SYSTEMS CHEMISTRY IN PARIS

2nd-3rd of February 2017

Ecole Normale Superieure (ENS; 24, rue Lhomond, 75005 Paris; Room E012)

2nd of February

8:50-9:20: Welcome

9:20-9:30: Introduction, Ludovic Jullien

9:30-10:30: *Invited lecture 1*: Synthesis of spatio-temporal structures with DNA molecular programs, André Estevez-Torres

10:30-11:00: Autocatalytic Sets and RNA Secondary Structure, Wim Hordijk

11:00-11:15: Coffee break

11:15-11:45: Nucleic acids templated supramolecular assemblies, Mathieu Surin

11:45-12:15: The Formidable Softness of Being DNA, Damien Baigl

12:15-13:30: Buffet

13:30-14:00: Remote asymmetric amplification with Soai reaction in synergistic and responsive autocatalytic systems, Mohamed Amedjkouh

14:00-14:30: Triggering Assembly and Disassembly of a Supramolecular Cage, Cristiano Zonta

14:30-15:00: Development of synapsis modulators using dynamic combinatorial chemistry, Ruth Pérez-Fernández

15:00-15:30: Programmable stimuli-responsive devices generating high-density digital information, Chiara Glionna

20:00-22:00 Speaker Dinner

3rd of February

9:00-10:00: *Invited lecture 2*: Investigating the Origin of Life and the Evolution of Biocatalysts Using Droplet-Based Microfluidics, Andrew D. Griffiths

10:00-10:30: (Self)-recognition in dynamic combinatorial libraries, Sijbren Otto

10:30-11:00: Unraveling the multistimuli responses of a dynamic complex system of macrocyclic pseudopeptides, Ignacio Alfonso

11:00-11:15: Coffee break

11:15-11:45: Complex Functions Emerging in Synthetic Replication Networks, Gonen Ashkenasy

11:45-12:15: Tripeptide hydrogelator (FFA) as a minimalist model of aggregation Aβ-proteins, Leo Frkanec

12:15-12:45: Bacterial functional amyloids based supramolecular assemblies, Urartu Seker

12:45-14:00: Buffet

14:00-15:00: *Invited lecture 3*: Natural systems biogeochemistry, François Guyot

15:00-15:30: Driving energy flow throughout chemical networks, Ludovic Jullien

15:30-16:00: On the Levels of Abstraction in Systems Chemistry, Daniel Merkle

SYNTHESIS OF SPATIO-TEMPORAL STRUCTURES WITH DNA MOLECULAR PROGRAMS

Jean-Christophe Galas[1], Anton Zadorin[1], Adrian Zambrano[1], Yannick Rondelez[2] and André Estevez-Torres[1]

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Abstract

Biological systems combine two levels of molecular complexity. First, they synthesize molecular structures with exquisite chemical properties. Second, they construct out-of-equilibrium chemical reaction networks displaying capabilities that are uncommon in man-made molecular systems: measure time and space and compute. Chemistry has a longstanding history of synthesizing molecular structures. The question that motivates our research is: can we also synthesize reaction networks with predefined properties, in particular spatio-temporal order?

In an attempt to answer this question I will describe a systems chemistry approach relying on the programmability of DNA. Firstly, I will introduce a set of highly reconfigurable synthetic chemical reaction networks based on DNA. Secondly, I will describe how we have used it to synthesize different spatio-temporal patterns, such as travelling waves[1] and stationary fronts[2]. Finally I will discuss the possibility of exploiting these patterns for fabricating materials inspired from embryonic development.

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THE COEXISTENCE OF RNA REPLICATORS AND PARASITES IN COMPARTMENTALIZED SYSTEMS (CANCELLED)

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Abstract

The appearance of molecular replicators (molecules that can be copied) was probably a critical step in the origin of life at the early stages of the RNA world[1]. However, error prone replication results in sequences that are not usefull, but can be replicated faster than the ribozymes. Thus parasites form. They take over a well mixed system, and would have prevented life from taking off, unless the replicators were compartmentalized in reproducing ribocells.

