SysChem 2015
19-22 May 2015 ♦ Abdij Rolduc ♦ the Netherlands

www.systemschemistry.com/syschem2015/
Venue details:

Abdij Rolduc
Heyendallaan 82
6464 EP Kerkrade
The Netherlands
Phone: +31 (0)45 546 6888
www.rolduc.nl

Internet connection:

Free wifi (main building only): Abdij Rolduc WiFi

(Maps of the venue can be found on the next pages)

Other conference information:

Email: syschem2015@rug.nl
Twitter: @syschem2015
Web: www.systemschemistry.com/syschem2015/

Abstract booklet can be found on our website.
Welcome to SysChem2015

Welcome to the 2015 meeting on Systems Chemistry. This year's meeting is co-organized between the EU COST network CM1304 (Emergence and evolution of complex chemical systems, chaired by Sijbren Otto) and the Dutch research center for functional molecular systems (FMS; chaired by Bert Meijer).

The EU COST network is the latest one in a series that originated from the origin-of-life field (previous Actions involved prebiotic chemistry and early evolution and systems chemistry). It aims to bring together three still rather poorly connected fields: far-from-equilibrium chemical systems, origin of life and supramolecular chemistry. Currently well over 80 European research groups from 23 countries are taking part in this COST network, which funds conferences, working group meetings, exchange of co-workers through collaborative visits, and training schools. For further details, see: www.systemschemistry.com/cm1304.

The Dutch FMS research center is a partnership of the organic and macromolecular chemistry teams of the Eindhoven University of Technology, the Radboud University Nijmegen, and the University of Groningen, brought together to extend the frontiers of chemical self-assembly targeting the construction of functional life-like molecular systems. The FMS research center is a 10-year multi-million program that directly funds research at the participating universities. More information can be found on: www.fmsresearch.nl.

Bringing these two initiative under one roof for a few days will undoubtedly spark many new ideas. True to the spirit of previous meetings on Systems Chemistry the program allows ample time for discussions to develop these ideas into new collaborative research directions.

In the remainder of this booklet you will find a map of the venue, the program, a list of posters and contact details of the participants. Abstracts of posters and talks can be found online at the conference website: www.systemschemistry.com/syschem2015.

We hope you will find this an enjoyable and inspirational meeting.

Annette Witter
Marta Comellas Aragones
Yigit Altay
Sijbren Otto
(the organizing committee)
1e Verdieping – 1ᵉ floor
0 Kleine eetzaal - Small dining room
P Bisschopszaal - Bisschopsroom
Q Rococo bibliotheek - Library

6 Zaal 6 – Room 6
7 Zaal 7 – Room 7
8 Zaal 8 – Room 8
9 Zaal 9 – Room 9
9A Zaal 9A – Room 9A
10 Zaal 10– Room 10
11 Zaal 11– Room 11
12 Zaal 12– Room 12
13 Zaal 13– Room 13

1e Verdieping – 1st floor
3101 – 3123 (hoofdgebouw - main building)
5101 – 5110 (Hoeve - Farmhouse)
6102 – 6107 (Hoeve - Farmhouse)

2e Verdieping – 2nd floor
1201 – 1218 (hoofdgebouw - main building)
2201 – 2227 (hoofdgebouw - main building)
3291 – 3222 (hoofdgebouw - main building)
5201 – 5217 (Hoeve - Farmhouse)
6201 – 6221 (Hoeve - Farmhouse)

3e Verdieping – 3rd floor
2301 – 2314 (hoofdgebouw - main building)
Program Syschem 2015

Monday 18 May
19:30 - 21:00  Registration and welcome drinks
(Registration desk is located close to the reception area)

Tuesday 19 May  Room: Aula Major
07:45 - 08:30  Registration
(Registration desk is located close to the reception area)
08:30 - 08:45  Welcome address

Chair: Peter Walde
08:45 - 09:25  P1  Tadashi Sugawara (University of Tokyo, Japan)
Recursive vesicle-based protocell constructed as a molecular system
09:25 - 09:50  O1  Kepa Ruiz-Mirazo (University of the Basque Country, Spain)
Life requires chemistry making its own dynamic boundaries
09:50 - 10:15  O2  Salvador Tomas (Birkbeck, University of London, UK)
Self assembly and reactivity in liposomes
10:15 - 10:20  General discussion

10:20 - 11:00  Coffee break

Chair: Andres de la Escosura
11:00 - 11:25  O3  Pall Thordarson (UNSW Australia)
Complexity in protein containing polymersomes: from light-induced proton pumping to revealing cargo location in compartmentalised polymersomes
11:25 - 11:50  O4  Yao Lin (University of Connecticut, USA)
Supramolecular polymerization from synthetic polypeptide-grafted subunits
11:50 - 12:30  P2  David Deamer (University of California Santa Cruz, USA)
Generation of oligonucleotides by non-enzymatic polymerization under hydrothermal conditions
12:30 - 12:35  General discussion

12:35 - 14:00  Lunch (Dining hall)

Chair: Robert Pascal
14:00 - 14:40  P3  Markus Ralser (University of Cambridge, UK)
From its origins to the modern metabolic network
14:40 - 15:05  O5  Christoph Flamm (University of Vienna, Austria)
Designing chemical transformation networks
15:05 - 15:30  O6  Leonard Prins (University of Padova, Italy)
Transient signal generation in a self-assembled nanosystem
15:30 - 15:35  General discussion

15:35 - 16:15  Coffee break
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<tr>
<td>16:15 - 16:55</td>
<td>P4</td>
<td>Yannick Rondelez (University of Tokyo, Japan)</td>
<td>DNA circuitry</td>
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<tr>
<td>16:55 - 17:20</td>
<td>O7</td>
<td>Agota Toth (University of Szeged, Hungary)</td>
<td>Morphology control by flow-driven precipitation</td>
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<td>17:20 - 17:45</td>
<td>O8</td>
<td>Vladana Vukojevic (Karolinska Institutet, Sweden)</td>
<td>Quantitative imaging of dynamical reaction-diffusion landscapes by massively parallel fluorescence correlation spectroscopy</td>
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<td>17:45 - 17:55</td>
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<td>General discussion</td>
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<td>18:30 - 20:00</td>
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<td>Dinner (Dining hall)</td>
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<td>20:00 - 21:30</td>
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<td>Poster session</td>
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<td>20:00 - 20:30</td>
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<td>Core group meeting (core group only)</td>
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**Wednesday 20 May**

