 260 kDa, corresponding to aggregates consisting of 50-70 Aβ42 monomers. Smaller aggregates are most abundant at the beginning of the process, as evident from the large N (Fig. 1D, 0 min). With time, the number of large aggregates increases and a shift toward long diffusion times is observed (Fig. 1D, 90 min). The molecular weight of these aggregates was estimated to be about 1×10^6 kDa, corresponding to aggregates consisting of more than 2×10^5 Aβ42 monomers.

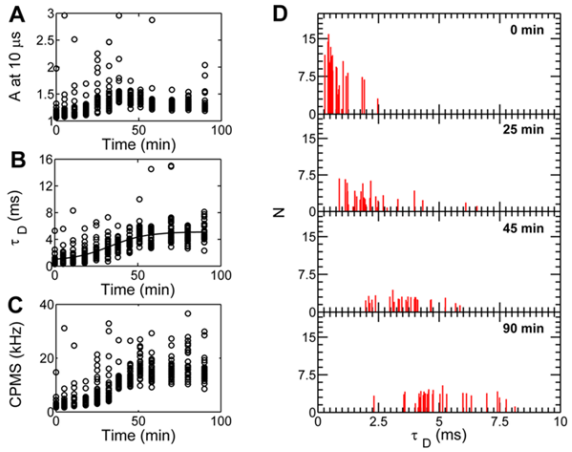

Fig. 1. **Time course of Aβ42 aggregation monitored by FCS** in a solution of 10 µM Aβ42 and 10 µM ThT in 20 mM HEPES, pH 7.0, T = 20 ºC. **A.** Changes in ACC amplitudes (A; open circles) during the course of aggregation. **B.** Changes in diffusion times (τ_D; open circles) during the course of aggregation. **C.** Changes in molecular brightness (open circles) assessed as counts *per* molecule and second (CPMS). In A-C a trend is seen as apparently filled areas are made up from the open circles in areas of highly populated values. **D.** Changes in the distribution of diffusion times during the course of Aβ42 aggregation

Our approach shows the most sensitive method that allows the detection of amyloid aggregates rich in β-structure with an ultimate, single-molecule sensitivity. FCS revealed the large heterogeneity of the process that bulk methods cannot expose. This not only explains many of the difficulties to achieve reproducible spectroscopic results, but allows us to quantitatively characterize the presence of transiently populated intermediates and the time course of their turnover.

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ARTIFICIAL VESICLES AS REACTION COMPARTMENTS AND REACTION REGULATORS

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Artificial vesicles are obtained *in vitro* by dispersing bilayer-forming amphiphiles in an aqueous medium (Fig. 1). Well studied are phospholipid vesicles, which were first identified as self-closed bilayer compartments by Bangham and Horn[1]. In addition to these naturally occurring amphiphiles, Gebicki and Hicks[2] later demonstrated that vesicles also form from simple fatty acids, and since the work of Kunitake and Okahata[3], it is known that artificial vesicles can also be obtained from a large number of fully synthetic amphiphiles, including amphiphilic block copolymers[4].

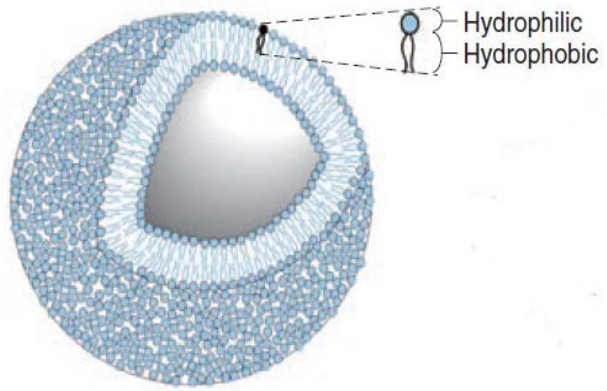

Fig. 1. **Schematic representation of an artificial unilamellar spherical vesicle built from amphiphilic molecules in an aqueous medium.** Through vesicle formation, an aqueous internal volume becomes separated from the bulk aqueous medium by a self-closed boundary layer of amphiphiles. Drawing from Furukawa[11]

Among the various fascinating properties of artificial vesicles − which have attracted much attention as compartment systems for drug delivery applications[5] and as protocell models[6,7] − two features are worth highlighting[8]: (i) the possibility of influencing the reactivity of reactants due to their confinement into the aqueous interior of the vesicles, and (ii) the possibility of shifting reaction pathways due to a confinement of reactants to the boundary of the vesicles.