Compartmentalization in itself does not solve all problems of the coexistence of replicators, and creates some of its own. Chief among them are the random division of cells, which can lead to loss of information[2]. Furthermore, nearly a hundred genes seem to be required for a minimal ribocell to function. How could such a system evolve considering that control of ribocell reproduction would seem to require a host of evolved replicators? We show here that a simpler population structure, based on cycles of transient compartmentalization and mixing of RNA replicators, is sufficient to prevent takeover by parasitic mutants[3]. Transient compartmentalization tends to select for ensembles of replicators that replicate at a similar rate, including a diversity of parasites that could serve as a source of opportunistic functionality. Thus transient compartmentalization could have allowed life to take hold.

References

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AUTOCATALYTIC SETS AND RNA SECONDARY STRUCTURE

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Abstract

The dominant paradigm in origin of life research is that of an RNA world [1]. However, despite experimental progress towards the spontaneous formation of RNA, the RNA world hypothesis still has its problems, and so far no one has been able to show that RNA can catalyze its own template-directed replication.

What has been shown, though, is that some RNA molecules can catalyze the formation of *other* RNA molecules from shorter RNA fragments. Moreover, there are experimentally constructed sets of RNA molecules that *mutually* catalyze each other's formation. Rather than each RNA molecule replicating itself, they mutually help each other in being formed from their basic building blocks, in a network of molecular cooperation.

Such a cooperative RNA network is a realization of an *autocatalytic set*, a concept that was originally introduced by Kauffman [2]. Informally, an autocatalytic set is a chemical reaction network in which (i) each reaction is catalyzed by at least one molecule from the set itself, and (ii) all molecules can be built up from an appropriate food source through a series of reactions from the set itself. This concept was made mathematically more rigorous and studied in detail, both theoretically and computationally, as RAF theory [3].

We introduce a novel computational model of chemical reaction networks based on RNA secondary structure, and analyze the emergence of autocatalytic sub-networks in random instances of this model. Our main result is that autocatalytic sets are highly likely to emerge, even for very small reaction networks and short RNA sequences. These findings could shed new light on the probability of the spontaneous emergence of an RNA world as a network of cooperative ribozymes.

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NUCLEIC ACIDS Ttemplated SUPRAMOLECULAR ASSEMBLIES

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Abstract

Nucleic acids-templated polymerization is an essential process of gene replication, transcription, and translation. DNA-templating processes have inspired many researchers, to evolve towards controlled architectures in terms of dimension and shape at the sub-nm scale. Since recently, the utilization of DNA as a template to direct the self-assembly or template the polymerization of synthetic molecules constitutes a sound approach, as the current control over DNA length and sequence permits to achieve -ideally- monodisperse and sequence-controlled polymers.[1-3]

We report our recent research efforts on nucleic acids-templating for directing the supramolecular self-assembly of molecules containing π-conjugated and/or photoactive moieties, these molecules interacting with DNA through different levels of interactions. By using nucleotides (adenosine phosphates) or long DNA templates, we observe template-dependent chiral organization processes in the hybrid supramolecular assemblies.[4,5] These supramolecular hybrids are of interest for chiroptical sensing, for instance to probe enzymatic activity, such as ATP hydrolysis by a phosphatase.[6]

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THE FORMIDABLE SOFTNESS OF BEING DNA

Damien Baigl

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Abstract

DNA is soft by nature, an apparent challenge (fragility) that can be turned into an opportunity (triggerability and reconfigurability) for chemists looking for programmable and dynamic functionality. More specifically, I will show in this talk how to exploit different aspects of DNA softness in applications ranging from synthetic biology to materials science. First, the semi-flexible polyelectrolyte nature of DNA[1] allows us to control its higher-order structure with light in a highly dynamic manner.[2,3] These light-triggered changes are used either to dynamically regulate gene expression,[4] resulting in spatio-temporal control of encoded protein activity,[5] or to directly modulate protein function in a new generation of giant DNA-protein hybrid systems.[6] Second, DNA is structurally soft, as its double-helix is maintained by thermally sensitive hydrogen bonds. This propensity to reconfigurability has been remarkably exploited in the growing field of DNA nanotechnology.[7] In this field, researchers have devised ways to redirect DNA base pairing principles into the possibility to fabricate a plethora of arbitrary-shaped nanoscale objects and scaffolds with exquisite spatial resolution and unprecedented programmability features.[8,9] To make DNA nanotechnology optically addressable, we have recently developed photosensitive intercalators allowing photoreversible melting and hybridization of any kind of DNA at constant temperature.[10] We are currently implementing this approach to create photocontrollable DNA origamis and exploit them as reconfigurable scaffolds for proteins and particles.

