ABSTRACTS

Darwinian Chemistry Autumn School

Proto-peptide Backbone Affects Assembly in Aqueous Solutions
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One of the most fascinating mysteries in the field of origins of life concerns the driving force that led to the selection of today's 20 universal L-alpha amino acids in biology. An essential aspect of life's emergence involves the formation of compartments, which offer encapsulation for target molecules and provide protection from hydrolysis in aqueous environments. Thus, polymers capable of assembly may have had a chemical evolutionary advantage over polymers that lacked this ability. We postulated that primordial peptide assembly could be one of the driving forces that led to the chemical selection of alpha amino acids in life today. To test this hypothesis, we generated depsipeptides, oligomers composed of ester bonds and peptide bonds that form readily under mild drying conditions, as model prebiotic peptides. However, it is unknown whether depsipeptides form assemblies in an aqueous environment similarly to peptides and proteins. To test the hypothesis that depsipeptides with alpha backbones will form assemblies more readily than beta backbones, we synthesized depsipeptides using a matrix of eight alpha- and beta- hydroxy acids and six alpha-, beta-, and gamma- amino acids. The reaction products were analyzed by microscopy and a physical stability analyzer to study assembly formation as well as various analytical techniques for chemical analysis. Our results demonstrate assembly formation in depsipeptide systems containing hydrophobic hydroxy acids and indicate that depsipeptide assemblies containing alpha hydroxy acid backbones are significantly more stable than beta analogs. Overall, our results offer an assembly-driven mode of selection for the alpha backbone in present-day biology.

Design, screening, or simple emergence of artificial folded molecules: exploring (the lack of) sequence space
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Biopolymers like proteins and nucleic acids adopt folded conformations that enable them to perform their functions. Chemists have shown that folding is not unique to biopolymers. Numerous synthetic backbones - foldamers - have been shown to also adopt folded conformations. Aromatic foldamers - foldamers with aryl rings in their main chain - constitute a distinct and promising class of molecules whose folded conformations are particularly stable and predictable. Such molecules provide simple systems to explore the sequence-structure-function paradigm. How large does a sequence space need to be for structure and function to emerge? Can complex folded conformations be obtained with a single monomer, that is, without any sequence information? Can folding drive the selection of a sequence?

Synthetic cells out of equilibrium
Job Boekhoven
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I will present our recent efforts to construct synthetic cells that can only exist out of equilibrium by consuming chemical fuels. Drawing inspiration from life's reliance on constant energy turnover, we design compartmentalized systems—based on coacervate droplets and vesicles. Due to their chemically fueled nature, these compartments spontaneously emerge in response to chemical energy; they keep themselves "alive" by continuously making their own building blocks, and if one stops feeding them, they will decompose. These compartments start to display some of the hallmarks of life. Under specific conditions, they can even self-divide.
For them to become alive, they need to also be subjected to Darwinian evolution. I'll discuss our latest endeavours in that direction.

Kinetic Analysis of Reaction Networks: Elucidation of Reaction Mechanisms in Asymmetric Autocatalysis
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Chemical reactions that lead to a spontaneous symmetry breaking or amplification of the enantiomeric excess are of fundamental interest in explaining the formation of a homochiral world. An outstanding example is Soai's asymmetric autocatalysis, in which small enantiomeric excesses of the added product alcohol are amplified in the reaction of diisopropylzinc and pyrimidine-5-carbaldehydes. Comprehensive kinetic experiments and modelling of the hemiacetal formation in the Soai reaction allow the precise prediction of the reaction progress, the enantiomeric excess as well as the enantiomeric excess dependent time shift in the induction period of this autocatalytic reaction. New software tools will be presented for detailed and precise kinetic analysis.

What Darwinian chemists ought to know about evolutionary dynamics
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- *Institute of Evolution, HUN-REN Centre for Ecological Research, Budapest*

I shall survey the key concepts and model of evolutionary theory with clear applications in (systems) chemistry. The list includes units of selection and evolution, growth laws (subexponential, exponential and hyperbolic), the quasicpecies model and the error threshold, the replicator equation, population structure and multilevel selection. Explicit chemical examples will be considered for all cases.
Paczkó, M., Szathmáry, E., Szilágyi, A. (2024) Stochastic parabolic growth promotes coexistence and a relaxed error threshold in RNA-like replicator populations. *eLife* **13,** RP93208.
Lu, H., Blokhuis, A., Turk-MacLoad, R., Karupussamy, J., Franconi, A., Woronoff, G., Jeancolas, C., Abrishkamar, A., Loire, E., Ferrage, F., Pelupessy, P., Jullien, L., Szathmáry, E., Nghe, P., Griffiths, A.D. (2024) Small-molecule autocatalysis drives compartment growth, competition and reproduction. *Nature Chemistry* **16,** 70-78.
Adamski, P., Eleveld, M., Sood, A., Kun, Á., Szilágyi, A., Czárán, T., Szathmáry, E., Otto, S. (2020) From self-replication to replicator systems en route to de novo life. *Nature Rev. Chem.* **4,** 386–403.
Szilágyi, A., Kovács, V., Szathmáry, E., Santos, M. (2020) Evolution of linkage and genome expansion in protocells: the origin of chromosomes. *PloS Genet.* **16(10),** e1009155.