Examples illustrating these two features are shown for enzyme-catalyzed reactions[9,10].

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SELF-ASSEMBLIES WITH PROGRAMMABLE LIFETIMES AND AUTONOMOUSLY DYNAMIC MATERIALS

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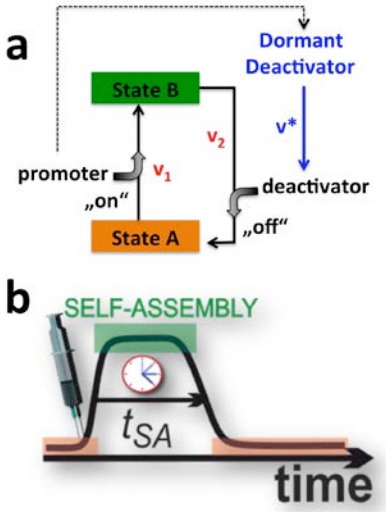
We present a generic concept to program lifetimes of self-assemblies in closed systems[1-3]. The key concept relies on separating the kinetic steps of formation and destruction of self-assemblies by controlling the availability of chemicals needed (i) to promote the assembly from the disassembled state A to the self-assembled state B (promoter) and (ii) its subsequent decay (deactivator; from B to A, Scheme 1). We conceive dormant deactivators that slowly chemically degrade, or are activated by introduction of the promoter, to furnish the active deactivator. The combination of fast promoters and dormant deactivators in a single injection enables a unique kinetic balance to establish an autonomously self-regulating, transient pH-state. Coupling of this non-equilibrium state to fuel pH-switchable self-assemblies allows predicting their assembly/disassembly fate in time - similar to a precise self-destruction mechanism. The duration of this transient state can be tuned over four orders of magnitude – from minutes to days.

We demonstrate the versatility of this platform approach by programming the lifetimes of self-assemblies of block copolymers, nanoparticles and peptides. Programming such autonomously self-regulating, transient states into switchable self-assemblies enables a new level of control in switchable materials and allows advancements towards dynamic materials, spawning self-regulation and transient memory functions.



Scheme 2. **Kinetic control to program self-regulating self-assemblies** in time by combination of rapid promoters and dormant deactivators. The time scales can be programmed by controlling v* and the ratio of promoter/dormant deactivator.

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AUTHOR INDEX

LATE PAPERS

SELF-SYNTHETIZING STIMULI-RESPONSIVE HYDROGELS

VAN DUC NGUYEN, ASISH PAL, FRANK SNIJKERS, MATHIEU COLOMB-DELSUC, GIULIA LEONETTI, GUILLERMO MONREAL SANTIAGO, JASPER VAN DER GUCHT, SIJBREN OTTO*

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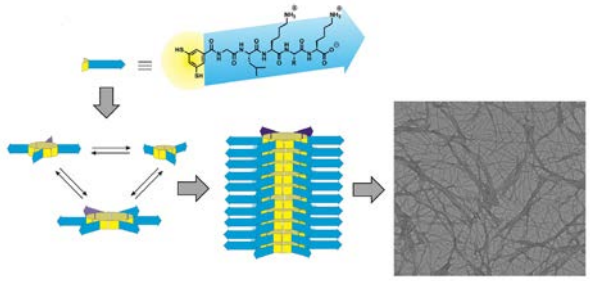
Hydrogels have an increasing number of applications in biomedical research, in fields such as cell culture, tissue engineering or drug delivery[1]. Supramolecular, self-assembled hydrogels have been proven useful in this field, due to their reversibility, their responsiveness, and the degree of control that can be achieved over them[2]. Recently, it has been shown that cells cultured in a gel matrix can also respond to its mechanical properties, sometimes even affecting their survival[3].