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REMOTE ASYMMETRIC AMPLIFICATION WITH SOAI REACTION IN SYNERGISTIC AND RESPONSIVE AUTOCATALYTIC SYSTEMS

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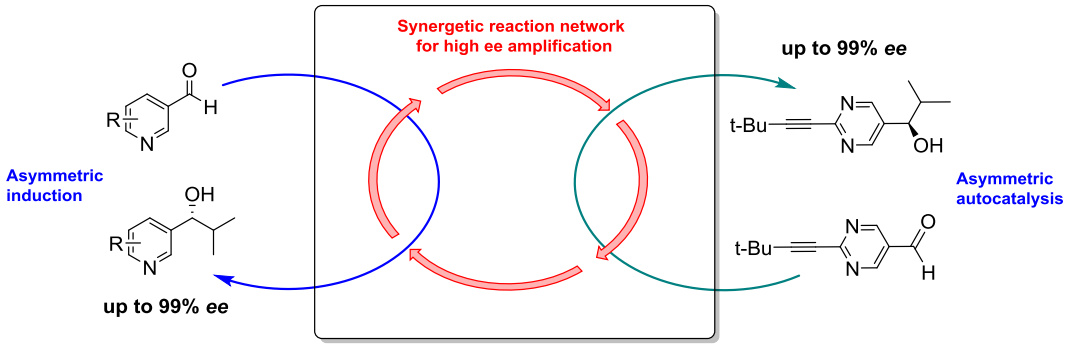
Abstract

Self-replicating assemblies of molecules have been constructed, and some are even capable of asymmetric amplification. By comparison the Soai chemical system is elegant in its simplicity, which offers overexpression of the product through a sequence of autocatalytic cycles.[1] The overall outcome represents a Darwinian like evolving system, which combines propagation of a chemical information, chirality, with exponential amplification.



Inspired by this work, in our research we explore interactive chemical systems in which asymmetric autocatalysis is coupled with asymmetric induction.[2] Recently, we discovered that the Soai autocatalyst also can cross-replicate with a partner organic molecule, which is not capable of such amplification on its own. This merger resulted in their mutual exponential growth and enabling self-sustained asymmetric amplificaton in a single cycle.[3] We illustrate these features with selected chemical transformations and provide insight into mechanistic behaviour of these replicators. We will also discuss how these systems become responsive to external chiral stimuli able to reflect and reproduce chirality.[4]

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TRIGGERING ASSEMBLY AND DISASSEMBLY OF A SUPRAMOLECULAR CAGE

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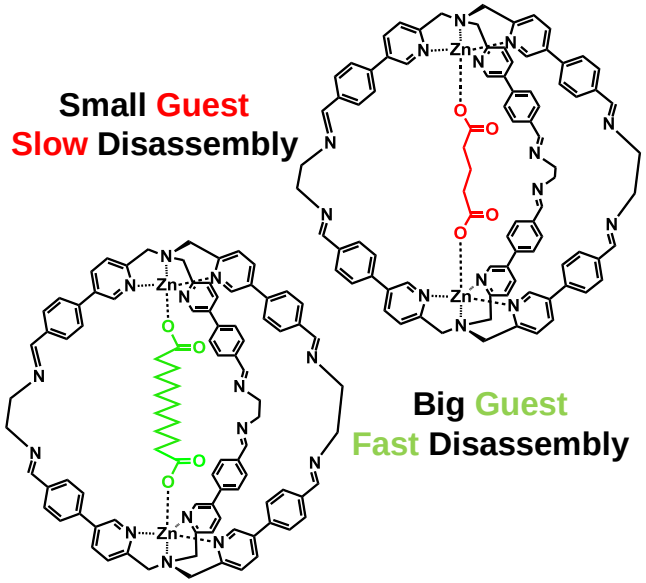
Abstract

A novel supramolecular cage built from the self-assembly of tris(2-pyridylmethyl)amine TPMA zinc complexes[1] through imine condensation chemistry is reported. The cage recognition properties over a variety of structurally related guests, together with the kinetic study of the template assembly and disassembly, have been investigated in detail. This knowledge has been used to selectively modulate the rate of both assembly and disassembly processes. In particular, a novel disassembly method induced by strain release of the guest has been developed.