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<tbody>
<tr>
<td>08:45 - 09:25</td>
<td>P5</td>
<td>Dick Broer (Eindhoven University of Technology, The Netherlands)</td>
<td>Surface dynamics in ordered networks</td>
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<tr>
<td>09:25 - 09:50</td>
<td>O9</td>
<td>Wesley Browne (University of Groningen, The Netherlands)</td>
<td>Spiropyran surface electrochemistry</td>
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<tr>
<td>09:50 - 10:15</td>
<td>O10</td>
<td>Tom de Greef (Eindhoven University of Technology, The Netherlands)</td>
<td>In-vitro synthetic biology: engineering biochemical reaction networks to display non-equilibrium behavior</td>
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<td>10:15 - 10:20</td>
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<td>General discussion</td>
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<td>10:20 - 11:00</td>
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<td>Coffee break</td>
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<tr>
<td>11:00 - 11:40</td>
<td>P6</td>
<td>Takuzo Aida (University of Tokyo, Japan)</td>
<td>Non-equilibrated supramolecular polymerization and materials science</td>
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<tr>
<td>11:40 - 12:05</td>
<td>O11</td>
<td>Bert Meijer (Eindhoven University of Technology, The Netherlands)</td>
<td>Spatiotemporal control in supramolecular polymers in water</td>
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<tr>
<td>12:05 - 12:30</td>
<td>O12</td>
<td>Ben Feringa (University of Groningen, The Netherlands)</td>
<td>Dynamic molecular systems</td>
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<td>12:30 - 12:35</td>
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<td>General discussion</td>
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<td>12:35 - 14:00</td>
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<td>Lunch (Dining hall)</td>
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<td>14:15 - 17:30</td>
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<td>Social program</td>
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<td>18:00 - 19:30</td>
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<td>Dinner (Dining hall)</td>
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**Chair: Wilhelm Huck**

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<tr>
<td>19:45 - 20:25</td>
<td>P7</td>
<td>Bartosz Grzybowski (UNIST, South Korea)</td>
<td>Chemical systems: large and small</td>
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<tr>
<td>20:25 - 21:05</td>
<td>P8</td>
<td>Jan van Esch (Delft University of Technology, The Netherlands)</td>
<td>Out-of-equilibrium biomimetic systems by dynamic and dissipative self-assembly</td>
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<td>Time</td>
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<tr>
<td>09.00-09:40</td>
<td>Josep M. Ribo (Chair: Jan van Esch)</td>
<td>Mechanochiral Effects in J-Aggregates of Amphiphilic Porphyrins</td>
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<td>09:00-09:20</td>
<td>Opening (Chair: Nicolas Giuseppone)</td>
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<td>09:00-09:40</td>
<td>Ziwei Liu (Chair: Peter Walde)</td>
<td>New developments on the prebiotic chemistry of phosphate esters mixed anhydrides of alpha-amino acids and peptides</td>
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<td>09:40-10:00</td>
<td>Vincent Marichez (Chair: Joezpf M. Ribo)</td>
<td>Tunable self-assembly using magnetic fields</td>
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<td>10.00-10:20</td>
<td>Bram Teunissen (Chair: Piotr Nowak)</td>
<td>A positive feedback loop based on supramolecular ring formation</td>
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<td>10:00-10:20</td>
<td>John McCaskill (Chair: Pierre-Alain Monnard)</td>
<td>Autonomous microscale electrochemical systems</td>
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<td>10:00-10:20</td>
<td>Jordi Sola (Chair: Pierre-Alain Monnard)</td>
<td>Topological studies in complex dynamic libraries of pseudopeptides</td>
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<td>11.00-11:40</td>
<td>Zeljko Cupic (Chair: Nathan McClenaghan)</td>
<td>Manifolds of the Bray-Liebafsky oscillating reaction</td>
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<td>11:00-11:20</td>
<td>Andres de la Escosura (Chair: Pierre-Alain Monnard)</td>
<td>Protein cages as nanocompartments in systems chemistry</td>
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<td>11:00-11:40</td>
<td>Emiliano Altamura (Chair: Nathan McClenaghan)</td>
<td>Giant vesicles as microsized bio-reactors</td>
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<td>11:40-12:20</td>
<td>Thomas Pfohl (Chair: Nathan McClenaghan)</td>
<td>Systematic manipulation of DNA functionality by controlled self-assembly and disassembly</td>
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<td>11:40-12:20</td>
<td>Piotr Nowak (Chair: Nathan McClenaghan)</td>
<td>Localized template-driven functionalization of nanoparticles using dynamic combinatorial chemistry</td>
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<td>11:40-12:20</td>
<td>Fabio Mavelli (Chair: Nathan McClenaghan)</td>
<td>Modelling enzymatic reactions inside giant vesicles</td>
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**Thursday 21 May**

Parallel sessions of the four working groups:

**WG1** Room: zaal 1
Far-from-equilibrium self-assembly
Chair: Jan van Esch

**WG2** Room: zaal 2
Self-synthesizing materials and evolving replicators
Chair: Nicolas Giuseppone

**WG3** Room: aula minor
Compartmentalization
Chair: Peter Walde

**WG4** Room: zaal 6 (1st floor)
Information-rich molecules, from information to structure, function and chirality
Chair: Robert Pascal
11:45-12:15 **Clemens Richert**
Experimental conditions leading to the simultaneous oligomerization of nucleotides and amino acids

12:15-12:30 **Adam Kun**
Evolution of the division of labor between genes and enzymes in the RNA world

12:00-12:20 **Christophe Danelon**
Towards growth and division of a minimal cell

12:00-12:10 **Peter Strazewski**
Fluorescent and “incomplete” lipids as useful tools for the study of giant vesicles in “growth and division” experiments

12:00-12:20 **Erwan Bigan**
Chemical requirements for a self-replicating protocell

12:35-14:00 Lunch (Dining hall)
Chair: Zeljko Cupic
Chair: Andres de la Escosura
Chair: Peter Strazewski
Chair: Harold Fellermann

14:00-14:40 **Terence Kee**
Towards convergent abiogenic processes. Peptide and protocell formation driven by the same energy currency system

14:00-14:30 **Beatriz Escuder**
Self-assembled functional fibrillar networks: road to complexity