In our group we have developed a material that can form rigid fibers by supramolecular stacking of macrocycles. These macrocycles are part of a dynamic combinatorial library, and upon stacking they drive the equilibrium of the system towards their own formation and consume the other members of the library. Therefore, the material is not only self-assembled but also self-synthetizing (Scheme 1)[4].

The nucleation process for this polymer is very slow, and the chain breakage and recombination processes are controlled by the mechanical stress applied to the solution. Therefore, under certain conditions, a living supramolecular polymerization can be achieved, with precise control over the polydispersity and the length of the fibers[5].

We can also control the final properties of the material by photo-irradiation or fiber crosslinking[6,7]. All of the above combined gives us the possibility of producing different self-assembled hydrogels with different mechanical properties starting from the same building blocks.



Scheme 1. **General scheme of the self-synthetizing material formation**

This control over the mechanical properties and the possible tunability of the peptide chain of our gels make this material desirable for cell culture. The biocompatibility and practical uses of gels formed from this material in 2D and 3D cell culture will be explored.

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EXEPTIONAL AMPLIFICATION OF ENANTIOMERIC EXCESS IN A ONE-POT SYSTEM COMBINING SOAI'S AUTOCATALYTIC REACTION AND CATALYTIC ADDITION OF Zn(*i*Pr)$_2$ TO AZAARYL ALDEHYDES

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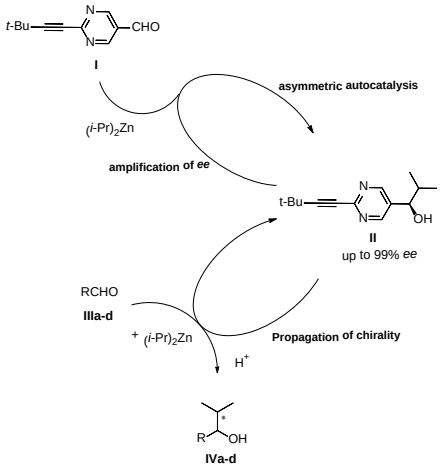
The pioneering work of Soai et *al*. on a practically perfect asymmetric amplification in the asymmetric autocatalysis of (5-pyrimidyl)alkanol ***II*** by addition of Zn(*i*Pr)$_2$ to (5-pyrimidyl) aldehyde ***I***, introduced a new entry into optically pure compounds and has been regarded as a triumph for reductionism[1]. Later, they described an elegant and efficient system of consecutive asymmetric autocatalysis and an asymmetric catalysis with significantly larger amplification indexes than those of the existing asymmetric amplification[2].

Inspired by the work of Soai, we described a reaction network combining simultaneous enantioselective autocatalysis with asymmetric induction in the alkylation of azaaryl substrates, which are unable of such asymmetric amplification on their own[3]. Moreover we observed remarkable asymmetric induction properties when these two systems perform together in one single cycle, often giving high values of *ee* for both compounds produced in the process. Surprisingly, the initial *ee* values of the chiral initiator seem to have no relevant effect on the final enantiopurity of both the product (*R*)-***IV*** and the Soai alkanol (*R*)-***II*** which are obtained[4] in values of 97-99 *ee* %. However, the initial *ee* values of the chiral seeds are proven to affect the speed of the reaction and the rate of conversion to products, showing a similar behaviour to the model described by Blackmond and Brown regarding the Soai autocatalytic process[5].

This work was supported by the Research Council of Norway (FRIPRO program 205271), the University of Oslo, and COST Action, Emergence and Evolution of Complex Chemical Systems (CM 1304).



Scheme 1. **Asymmetric autocatalysis with amplification of ee of the pyrimidyl alcohol and its use as a chiral catalyst**