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DEVELOPMENT OF SYNAPSIS MODULATORS USING DYNAMIC COMBINATORIAL CHEMISTRY

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Abstract

Dynamic combinatorial chemistry (DCC) has proven its potential in drug discovery speeding the identification and optimization of modulators of biological targets.[1]

We present the discovery of novel ligands of Frequenine-2 (Frq2), a high-affinity Ca^{2+}-binding protein conserved from yeast to humans (named Neuronal Calcium Sensor-1). Frq2 is involved in pathologies that result from an abnormal synapse number such as Fragile X syndrome (FXS).[2] Fragile X syndrome is the most common inherited cause of intellectual disability and a common known single gene cause of autism spectrum disorders.

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PROGRAMMABLE STIMULI-RESPONSIVES DEVICES GENERATING HIGH-DENSITY DIGITAL INFORMATION

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Abstract

Living organisms respond to internal and external stimuli to maintain and sustain their lives. Recently, inspired by nature, scientists invested great effort for the development of stimuli-responsive surfaces, which can switch properties by undergoing to specific programmable triggers, convinced that diverse technological fields could benefit by such dynamic platforms. In such devices, the stimuli-responsive molecules functionalizing the surfaces dictate their specific switchable properties. Herein, coiled coil protein assemblies are suggested as new candidates for this task, due to their versatile properties and functionalities.[1] A convenient approach to concisely analyze such stimuli-responsive systems is using Boolean logic operations.[2, 3] Our group previously reported studies on complex coiled coil networks in solution describing logic operations.[4] Herein, we present reversible surface attachment-detachment processes involving coiled coil proteins and describe orthogonal logic operations. To this end, coiled coil peptides have been designed, synthesized and characterized in solution by circular dichroism and fluorescence spectroscopies. Several reversible binding and releasing, folding and unfolding processes of heterodimeric coiled coil proteins have been performed on silicon nitride and gold surfaces. The surface layer was characterized by ellipsometry, fluorescence and contact angle measurements after each step to probe the reaction efficiency. Finally, the programmable reactions have been performed demonstrating Boolean logic operations. The coiled coil peptides were labelled with a FRET couple, allowing the parallel implementation of different two- and three-input logic gates, NOR-OR and AND-INH-NAND, by following different readout: monolayer thickness, donor quenching, and wettability. The experiments accomplished demonstrated the feasibility of this system for reversible protein self-assembly on solid surfaces. Surface properties can be dynamically dictated by functionalization with appropriate designed proteins depending on the targeted device application. We believe that this new approach of programmable manipulation of synthetic proteins on solid surface can pave the way to the development of more effective, robust and flexible biosensing devices.

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INVESTIGATING THE ORIGIN OF LIFE AND THE EVOLUTION OF BIOCATALYSTS USING DROPLET-BASED MICROFLUIDICS

Andrew D. Griffiths

ESPCI Paris

Abstract

Microfluidic systems allow droplets of picolitre volume to be made and manipulated with high precision and at high speed (~1000 droplets s^{-1}). These systems are powerful tools to study the potential role of compartmentalization on pre-biotic chemistry and the origin of life.

The thermodynamic unfavorability of synthetic chemical reactions has led to strong criticism of the prebiotic broth theory for the origin of life. However, we have shown that both the kinetics and thermodynamics of synthetic reactions can be enhanced by compartmentalization at the mesoscale—without confinement on the molecular scale— in micrometer-diameter droplets, a feature considered as a sharp advantage in "prevolutionary dynamics" (1).

Furthermore, after the appearance of the first molecular replicators, which was probably a critical step in the origin of life, parasitic replicators would take over and would have prevented life from taking off unless the replicators were compartmentalized in reproducing protocells. Paradoxically, control of protocell reproduction would seem to require evolved replicators. We have shown that a simpler population structure, based on cycles of transient compartmentalization (TC) and mixing of RNA replicators, is sufficient to prevent takeover by parasitic mutants (2). TC tends to select for ensembles of replicators that replicate at a similar rate, including a diversity of parasites that could serve as a source of opportunistic functionality. Thus, TC in natural, abiological compartments—for example, atmospheric aerosol droplets, microcompartments in hydrothermal vents, ice eutectic phases, clusters on mineral surfaces, or lipid vesicles may have played an important role in the origin and takeof of life.