14:00-14:20 **Andreas Zumbuehl**
Shear-stress responsive liposomes

14:00-14:40 **Nathan McClenaghan**
Chemical communication between functional molecules via photocontrolled ions in polymeric nanocapsules

14:40-15:00 **David Williams**
Designing biodegradable protocells via the modular self-assembly of polymers

14:40-15:00 **Alessandro Sorrenti**
Dissipative self-assembly controlled by enzyme switching

14:30-14:45 **Josh Richards**
Gel-based phase separation enhances selectivity in dynamic self-replicating systems

14:20-14:40 **Peter Walde**
Dendronized polymer-enzyme conjugates for localized enzymatic cascade reactions

15:00-15:20 **Bas Rosier**
Multivalent enzyme kinetics using DNA origami scaffolds

15:00-15:20 **Tilde Pellegrini**
Auto-inductive effects in the asymmetric Cu(I)-catalyzed 1,2-addition of alkyl-Grignard reagents to α,β-unsaturated carbonyl compounds

14:45-15:15 **Daniel Merkle**
Autocatalytic pathways from HCN to glyoxylate

14:40-15:00 **Sjoerd G. J. Postma**
Rational design of enzymatic reaction networks showing multiple complex behaviours

15:00-15:20 **Carlo Bravin**
New multimetallic cages synthesized via imine condensation chemistry

15:15-15:30 **Fatma Yuksel**
Phthalocyanine macromolecules for applications

15:15-15:30 **Tim Paffen**
Supramolecular buffering by ring-chain competition

15:35-16:15 Coffee break
Chair: Jan van Esch
Chair: Beatriu Escuder
Chair: Peter Walde
Chair: Robert Pascal

16:15-16:45 **WG1 discussion**
16:15-16:30 **Jan Sadownik**
Speciation and competition in a network of replicators

16:15-16:35 **Stefano Piotto**
Role of lipid confinement in symmetry breaking

16:35-17:00 **WG3 discussion**
General discussion and future activities

16:15-16:45 **WG4 discussion**

17:15-18:30 Management committee meeting (Room: zaal 1)

18:45 Conference Dinner (Dining hall)
Friday 22 May  

Room: Aula Major

Chair: Gonen Ashkenasy

08:45 -09:25  P9 Gerard Roelfes (University of Groningen, The Netherlands)  
_Supramolecular assembly of artificial metalloenzymes based on DNA and protein scaffolds_

09:25 - 09:50  O13 Roman Jerala (National Institute of Chemistry, Slovenia)  
_In vivo self-assembly of de novo designed protein origami_

09:50 - 10:15  O14 Hannes Mutschler (University of Cambridge, UK)  
_FREEZE-THAW CYCLES AS DRIVERS OF RNA ASSEMBLY_

10:15 - 10:20  General discussion

10:20 - 11:00  Coffee break

Chair: Sijbren Otto

11:00 - 11:40  P10 Roeland Nolte (Radboud University, The Netherlands)  
_CONTROLLING MOLECULAR COMPLEXITY: DESIGN OF BIO-INSPIRED MATERIALS_

11:40 - 12:05  O15 Thomas Hermans (Université de Strasbourg / ISIS, France)  
_DISsIPATIVE SELF-ASSEMBLY STEADY STATES: FROM BATCH TO OPEN SYSTEMS_

12:05 - 12:30  O16 Mohamed Amedjkouh (University of Oslo, Norway)  
_Efficient remote asymmetric amplification in synergistic autocatalytic systems_

12:30 - 12:40  General discussion and concluding remarks

12:40 - 14:00  Lunch (Dining hall) and departure
### Poster presentations

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<td>Alasibi</td>
<td>Adaptive peptide-metal complexes towards Fabrication of Nanometer Scale Structures</td>
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<td>2</td>
<td>Yigit</td>
<td>Altay</td>
<td>In the Search of Bigger Replicators from Dynamic Combinatorial Libraries</td>
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<td>3</td>
<td>Devrim</td>
<td>Atilla</td>
<td>Novel Donor-Acceptor Systems</td>
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<td>4</td>
<td>Boris</td>
<td>Bartolec</td>
<td>Towards Self-Replicating Molecules Capable of Forming Compartments</td>
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<td>5</td>
<td>Tjalling</td>
<td>Canrinus</td>
<td>Anionic ligands for Lanthanide emission</td>
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<td>6</td>
<td>Miriam</td>
<td>Corredor</td>
<td>Dynamic Combinatorial Chemistry for the identification of potential inhibitors of a protein-protein interaction system</td>
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<td>Anniek</td>
<td>den Hamer</td>
<td>14-3-3 proteins as a scaffold for small molecule controlled signaling platforms</td>
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<td>8</td>
<td>Santiago</td>
<td>Díaz-Oltra</td>
<td>Molecular hydrogel catalysis of three component cascade reactions</td>
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<td>9</td>
<td>Emilien</td>
<td>Dubuc</td>
<td>An in vitro gene expression platform to study far from equilibrium synthetic gene networks</td>
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<td>10</td>
<td>Zoubir</td>
<td>El Hachemi Metni</td>
<td>Nanotubes versus layered structures in J-aggregates of amphiphilic porphyrins</td>
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<td>11</td>
<td>Leo</td>
<td>Frkanec</td>
<td>Molecular recognition of ConA and mannose on liposome surface</td>
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<td>Simone</td>
<td>Hendrikse</td>
<td>Biofunctionalized supramolecular hydrogels for intestinal organoid expansion</td>
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<td>13</td>
<td>Andreas</td>
<td>Hussain</td>
<td>Two Replicators Competing for a Common Building Block</td>
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<td>14</td>
<td>Luuk</td>
<td>Kortekaas</td>
<td>Redox controlled emission in a novel D-A-D polymer film</td>
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<td>15</td>
<td>Maria</td>
<td>Lafuente</td>
<td>Adaptive processes in a topologically diverse dynamic library of pseudopeptides</td>
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<td>16</td>
<td>Ruben</td>
<td>Maaskant</td>
<td>Bio-orthogonal metalloporphyrin catalysts for in vivo chemistry</td>
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<td>Munejuki</td>
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<td>Morphological diversity emerged by complexation between DNA and catalysts in vesicle-based protocell</td>
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<td>18</td>
<td>Lenny</td>
<td>Meijer</td>
<td>A generic approach to trigger downstream DNA-based biochemical processes</td>
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<td>Xiaoming</td>
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<td>Selective Functionalized Nanoparticles’ Surface Based on Dynamic Imine Chemistry in The Presence of Biotemplate</td>
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<td>Marlies</td>
<td>Nijemeisland</td>
<td>Compartmentalized metabolic network leads to autonomous movement on natural substrates</td>
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<td>Tim</td>
<td>Paffen</td>
<td>Evolving Single Chain Polymeric Nanoparticles for Cooperative Folding</td>
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<td>Federico</td>
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<td>Communication pathways among liposomes encapsulating a chemical oscillatory reaction</td>
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<td>Gael</td>
<td>Schaeffer</td>
<td>Dynamic combinatorial libraries operated far from equilibrium</td>
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<td>Gijs</td>
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<td>The folding process of a single polymer chain with a chiral internal secondary structure</td>
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<td>Meniz</td>
<td>Tezcan</td>
<td>Design and Length Control of Mixed Block Co-fibers From Dynamic Combinatorial Libraries</td>
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<td>M. Yagiz</td>
<td>Unver</td>
<td>Fragment Linking of Inhibitors of the Aspartic Protease Endothiapepsin Facilitated by Protein-Templated Click Chemistry</td>
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<td>van Brussel</td>
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<td>Susan</td>
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<td>Active materials fueled by a chemical reaction</td>
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<td>Depeng</td>
<td>Zhao</td>
<td>Photo-switchable Chiral Phosphine Ligands for Pd-catalyzed Asymmetric Allylic Amination</td>
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<td>Abdelmohsen</td>
<td>Loai</td>
<td><a href="mailto:l.abdelmohsen@science.ru.nl">l.abdelmohsen@science.ru.nl</a></td>
<td>Radboud University Nijmegen</td>
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<tr>
<td>Aida</td>
<td>Takuzo</td>
<td><a href="mailto:aida@macro.t.u-tokyo.ac.jp">aida@macro.t.u-tokyo.ac.jp</a></td>
<td>University of Tokyo</td>
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<td><a href="mailto:emiliano.altamura@uniba.it">emiliano.altamura@uniba.it</a></td>
<td>Chemistry Department Università degli Studi di Bari Aldo Moro</td>
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<td><a href="mailto:y.altay@rug.nl">y.altay@rug.nl</a></td>
<td>University of Groningen</td>
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Lecture
Abstracts
Giant vesicles as microsized bio-reactors