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THE POTENTIAL ROLE OF METALLOPEPTIDES IN THE ORIGINS OF LIFE

LUCA BELMONTE, DANIELE ROSSETTO, MICHELE FORLIN, SIMONE SCINTILLA, CLAUDIA BONFIO, SHEREF S. MANSY

Earth is rich in metal ions, between a third and a half of all proteins are metalloproteins, and nucleic acids are invariably associated with metal centers. Metal ions are important contributors to the folding of biological polymers, are constitutes of concentration gradients used to drive unfavorable chemical reactions, and can directly participate in catalyst. It seems likely, therefore, that metal ions played a role from the very beginning of evolution and at the origins of cellular life. To gain insight into the properties of model prebiotic peptides, DFT and molecular dynamics calculations were made on complexes inferred from known metalloprotein structures. Dipeptides were then synthesized in the laboratory and tested for metal affinity. The affinity trends matched the composition of seawater in that higher affinities were associated with metal ions found at lower concentrations, just as seen for contemporary proteins. Since all living systems also share a dependence on iron-sulfur clusters, we next investigated whether short peptide sequences could stabilize iron-sulfur clusters. A series of short peptides were evaluated by wet lab and computational methods demonstrating the ability of model prebiotic sequences to coordinate to iron-sulfur clusters and to evolve into longer polymers that mimic modern day ferredoxins.

TRIPEPTIDE HYDROGELATOR (Ac-FFA-NH_2) AS A MODEL OF BINDING SITE Aβ-PROTEIN; COMPARATIVE BINDING STUDIES WITH THIOFLAVIN T AND OTHER Aβ-BINDERS

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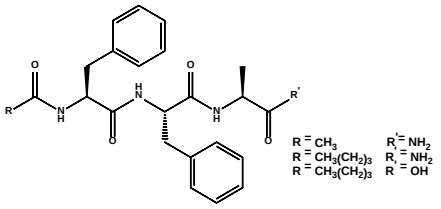
Numerous binding studies with Aβ-amyloid aggregates and short peptides with selected Aβ-protein sequence have pointed to the KLVFF fragment of the amyloid as the most probable binding site of small aromatic molecules. It was shown that the formation of Aβ-amyloids and the formation of gel fibers by the low molecular weight peptidic gelators share some common features[1,2].



Scheme 1. **Tripeptide FFA derivatives**

Series of tripeptide FFA derivatives was synthesized and tested for gelation of water and organic solvents (Scheme 1). Only Ac-FFA-NH_2 tripeptide exhibited gelation of water by self-assembly under physiological conditions. TEM of the Ac-FFA-NH_2 hydrogel and the methanol/water gel showed the presence of straight fibers with relatively uniform diameters of around 50 nm. FTIR and NMR investigation pointed toward the cross-β structure type of hydrogen bonding of the tripeptide in the gel aggregates.
Conjugated dyes (Thioflavin T and Congo Red) are commonly used to stain the plaques in histopathological studies[3]. Fluorescence titration of Ac-FFA-NH_2 aqueous solution bellow its minimal gelation concentration with Thioflavin T (ThT) showed increase of ThT emission with increased tripeptide concentration and formation of the 1 : 1 complex with significant association constant (Figure 1). Similar results were obtained with other Aβ-binders. These studies are expected to show if such Aβ-inspired hydrogelator aggregates could serve as a minimalist model of the Aβ-KLVFF binding site and possibly reveal its precise interaction with known and new binding molecules.

The study was supported by the Ministry of Science, Education and Sports of the Republic of Croatia and by the Croatian Science Foundation (HRZZ), Project No. IP-11-2013-7387.

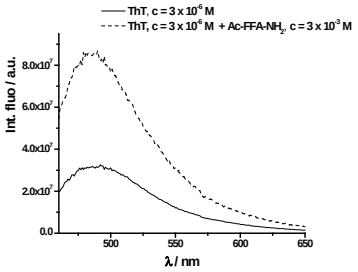


Fig. 1. **Increase of ThT fluorescence emission in the presence of AcFFA-NH_2**

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ENZYME-FREE FORMATION OF PEPTIDO RNA

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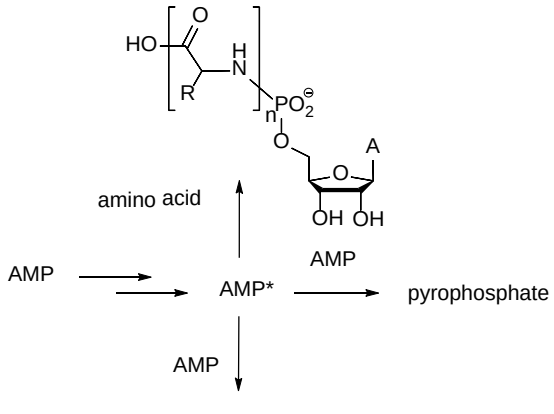
The enzyme-free formation of functional biopolymers from simple building blocks is a critical step in the processes leading to the first species that were capable of Darwinian evolution.