We are also investigating sytems in which droplets grow due to osmotically-driven flow, based on the efficiency of the autocatalytic reaction networks inside, and the droplets divide when they reach a critical size. Droplets containing more efficient reaction networks should grow and divide more quickly than those with less efficient networks, translating synthetic efficiency into fitness, a first step towards an evolving chemical system.

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(SELF)-RECOGNITION IN DYNAMIC COMBINATORIAL LIBRARIES

Sijbren Otto

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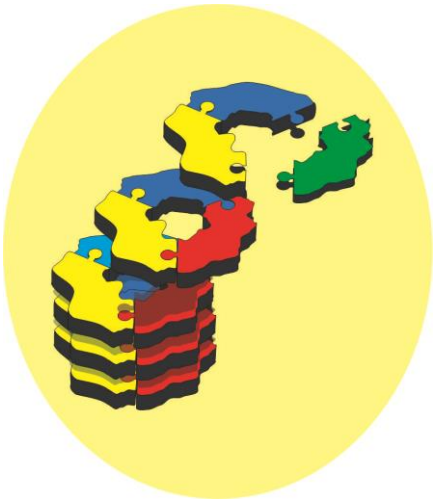
Abstract

Dynamic combinatorial libraries[1] are mixtures of molecules that exchange sub-components continuously. Molecular recognition events tend to shift the product distributions of such mixtures in the direction of those molecules that are most efficiently stabilized by non-covalent interactions. Thus, addition of external templates can cause specific molecules to be stabilized, leading to synthetic receptors or ligands for biomolecules. Alternatively, even without the use of external templates, amplification of specific products can occur through interaction within or between molecules, channelling the building blocks into foldamers, interlocked structures or self-assembling, self-synthesising (potentially self-replicating) structures.



In this lecture I will show examples of most of these different types of template effects both in isolation[2] and in combination.[3] I will also show interesting out-of-equilibrium behaviour in systems built solely from interactions and bond formation processes that are individually all reversible. Such systems represent an exciting step up in complexity and start to capture behaviour that has thus far been mostly encountered within the domain of living systems.

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UNRAVELING THE MULTISTIMULI RESPONSES OF A DYNAMIC COMPLEX SYSTEM OF MACROCYCLIC PSEUDOPEPTIDES

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Abstract

Complexity is an appealing concept that has recently attracted the Chemistry research community.[1] Regarding that, dynamic combinatorial libraries[2] have proved to be excellent models to study the stimuli-responsiveness of chemical networks.[3] However, these complex systems are often difficult to analyze with conventional methods, since many variables and interconnections have to be considered for their full understanding. Here we propose the use of statistical and multivariate analyses to bisect the evolution of a complex synthetic dynamic library of pseudopeptidic macrocycles.[4] Several stimuli (ionic strength, pH and the presence of a biogenic polyamine) were applied to the same dynamic mixture, and the adaptation of the whole system was analyzed (HPLC) with Principal Component Analysis[5] and Multivariate Curve Resolution-Alternating Least Squares[6] methods. These approximations are an excellent combination to extract both qualitative and quantitative conclusions about the adaptive process of the library. The chemometric resolution is especially useful when two interconnected stimuli were combined in the same dynamic system, underscoring the applicability of these tools in the emergent field of Systems Chemistry.[7]

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COMPLEX FUNCTIONS EMERGING IN SYNTHETIC REPLICATION NETWORKS

Gonen Ashkenasy, *Rakesh Mukherjee, Indrajit Maity, Nathaniel Wagner*

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Abstract

Like many other open systems in nature, living organisms are replete with rhythmic and oscillatory behavior at all levels, to the extent that oscillations have been termed as a defining attribute of life. Additionally, living organisms contain internal circadian clocks that produce rhythms of a 24 hour cycle. Recently, we have started to investigate an important challenge in contemporary Systems Chemistry, that is, to synthetically construct "bottom-up" molecular networks that display such complex behavior. Towards this aim, we utilize catalytic replication networks, which have already served to study emergent phenomena in complex mixtures.[1,2] In the first part of this talk, I will describe the kinetic behavior of small networks of coupled oscillators, producing various functions such as logic gates, integrators, counters, triggers and detectors. These networks are also utilized to simulate the connectivity and network topology observed for the Kai-proteins circadian clocks from the S. elongatus cyanobacteria, thus producing rhythms whose constant frequency is independent of the input intake rate and robust towards concentration fluctuations.[3,4] Then, in the second part, I will disclose our experimental results, showing for the first time that the replication process can also lead to bistability in product equilibrium distribution.[5,6] We believe that these recent studies may help further reveal the underlying principles of complex enzymatic processes in cells and may provide clues into the emergence of biological clocks.