Altamura E., Stano P., Mavelli F.

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Giant lipid vesicles (GVs) are widely used as model systems to study lipid and membrane protein behavior, in the hydrophobic domain, and compartmentalized enzyme reactions in the water core. In size and composition, these compartments well mimic the simplified cell environment; for this reason GVs are the perfect candidates for synthetic cell construction [1][2].

One of the most important problem about the GVs preparation is related to the controlled encapsulation of solutes. All the common preparation methods, such as gentle hydration and electroswelling, don’t allow a well-controlled entrapment. In 2003 Pautot et al. [3] proposed a successful method for giant vesicle preparation called “droplet transfer method”. This method is based on a water in oil macroemulsion and after centrifugation, the droplets are converted in GVs. In this case the water phase of the emulsion contains all the solutes at known concentration.

Thanks to this procedure, a large variety of compounds can be encapsulate such as enzymes [4], membrane proteins with high molecular weight [5], small fluorescent molecules, synthetic highly charged polymers [6], nucleic acids with gene expression kit [7] etc.

In this contribution we present the possibility to study these compartmentalized systems as bioreactor that can communicate with an external input giving and internal reaction as output. In the inner aqueous core a simplified metabolic pathway is entrapped able to produce a fluorescent signal when essential substrates, for the cascade reaction, are produced and/or added outside the preformed giant vesicles (Figure 1). This process can be monitored by visual inspection (confocal microscopy) for single object analysis or by High-throughput analysis (flow cytometry).

References:

Figure 1 Scheme of cascade reaction in GV: substrate 1 can easily diffuse trough the lipid bilayer, enzyme 1 converts substrate 2 in product 1 that can also permeate the membrane. Once these two species are inside the vesicle, enzyme 2 can produce product 2 and consequently, enzyme 3 can produce a fluorescent product (product 3).
Efficient remote asymmetric amplification in synergistic autocatalytic systems

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Self-replicating assemblies of molecules have been constructed, and some are even capable of asymmetric amplification. By comparison the Soai system is elegant in its simplicity, and has even been regarded as a triumph for reductionism. The Soai reaction is unique, and to date the only, as it offers overexpression of the product through autocatalysis and also amplifies the enantiomeric excess in the chiral product from very low to virtual enantiopurity. Although Frank suggested a theoretical basis for the evolution of high optical activity in 1953 [1], experimental proof of such a concept eluded scientists until a remarkable report by Soai and co-workers in 1995 [2]. We are currently studying chemical systems where an autocatalytic asymmetric amplification is coupled with a second autocatalytic but non-selective process to operate in parallel. Our findings indicate a synergistic relationship, namely asymmetric amplification remains efficient in Soai reaction and lead to a remote propagation of asymmetric amplification in the second chemical process.

Reconciling Ribozyme Activity with Fatty Acid Vesicle Stability

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The “RNA world” and the “Lipid world” theories for the origin of cellular life are often considered incompatible due to the differences in the environmental conditions at which they can emerge [1]. One obstacle resides in the conflicting requirements for divalent metal ions, in particular Mg$^{2+}$, with respect to optimal ribozyme activity, fatty acid vesicle stability and protection against RNA strand cleavage. In this contest we report [2] on the activity of a short L1 ligase ribozyme in the presence of myristoleic acid (MA) vesicles at varying concentrations of Mg$^{2+}$. The ligation rate is significantly lower at low-Mg$^{2+}$ conditions. However, the loss of activity is overcompensated by the increased stability of RNA leading to a larger amount of intact ligated substrate after long reaction periods. Combining RNA ligation assays with fatty acid vesicles we found that MA vesicles made of 5 mM amphiphile are stable and do not impair ligase ribozyme activity in the presence of 1 mM of “free” Mg$^{2+}$.

Moreover, an enhancement of ribozyme activity in presence of low-concentration preformed vesicles was identified; the exact mechanism (direct or indirect interaction) needs to be investigated. Remarkably, a preference for the ligase to operate at low temperature was observed, which may circumvent the problem related to the “warm and wet” conditions usually assumed for the RNA world emergence [3].