Demonstrating experimentally that amino acids and nucleotides oligomerize into biopolymers that can encode genetic information and that can catalyze metabolic reactions has been difficult. While studying enzyme-free primer extension[1,2,3] with *in situ* activation, we observed the *de novo* formation of RNA strands[4]. When amino acids were added, the formation of peptidyl RNAs was observed in the same aqueous buffer that induced formation and copying of RNA sequences[5]. The concurrent processes occurred without pre-activation of either the amino acids or the ribonucleotides. Through mixing simple starting materials in an aqueous buffer containing a condensation agent and an organocatalyst, the formation of oligomers is initiated. Chain growth can be monitored by MALDI-TOF mass spectrometry, IE-HPLC and NMR. When the proper precursors are used, the same reaction conditions that induce chain growth and genetic copying also lead to the formation of the cofactors ATP, NAD^+ and FAD that are pivotal for primary metabolism.



Scheme 1. **Reactions of activated AMP with amino acids and ribonucleotides.**

We are now developing a systems chemistry approach for monitoring and modeling reaction networks of mixtures containing amino acids, ribonucleotides, organocatalysts and a condensing agent, in one homogeneous solution. Our results shed light on the intrinsic reactivity of the molecules found in today's biochemical machinery and provide a framework for the systems chemistry of similar systems of biomolecules.

This work is support by DFG (grant No. RI 1063/8-2 to C.R.) and EU COST action CM1304.

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CZECH CHEMICAL SOCIETY SYMPOSIUM SERIES • ročník/volume 14 (2016), čís./no. 3 • ISSN 2336-7202 (Print), ISSN 2336-7210 (On-line) • ISSN 2336-7229 (CD-ROM) • evidenční číslo MK ČR E 21999 • Vydává Česká společnost chemická jako časopis Asociace českých chemických společností ve spolupráci s VŠCHT Praha, s ČSPCH a ÚOCHB AV ČR za finanční podpory Rady vědeckých společností ČR, Akademie věd ČR, Nadace Český literární fond a kolektivních členů ČSCH • IČO 444715 • Published by the Czech Chemical Society • VEDOUCÍ REDAKTOR/EDITOR-IN-CHIEF: B. Kratochvíl • REDAKTOŘI/ EDITORS: J. Barek, Z. Bělohlav, P. Drašar, P. Holý, J. Horák, P. Chuchvalec, Z. Kolská, B. Kratochvíl, J. Podešva, P. Rauch; Webové stránky: P. Zámostný • TECHNICKÁ REDAKTORKA/EDITORIAL ASSISTANT: R. Řápková • Redakce čísla (ISSUE EDITOR) P. Drašar • ADRESA PRO ZASÍLÁNÍ PŘÍSPĚVKŮ/ MANUSCRIPTS IN CZECH, SLOVAK OR ENGLISH CAN BE SENT TO: Chemické listy, Novotného lávka 5, 116 68 Praha 1; tel./phone +420 221 082 370, +420 222 220 184, e-mail: chem.listy@csvts.cz • PLNÁ VERZE NA INTERNETU/FULL VERSION ON URL: http://www.ccsss.cz • TISK: Garamon s.r.o., Wonkova 432, 500 02 Hradec Králové • SAZBA, ZLOM: ČSCH, Chemické listy • Copyright © 2016 Czech Chemical Society Symposium Series/Česká společnost chemická • Cena výtisku 180 Kč • This journal has been registered with the Copyright Clearance Center, 2322 Rosewood Drive, Danvers, MA 01923, USA, where the consent and conditions can be obtained for copying the articles for personal or internal use • Pokyny pro autory najdete na http://www.ccsss.cz , zkratky časopisů podle Chemical Abstract Service Source Index (viz http://cassi.cas.org/search.jsp) • Molekulární námět na obálce: Vladimír Palivec • Dáno do tisku 20.4.2016.