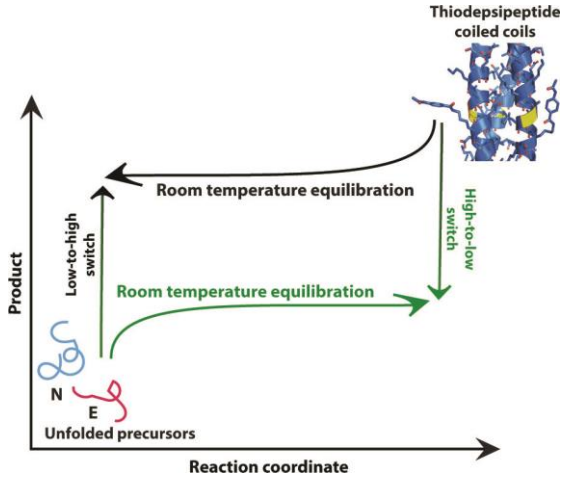

Figure 1. Bistable behavior observed along thiodepsipeptide equilibration experiments.

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TRIPEPTIDE HYDROGELATOR (FFA) AS A MINIMALIST MODEL OF AGGREGATION OF Aβ PROTEINS

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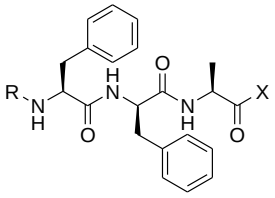
Abstract

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. [1-3]



R = Ac-, $CH_3(CH_2)_3$-, Cbz-,
X = -OMe, -OH, $-NH_2$

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-NH2 tripeptide exhibited gelation of water by self-assembly under physiological conditions. TEM of the Ac-FFA-NH2 hydrogel and the methanol/water gel showed the presence of straight fibers with relatively uniform diameters of around 30 nm. FTIR and NMR investigation pointed toward the cross-β structure type of hydrogen bonding of the tripeptide in the gel aggregates.

Conjugated dyes (Thioflavine T and Congo red) are commonly used to stain the plaques in histopathological studies. [4] Fluorescence titration of Ac-FFA-NH2 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. 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.

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BACTERIAL FUNCTIONAL AMYLOIDS BASED SUPRAMOLECULAR ASSEMBLIES

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Abstract

Bacterial amyloids are generally formed by more than one protein, in *E. coli* (CsgA and CsgB), in *Pseudomonas* (FapB and FapC) or in *Bacillus* (TasA and TapA).[1] These protein are interacting each other and forming the matrix materials of the biofilm through molecular self-assembly. Final products are formed in the shape of fibrillar structures. Biofilm proteins are offering many possibilities to be used a molecular building blocks to form new generation of material systems. These proteins can be easily functionalized with chemical groups through protein engineering strategies resulting in functional self-assembled entities. We aimed to program CsgA and CsgB proteins to form strategies for the utilization of these proteins as functional material systems. We followed two different routes, in the first approach we used the purified proteins of CsgA and CsgB (CsgA is the major biofilm protein whereas CsgB is the minor protein). We exploit the assembly properties of CsgA and CsgB proteins to form ordered material systems in vitro. Electron microscopy images showed that purified CsgA forms long range nanowires whereas the purified CsgB tend to form large spherical micro/nanoparticles on gold surface and their equimolar mixture forms nanowires or spherical particles with an extension of short wires depending on which protein is added first. Structural characterization of the aged self-assembled protein polymers supported the transition of the pure biofilm proteins into ordered structures. Additionally, resulting nano/microstructures found to have strong fluorescence signal in aqueous environment as well as in chloroform while conserving the biofilm protein enabled fiber networks intact. Biofilm proteins offer opportunities as cheap, useful, easy-to-synthesize biomaterials that can be functionalized through protein engineering. In the second approach we programmed cellular circuits to secrete biofilm proteins using recombinase protein based genetic logic gates to control the morphology of the final biofilm structures. These enabled us to control the final material properties of a self-assembled protein based nanowire systems. Functional amyloids of bacteria are promising biomaterial systems for functional applications ranging from bioelectronics to tissue engineering. [2]