Feedback regulated catalysis

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Drawing inspiration from the interplay between catalysis and oscillatory behavior in biological systems, our research group has developed organic molecule based catalytic oscillator.
The design, modelling, development and potential applications of catalytic organic oscillators will be presented.

EXPERIMENTAL CHALLENGES IN THE USE OF VESICLES AS PROTOCELL MODELS

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Vesicles are examples of protocells, which are defined here as hypothetical prebiological compartment systems, i.e., molecular assemblies that may have preceded the first cells at the origin of life. Vesicles are cell-like structures ranging in size from less than one micrometer to several micrometers, consisting of membrane-forming amphiphiles and an internal aqueous volume separated from an aqueous solution in which the vesicles are dispersed. The formation of vesicles in aqueous solutions occurs from many different types of biological or synthetic amphiphiles or from mixtures of amphiphiles. Some of the known vesicle-forming amphiphiles are even prebiotically plausible. The preparation of vesicles in which chemical transformations take place that not only contribute to the growth and division of the vesicles but also lead to the replication of the vesicle-confined molecules that cause these chemical transformations, is a very challenging goal. Important to address are questions concerning the permeability of the vesicle membrane and the possibilities for encapsulating catalytically active compounds in the vesicles. One of the major experimental challenges in the preparation of vesicle-based model protocells in the laboratory is to achieve sustainable growth and controlled division of the vesicles through chemical reactions that are confined to the vesicles.

Approaching the De-Novo Synthesis of Life

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How the immense complexity of living organisms has arisen is one of the most intriguing questions in contemporary science. We have started to explore experimentally how organization and function can emerge spontaneously from networks of interconverting molecules in aqueous solution.[1] Molecular recognition between molecules in such mixtures leads to their mutual stabilization, which drives the synthesis of more of the privileged structures amounting to their self-replication.[2] These replicators can also catalyse the formation of other components of the system, including molecules that assemble into coacervate compartments, amounting to a primitive metabolism.[3,4] Rudimentary Darwinian evolution of purely synthetic replicators has also been achieved[5,6] and current efforts focus on extending this behaviour to compartmentalised replicators.

1. Otto, S. *Acc. Chem. Res.* **2022**, *55*, 145-155.
2. Carnall, J. M. A.; Waudby, C. A.; Belenguer, A. M.; Stuart, M. C. A.; Peyralans, J. J.-P.; Otto, S. *Science* **2010**, *327*, 1502-1506.
3. Monreal Santiago, G.; Liu, K.; Browne, W. R.; Otto, S. *Nature Chem.* **2020**, *12*, 603-607.
4. Ottelé, J.; Hussain, A. S.; Mayer, C.; Otto, S. *Nature Catal*. **2020**, *3*, 547-553.
5. K. Liu, A. Blokhuis, C. van Ewijk, A. Kiani, J. Wu, .W.H. Roos, S. Otto *Nature Chem.* **2024**, *16*, 79–88.
6. Eleveld, M.; Geiger, Y.; Wu, J.; Kiani, A.; Schaeffer, G.; Otto, S. *Nature Chem.* **2025**, *17,* 132-140.

Regulation of coacervate properties by molecular flux

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Coacervates provide a plausible route to primitive compartmentalisation. It has been proposed that coacervates, can serve as a compartment to host prebiotic reactions during the Origin of Life [1]. There has been progress in uncovering new chemical routes to the synthesis of key biological molecules and metabolites. In parallel, it is well established that key biological molecules and metabolites can form coacervates. Despite this there has been little focus on the effect of molecular flux on coacervate properties.

Here, we focus on coupling compartmentalisation with reactions and show how molecular flux can tune the material properties of the dispersion and the phenotype of coacervate droplets. Our systems are primary examples of minimal active matter that are regulated by molecular flux.

[1] Oparin, A. I. The Origin of Life. 1938 New York. *NY: Dover Publications (transl. with annotations by S. Morgulis Macmillan republished in 1953, 1965 and 2003)*.