Altogether, these results provide a scenario in which catalytic RNA and primordial membrane assembly can coexist in the same environment, increasing the likelihood for the creation of a riboprotocell.

References:

Living organisms and individual cells function far from equilibrium, at times exhibiting steady-state behavior, and always interacting with their environment by importing nutrients and energy and exporting waste products and heat. Like 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 have utilized catalytic replication networks, since these entities have already served to study emergent phenomena in complex mixtures.\(^1\)\(^-\)\(^2\) Our studies with peptides, for example, have shown how small networks may be designed to perform Boolean logic operations and to mimic network motifs.\(^3\) In first part of this talk, we 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 (Fig. 1).\(^4\)\(^-\)\(^5\) Then, in the second part, we will disclose our experimental results, showing for the first time that the replication process can also lead to bistability in product equilibrium distribution. 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.** Proposed diagram of the recently studied circadian network. The robust network oscillatory production of \(T_3\) is compared to its oscillatory production in a simple autocatalytic reaction out of equilibrium.

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Chemical requirements for a self-replicating proto-cell

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We show that self-replication of a chemical system encapsulated within a membrane growing from within is possible without any explicit feature, and without the need for their emergence through complexity. We use a proto-cell model relying upon random conservative chemical reaction networks with arbitrary stoichiometry, and we investigate the proto-cell capability for self-replication with varying the number of reactions in the network. We elucidate the underlying mechanisms in terms of simple minimal conditions pertaining only to the topology of the embedded chemical reaction network. A necessary condition is that each moiety must be fed. And a sufficient condition is that each siphon be fed.\textsuperscript{1} Although these minimal conditions are purely topological, further endowing conservative chemical reaction networks with thermodynamically-consistent kinetics we show that the growth rate tends to increase with increasing the Gibbs energy per unit molecular weight of the nutrient and with decreasing that of the membrane precursor.\textsuperscript{2}

Figure: Example of a random conservative network, with 10 species and 71 reactions. The necessary and sufficient conditions were met for any choice of nutrient and membrane precursor with only the first 9 reactions (wide blue lines).

References:


C-Terminus Activation of Peptides as a Prebiotically Plausible Pathway

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Prebiotic peptide formation promoted by activating agents can take place either through the reaction of α-amino acid monomers, generally converted into N-carboxyanhydrides (NCA) or through the activation of the peptide C-terminus.¹² Our recent investigations have shown that C-terminus activation of peptides promoted by EDC (a water-soluble carbodiimide) or cyanamide (a prebiotically relevant activating agent) proceeds through a 5(4H)-oxazolone pathway;³ while the fast epimerization of the oxazolone intermediate (being not detrimental in a prebiotic context) influences the stereoselectivity of subsequent peptide coupling.⁴

In order to draw a consistent scenario of the emergence of homochirality in a "amino acid / peptide world", we then investigated the C-terminus activation of free dipeptides in dilute aqueous medium, upon which the competitive formation of diketopiperazine (DKP) can also occur. The reaction of free dipeptides with activating agents such as EDC, EEDQ or IBCF, actually resulted in limited DKP formation, while the 5(4H)-oxazolone pathway remained preponderant as with N-acylated peptides. Conversely, non/moderately activated dipeptide esters (−OMe, OPh, OSu), spontaneously lead to the formation of DKP in significant extent, however with unexpected diastereoselectivities, thus suggesting further mechanistic studies.

Figure. C-terminal activation of free dipeptide: competition between 5(4H)-oxazolone and diketopiperazine (DKP) formation.

References:

New multimetallic cages synthesized via imine condensation chemistry.

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Recently, dynamic covalent chemistry (DCC) have been successfully applied to synthesize a wide variety of molecular cages in very good yields starting from small precursors.[1] We planned to take advantage from DCC for the synthesis of molecular cages bearing in the inner cavity metals with coordination sites available for binding. The synthetic strategy use imine formation of opportunely designed tris(2-pyridylmethyl)amine TPy Zn(II) complexes. The reaction of TPy Zn(II) and ethylenediamine allow the formation of the cage 2 (Scheme 1).

Scheme 1. Imine condensation reaction of complexes 1 with ethylenediamine.

TPy complexes are known to furnish stable species that have been previously used for carboxylic acids recognition.[2] Cage 2 has shown the possibility to perform molecular recognition of dicarboxylic acids.

References:


Morphing dynamics in light-triggered molecularly ordered polymer networks

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Polymers that can change shape or can change their surface topography in response to a trigger have a wide application potential varying from micro-robotics to avionics. Preferably this morphing proceeds fast and reversibly. We developed new morphing principles based on in-situ photopolymerized liquid crystal networks. Commonly the triggers are temperature, light, pH or the presence of chemicals or other moisture. In the lecture we will focus on UV actuation and demonstrate that by accurate positioning of molecules in the space of a thin film or coating the deformation figures can be predetermined and can be made very complex. In a special case the surface topography can be altered by light such that either regular surface structures are being such as line grating or irregular structures such as fingerprints or randomly switching polydomains (Figure 1). The surface topographies are dynamic and disappear as soon as the light is switch off. An interesting feature is that the surface tribology can be altered be UV exposure.

Figure 1. Interference microscope images and the corresponding surface profiles of polydomain liquid crystal polymer surfaces measured in the dark (left and under illumination (right).

References:
Spiropyran surface electrochemistry

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Responsive surfaces built on functional molecular systems open up a myriad of opportunities in the development of smart surfaces – enabling chemical fine tuning and often reversible control of surface properties such as wetting, adhesion, catalytic activity. A central question arises however in immobilising molecular systems on surfaces as to how their properties are influenced by confinement. In this contribution the functionality of several molecular switches in solution and in monolayers, in particular spiropyrans, will be discussed.

As an example of the effect of lateral interactions on conformational freedom self-assembled monolayers (SAM) of a bithiaxanthylidene redox switch (1, Fig. 1) which shows excellent bistability, will be explored. In particular the methods available to explore its photochromic, thermal and electrochemical properties.

The main part of the presentation will focus on the well-known spiropyran motif however in which it will be demonstrated that the photo- and electrochemical properties are heavily influenced by both immobilisation and, critically, by the invasiveness of spectroscopic techniques used to characterise the functioning of the hybrid inorganic-organic devices formed.