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NATURAL SYSTEMS BIOGEOCHEMISTRY

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Abstract

It is interesting that one of the first occurrences of the term « systems chemistry » seems to have been in the field of prebiotic chemistry and early evolution of life. If a possible definition of systems chemistry is to make and study chemical systems that can to some extent adapt to perturbation, then biogeochemical systems that govern fluxes of matter in the Earth system follow the rules and concepts of this science. In this work, I will take the example of the planetary terrestrial carbon cycle. I will discuss how it responds and adapts to perturbations (e.g. forcing of the CO_2 atmospheric concentration), what are the limits of these adaptations and how a new biogeochemical system may settle down. A characteristic of systems chemistry is the multicomponent character of the chemical network considered. I will make a parallel between this multicomponent character required in systems chemistry and the complex ecology of ocean phytoplankton with regard to specific chemical reactions (e.g. biomineralization) . This systems biogeochemistry allows adaptation (or not if some limits are exceeded) to external forcing such as increased atmospheric CO_2 concentration. Major crises of system Earth, including the great oxidation event and possibly the emergence of life itself will be analyzed according to this systems chemistry approach.

DRIVING ENERGY FLOW THROUGHOUT CHEMICAL NETWORKS

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Abstract

Envisioned as organized matter, any living system necessarily exists in a dissipative non-equilibrium state. Otherwise it would reduce to immutably stable combinatorial mixtures of chemical compounds. Indeed, whatever the adopted theoretical perspective on the origins of Life, energy has been much in demand to achieve free energy-consuming processes encountered in living systems such as, for instance, concentration of diluted matter, activation of stable building blocks towards subsequent chemical reactions, biochemical oscillations, active metabolic regulation, hypersensitivity for biological control, kinetic proofreading to overcome the thermodynamic limits during replication, or oriented molecular motion.

In fact, Earth has been (and is still) rich of energy: its solid crust is not chemically equilibrated with its fluid (liquid and gaseous) envelopes so as to generate primary sources of chemical energy, radioactivity has generated heat transfer from the depth to the surface of the planet, and Earth surface has been submitted to illumination from the Sun. The existence of abundant sources of energy was a prerequisite to make possible the emergence of Life envisioned as a dissipative chemical process. However, this thermodynamic constraint alone did not guarantee that sets of chemical reactions could extract from these sources the energy to emerge, reproduce, and evolve; an up-conversion chemical technology coupling primary energy sources to the sets of chemical reactions and involving much kinetic constraints had to be found.

In this lecture, I will introduce a simple and generic coupling strategy to propagate energy throughout chemical networks. It exploits spatial gradients of intensive thermodynamic parameters such as temperature, chemical potential, or affinity to activate and sustain futile cycles of reaction-diffusion bearing analogies with protometabolisms. Such situations are precisely encountered in deep-sea hydrothermal systems in which mixing between seawater and hydrothermal fluids generates steady-state gradients of temperature, pH, and redox potential.

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ON THE LEVELS OF ABSTRACTION IN SYSTEMS CHEMISTRY

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Abstract

Computational techniques are required for narrowing down the vast space of possibilities to plausible prebiotic scenarios, since precise information on the molecular composition, the dominating reaction chemistry, and the conditions for that era is scarce. The exploration of large chemical reaction networks is a central aspect in this endeavour. While quantum chemical methods can accurately predict the structures and reactivities of small molecules, they are not efficient enough to cope with large-scale reaction systems. The formalization of chemical reactions as graph grammars provides a generative system, well grounded in category theory, at the right level of abstraction for the analysis of large and complex reaction networks. An extension of the basic formalism into the realm of integer hyperflows allows for the identification of complex reaction patterns, such as auto-catalysis, in large reaction networks using optimization techniques. We will present methods for graph grammar rule composition in the context of prebiotic chemistry. The approaches are already highly automated, and will bring wetlab and *in silico* experiments closer together. We argue that the intermediate-level theory outlined here holds promise in many fields of chemistry. In particular, we suggest that it is a plausible substrate for a predictive theory of prebiotic chemistry.

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