Regulating the Upcoming Synthetic Cells Using Signaling Modules and Network Motifs

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The design and organization of man-made life constitute a long-standing target for chemistry and biology laboratories. Systems Chemistry research on this topic focuses on taking small steps towards the construction of unicellular systems, containing self-organized networks that feature three of the main characteristics of a living cell: (i) boundaries that fix the active molecules in specific settings, (ii) autonomous replication of individual molecules or molecular assemblies, and (iii) metabolism via the exchange of energy and materials with the environment. In order to maintain smooth life cycles and respond to changes in their environment, these future synthetic cells would need to receive and process signals that originate inside or outside their borders and integrate that information into a unified action plan. We will show recent examples of how this can be achieved via the design of bistable[1] and oscillatory[2] signaling elements, and network motifs[3], all producing entities of codes with specific information, which in turn induce downstream activity.

[1] I. Maity, N. Wagner, D. Dev, G. Ashkenasy "Bistable Functions and Signaling Motifs in Systems Chemistry: Taking the Next Step Toward Synthetic Cells" *Acc. Chem. Res.* **2025**, 58, 428–439.
[2] D. Dev, N. Wagner, B. Pramanik, B. Sharma, I. Maity, R. Cohen-Luria, E. Peacock-Lopez, G. Ashkenasy "A Peptide-Based Oscillator" *J. Am. Chem. Soc.* **2023**, 145, 26279–26286.
[3] M. Samanta et al. "Network Motifs Regulating Primitive Peptide-Carbohydrate Networks" in preparation.

Darwinian evolution in autocatalytic chemical reaction systems

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Darwinian evolution, which is based on the principles of variation, selection and inheritance, has had a profound impact on our understanding of biological complexity. However, applying these principles to prebiotic chemistry is both conceptually challenging and experimentally elusive. While some models propose that basic chemical networks could exhibit evolutionary behaviour, these analogues often lack the fidelity and stability required for genuine Darwinian evolution. The aim here is to critically evaluate the extent to which Darwinian evolution can be meaningfully applied to prebiotic chemistry. To this end, I will explore the conceptual boundaries between chemical and biological evolution, examine experimental models that attempt to simulate evolutionary behaviour and discuss the conditions required for such chemical systems to exhibit self-reproduction and Darwinian evolution. Ultimately, I conclude that while Darwinian principles offer valuable insights, they must be adapted to account for the unique constraints and mechanisms of prebiotic systems.

Is there a 'Hydrogen Atom' of Biology?

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The hydrogen atom is the smallest representation of a chemical element and considered to be the most complex form of matter that can be analytically calculated, i.e. understood from first principles, by quantum mechanics. Thus, it has become a paradigm for understanding the material world in the perspective of physicists and chemists. Such a minimal system that aids the development of fundamental theories and hypotheses, however, has not yet been identified in biology. To the contrary, life sciences have from their very beginnings dealt with incomprehensively complex systems, such as animals and plants, and only the past decades have allowed us to elucidate their molecular makeup and formulate quantifiable laws that can be, albeit often with disappointingly low statistical confidence, addressed by physical methods and technologies. Our very simple question, which is however extremely challenging to answer, is whether something like a minimal system, reminiscent of the hydrogen atom for physics and chemistry, could also be identified for biology – the smallest possible representation of a living cell (being by definition the smallest unit of life). By methods of molecular biology and biochemistry we try to identify fundamental functional units in proteins or nucleic acids, the combination of which allows a system to develop emergent behavior to the point of establishing essential features of life, such as metabolism, replication, and functional evolution. Using cutting edge biophysical methods, we analyze these functions on the single molecule level and thereby aim to formulate a canonical set of functions that would be required for matter to become alive, independent of the carbon-based representation of life on earth.

Microfluidics: from research to innovation

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Microfluidics is a wonderful tool to for research in different fields, such as biology (ex: organ-on-chip), chemistry (ex: reaction encapsulation) or environment (ex: soil remediation). Interestingly, it is also used by industries in those fields and others. For example, in chemical applications, microfluidics has a high relevance for pharmaceuticals through drug screening and continuous flow synthesis, and medicine, agriculture or inks industries benefit a lot from nanoparticle synthesis.

We will have an introduction to microfluidics, and then discuss one main difference between a research group and a company: innovation towards industry. To achieve a symbiosis between research-oriented microfluidics and new innovations, we must understand additional aspects such as market research and use tools like beta-testing. We will review those aspects, which are the key to bring a new dimension of innovation in addition to research.