References:
Manifolds of the Bray-Liebhafsky oscillating reaction

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Apparently simple oscillatory reaction, known as the Bray-Liebhafsky one, (BL) represents the catalytic decomposition of the hydrogen peroxide in acid medium, with iodate ions as catalysts. Under the CSTR conditions, BL reaction can maintain indefinitely wide range of different phenomena including simple oscillations, mixed mode oscillations, or even chaos. All sorts of this phenomena are reproduced by the previously proposed model. [1] BL reaction is a multiple-time-scale process with several fast species and one or two slow species. Two dimensional slow manifold of such reaction system governs significant part of the dynamics. (See Figure 1.)

Figure 1. Slow manifold and trajectory of the mixed-mode oscillations In the BL reaction simulation based on proposed model. The fold line is also given.

We investigate complex transitions between dynamic states during the complex mixed mode oscillations in numerical simulations, by the analysis of the manifold structure of the proposed model and its relation to the simulated trajectory. We found that the H$_2$O$_2$ is typical slow species with much larger concentration than any other. However, I$_2$ is sometimes slow and sometimes fast species. [2] Hence, corresponding nullclines, as one dimensional manifolds, become very important for the nonlinear dynamics of the BL reaction.

References:

Towards Growth and Division of a Minimal Cell

Christophe Danelon, Andrew Scott, Paul de Graaf, Marek Noga, Jonas Noguera Lopez

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Given the tremendous complexity of even the simplest living organisms, one can question if such complexity is really essential for life, or whether, instead, cellular life might be supported by less components. Our goal is to assemble an elementary cell using a minimal set of well-defined and purified components.

I will first present our experimental framework, namely the functional encapsulation of a reconstituted cell-free gene expression system within lipid vesicles actively interfacing with the environment \[^{[1,2]}\]. The engineered liposome membrane acts as an exchange platform that enables the uptake of all necessary nutrients and tRNAs supplied in the outside medium, which triggers the internal production of mRNAs and proteins from a DNA template. We showed that transcription and translation kinetics could simultaneously be monitored in real-time using the Spinach RNA aptamer technology \[^{[3]}\]. In a second part, I will describe the lipid biosynthesis and membrane-deforming routes that we propose to achieve vesicle growth and division, which is one of the biggest challenges towards the construction of a self-replicating artificial cell \[^{[4]}\].

References:

Generation of oligonucleotides by non-enzymatic polymerization under hydrothermal conditions

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Abstract

We previously reported that 5'-mononucleotides organized within a multilamellar lipid matrix can produce oligomers during the anhydrous phase of hydration-dehydration cycles [1]. Because hydrolysis of oligomers can also occur during the hydration phase, it is important to understand the steady state in which ester bond hydrolysis is balanced by synthesis. To this end we established a simulation of hydration-dehydration cycles that would occur in hydrothermal fields associated with volcanism on the early Earth [2]. We confirmed that the chemical potential made available by cycles of hydration and dehydration is sufficient to drive synthesis of ester bonds so that oligomers resembling RNA are produced and exist in a steady state with their monomers [3, 4]. Furthermore, when mononucleotides were present that can form complementary base pairs, some of the products have properties suggesting that secondary structures are present, including duplex strands stabilized by hydrogen bonds.

References:


Protein Cages as Nanocompartments in Systems Chemistry

Andres de la Escosura, Eduardo Anaya-Plaza, Francesca Setaro, Eveline van de Winckel, Jose R. Castón, Jeroen J. L. M. Cornelissen, Tomas Torres

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Typical goals of systems chemistry are the evaluation of structural and dynamic requisites leading to self-replication and self-reproduction, the integration of replicating networks and compartment subsystems into artificial cells, and the quest for the roots of Darwinian evolution in chemical systems. The study of compartmentalized complex molecular networks and assemblies, in particular, is a clear objective in the field, since compartmentalization provides them with the ability to keep components together and separate their own chemical processes from each other and the environment. Yet, because of the synthetic, bottom-up character of the systems chemistry approach, these tasks do not necessarily have to be performed with biological building blocks. In contrast, a pertinent question is whether protocells could be constructed from non-natural components. Research on nucleic acid analogues, metabolic networks based on chemistries different from the current biochemistry, and protein compartments instead of lipid membranes, is an interesting approach because it allows exploring some properties of life without the restrictions of the historical pathway that Darwinian evolution took. In this talk, some results concerning the use of virus capsid (nano)compartments for self-organizing materials, toward drug delivery and other biotech applications, will thus be shown, arguig how the encapsulation of self-synthesizing networks and assemblies inside these protein cages (Figure 1) may have a great potential as the next step in the route to life-like materials, both at the fundamental level and from an applied perspective.

Figure 1 Schematic representation of hypothetical protein cage-compartmentalized (a) molecular networks and (b) self-synthesizing materials.

References:

Self-assembled functional fibrillar networks: road to complexity

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Self-assembled fibrillar networks (SAFINs) represent an example of bottom-up construction going from low molecular-weight information-rich building blocks towards a functional supramolecular material. In this process not only is the simple molecular information transferred into the material but new features may emerge as a consequence of either cooperative or antagonistic interactions between the components. Here we will present some examples of single- and multicomponent fibrillar systems based in low molecular weight compounds that show emergent catalytic behavior and reveal either orthogonal or interconnected functions.
Computational Combinatorial Chemistries

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Traditional test tube chemistry typically operates with few purified chemical reagents. This convenience is lost when chemical systems approach the complexity of living systems which are prone to involve a multitude of interacting reagents. Particularly when molecules are able to polymerize and form heteropolymers, the space of potential chemical species becomes infinite. While a plethora of computational techniques exists for finite, small-sized reaction systems, computational tools for combinatorial chemistries over infinite dimensional system spaces are still an area of active development.

In my talk, I will introduce the use of stochastic calculi that are able to cope with the complexity of infinite dimensional reaction spaces. After a brief exposition of the framework, I will demonstrate their application to combinatorial chemical libraries, highlighting recent results pertaining to an artificial binary replicator chemistry, as well as models of real world combinatorial chemistries.
Various measures e.g. atom economy or number of used reactions are frequently used in Organic Synthesis to evaluate and compare synthesis plans. These measures shape the strategies how Organic chemists design a synthesis to a target molecule. Metabolic engineering, a subfield of Synthetic Biology, investigates the de-novo construction and design of enzyme catalysed reaction networks for \textit{in vitro} and/or \textit{in vivo} production of commodity chemicals. Since for many target molecules no natural pathways are known, recombination of enzyme functionality under optimality criteria becomes important to guide the design efforts. I will present a computational framework which allows to explore and rank the entire network design space spanned by a set of enzymes.
Using Molecular Dynamics in Systems Chemistry

Pim W.J.M. Frederix, Peter C. Kroon, Siewert-Jan Marrink, Sijbren Otto

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Systems Chemistry often deals with complex and dynamic mixtures of compounds, which suggests it does not overlap much with the realm of Molecular Dynamics (MD) simulations, which typically contain a fixed number of particles and bonds. However, many processes in systems chemistry are dominated by reversible molecular interactions and MD can provide a unique (visual) insight into their relative importance if applied correctly.

In this presentation I will discuss the usage of MD for the specific case of a dynamic combinatorial library of dithiol-modified peptides.\[1\] Certain members of these libraries are known to catalyse their own formation by self-assembling into 1D nanostructures. In the light of this concept, the use of non-equilibrium MD will be explained for determining the conformation of such nanostructures. Moreover, I will outline simulation protocols (such as coarse-graining and replica-exchange MD) to overcome the many kinetic barriers in the free-energy landscape of such a library. Finally, a new implementation of MD to allow dynamic formation of covalent bonds will be explored.

References:


Figure: Steered Molecular Dynamics simulation ‘pulling’ a peptide macrocycle from a fibre end.
Traditionally, synthetic chemistry has focused on the synthesis of molecules in a step-by-step fashion, whereby preparation of each intermediate is followed by time consuming and costly purification procedures. This strategy is in sharp contrast to how biological organisms operate large systems/networks of chemical reactions in synchrony and how they can synthesize various small molecules and macromolecules in massively parallel ways. Drawing inspiration from biology, one of the challenges for chemistry in the XXI century is thus to learn to assemble and control chemical systems rather than individual reactions. At present, we know precious little about wiring individual reactions into networks, building-in control elements into these networks (including non-linear interactions, feedback, etc.), or "programming" their overall functions.

My talk will illustrate a two-pronged effort aimed at making chemical systems an experimental reality. The bottom-up approach focuses on combining individual chemical phenomena into entities of increasing complexity. Examples here will include the coupling of chemical oscillators to self-assembly phenomena involving small molecules or nanosized objects. The influence of system’s geometry on its function will also be discussed. In the top-down approach, I will illustrate how we can prune the existing body of chemical knowledge to identify chemical network "motifs" that can act as stand-alone chemical systems. This part of the talk will introduce algorithms that allow for automated identification of sequential reactions, which can be performed in one flask without the need for intermediate purification. The overall message I hope to convey is that by combining experiments with theory, it is possible to synthesize not only individual molecules but chemical systems of increasing complexities and acting on different length scales.
Dissipative self-assembly steady states: from batch to open systems

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Living organisms reside in far-from-equilibrium states\(^1\): they need to consume nutrients, fluids, and oxygen to power the continuous chemical processes occurring in each of their cells, in order to stay alive. When the supply of food or nutrients is stopped for a certain time, the living systems relax to their thermodynamic equilibrium state, that is, death. Up to now, scientists in the field of supramolecular chemistry have managed to fabricate synthetic analogs of many of the intricate structures found in nature.\(^2\) These synthetic supramolecular structures, impressive as they are mostly at thermodynamic equilibrium, or in kinetically trapped states. In sharp contrast with nature, however, we still struggle to keep self-assembled structures in a continuously dissipative—that is, an energy consuming—state. Here, we present different supramolecular systems that change their structure in response to magnetic fields, or by undergoing enzyme-mediated chemical reactions. The key challenge is to create supramolecular systems that can be switched rapidly and in a completely reversible way, so that many assembly/disassembly cycles can be performed in a short time. The structure and dynamics of the assemblies depends on the switching frequency, and thus on the distance from the equilibrium state.\(^3\)

References:


Understanding the dynamics of complex enzymatic reactions in highly crowded small volumes is crucial for the development of synthetic minimal cells. Compartmentalised biochemical reactions in cell-sized containers exhibit a degree of randomness due to the small number of molecules involved. However, it is unknown how the physical environment contributes to the stochastic nature of multistep enzymatic processes. We present a robust method to quantify gene expression noise in vitro using droplet microfluidics. We study the changes in stochasticity in cell free gene expression of two genes compartmentalised within droplets as a function of copy number and macromolecular crowding. We find that decreased diffusion caused by a crowded environment, leads to the spontaneous formation of heterogeneous micro-environments as local production rates exceed diffusion rates of macromolecules. This heterogeneity caused by strongly reduced diffusion, leading to higher probabilities of the molecular machinery to remain within one microenvironment, directly increases the systems stochasticity. Our experiments enable us not only to take into account, but also predict, control and exploit the magnitude of stochasticity when designing synthetic chemical pathways in artificial cell-like systems.

**Figure 1** Noise in YFP vs. CFP expression levels in picoliter droplets as a function of crowding.
Proteins are the most advanced nanostructures, defined by the sequence of amino acids. Nature provides a limited number of protein folds, which have been optimized during evolution. New protein folds are very challenging to design due to the delicate balance of numerous weak long range noncovalent interactions stabilizing proteins structure. New protein assemblies have been designed from combinations of protein oligomerizing domains or from tandem repeat proteins. Those strategies rely on nearest neighbor local interactions, which can only specify a limited range of shapes. Nucleic acids on the other hand have been repurposed by DNA nanotechnology to form almost any desired 3D shape based on the long-range specific interactions between segments that form complementary duplexes. We bypassed the problem of designing de novo topological protein folds by relying on the well-understood specificity of coiled-coil dimers and used them as modules to guide an Eulerian trail of polymer between vertices of polyhedra. This type of assembly includes long-range interactions which can specify complex folds. The principle was first demonstrated on the construction of a nanoscale protein tetrahedron, composed of a single polypeptide chain composed of 12 coiled-coil forming segments. In this assembly 6 edges of the polyhedron were defined by orthogonal coiled-coil dimers derived from the natural and designed coiled-coil pairs. This represents a new platform of structural scaffold formation that could be extended to other polyhedra. Design of polypeptide-based modular polyhedra was inspired by the DNA-based nanostructures. In comparison to coiled-coil dimers DNA can only form antiparallel dimers, which limits its range of polyhedra that could be formed from a single chain. Nevertheless DNA represents a useful platform for prototyping the design of the folding pathway for the subsequent transfer to the self-assembled polypeptide nanostructures. The second generation polypeptide polyhedra were designed, introducing the design of the folding pathway that enable protein polyhedra to self-assemble in vivo in bacteria, in mammalian cells as well as in vivo in mice. This demonstrates the compatibility of protein origami in the complex cellular milieu.

Figure 1. Comparison of natural protein fold, stabilized by the hydrophobic core and topological protein fold where the structure is defined by the topology of the chain stabilized by pairwise interactions.

References
Towards convergent abiogenic processes. Peptide and proto-cell formation driven by the same energy currency system

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Activated phosphorus(P)-based energy-currency molecules such as adenosine triphosphate, ATP, drive much of the metabolic activity of contemporary biochemistry.[1] Such molecules are able to selectively exploit small tranche of energy when mechanistically coupled, to drive endergonic chemical reactions. A significant problem in the field of abiogenesis concerns emergence of a P-based system of bioenergetics which can be shown to perform multiple, and ultimately convergent, chemical processes of potential value to primitive chemical machines within putative early earth environments, without the need to invoke sophisticated (ie: proteinaceous) catalysis.[2] Some challenging problems emerge: (i) could simpler P-based systems have preceded ATP as energy currencies, (ii) how could such systems have emerged within early earth geological environments and (iii) what chemical processes could such energy currency molecules have driven?

Pyrophosphate [PPi(V); P$_2$O$_7^{4-}$] has been proposed as a logical ancestor of ATP.[3] However, problems persist with PPi(V), including inherent low water solubility and low kinetic reactivity in the absence of suitable (enzyme) catalysts. We presume that PPi(V), and by association polyphosphates, would have emerged as key energy currencies only when catalyst systems were available to use them effectively in P-transfer chemistry. Here we review some of our recent studies on a close cousin of PPi(V), pyrophosphite [PPi(III); H$_2$P$_2$O$_5^{2-}$] including the (i) coupling of amino acids to peptides under mild conditions and (ii) amphiphile formation via phosphorylation of long-chain alcohols and amines to afford compartments.[4] We subsequently speculate on the significance of converging peptide and vesicle formation in the emergence of primitive complex chemical systems.

Figure. (left) Conversion of Gly to Gly-Gly [0.5M Gly & 1.0M PPi(III); 25°C], cryo-TEM images of (centre) organic-phase structures formed in the reaction between PPi(III) and oleylamine in a biphasic system of toluene:water; (right) the same experiment revealing ferritin (dark region indicated) within the organic phase structures demonstrating an aqueous interior to the structures.

References:
Evolution of the division of labor between genes and enzymes in the RNA world

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The RNA world is a very likely interim stage of the evolution after the first replicators and before the advent of the genetic code and translated proteins. Ribozymes are known to be able to catalyze many reaction types, including cofactor-aided metabolic transformations. In a metabolically complex RNA world early division of labor between genes and enzymes could have evolved, where the ribozymes would have been transcribed from the genes more often than the other way round, benefiting the encapsulating cells through this dosage effect. Here we show, by computer simulations of protocells harboring unlinked RNA replicators that the origin of replicational asymmetry producing more ribozymes from a gene template than gene strands from a ribozyme template is feasible and robust. Enzymatic activities of the two modeled ribozymes are in trade-off with their replication rates, and the relative replication rates compared to those of complementary strands are evolvable traits of the ribozymes. The degree of trade-off is shown to have the strongest effect in favor of the division of labor. Although some asymmetry between gene and enzymatic strands could have evolved even in earlier, surface-bound systems, the shown mechanism in protocells seems inevitable and under strong positive selection. This could have preadapted the genetic system for transcription after the subsequent origin of chromosomes and DNA.\cite{1}

References:
Supramolecular Polymerization from Synthetic Polypeptide-grafted Subunits

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Abstract: The helical and tubular structures self-assembled from proteins have inspired scientists to design synthetic subunits that can be “polymerized” into supramolecular polymers through coordinated, non-covalent interactions. However, chain-growth polymerization from synthetic macromolecules or nanoparticles remains a challenge because of the difficulty of controlling the interactions of these large subunits. Herein we discuss the synthesis of homopolypeptide-grafted comb polymers and nanoparticles, and the use of the tunable polypeptide interactions in solution to achieve the controlled assembly. The study shows that the chain growth of supramolecular polymers can be achieved from these synthetic subunits and the process occurs in two distinct stages, with a slow nucleation step followed by a faster chain propagation step. We discuss how the electrostatic interactions between the weakly charged monomers may play an important role in the polymerization process.
New developments on the prebiotic chemistry of phosphate esters mixed anhydrides of α-amino acids and peptides

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Aminoacyl adenylates are key intermediates of the peptide synthesis process in present day of living organisms. Their transient formation by reaction of α-amino acids in the active site of aminoacyl-tRNA synthetases (aaRS) leads to the subsequent aminoacylation of tRNA. Their participation to the evolutionary process that led to the emergence of translation is then mandatory. However, this participation has been discussed because of the possible conversion into amino acid N-carboxyanhydrides (NCAs) in the presence of hydrogen carbonate.[1–3] Previous studies demonstrated the possibility of formation of these mixed anhydrides from NCAs that already constitute efficient monomers for polymerization.[4,5] In this presentation, we will disclose the efficiency and relevance of this frequently overlooked pathway from model amino acid phosphate mixed anhydrides including aa-AMPs. We will also present the results of studies aimed at determining the pathway responsible for the polymerization of aminoacyl phosphate esters in prebiotic environments rich in carbon dioxide and then likely to promote the formation of amino acid N-carboxyanhydrides.[6] The results of on going investigations on the reactions of models of peptide segments activated under the form of 5(4H)-oxazolones with ribonucleotides will also be presented.

References:

Tunable self-assembly using magnetic fields

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One of the greatest challenges in supramolecular chemistry is to be able to grow self-assembled structures of a well-defined size and/or shape. Several studies have already shown methods to reach that goal using e.g., exact stoichiometry of the building blocks, steric hindrance, electrostatic repulsion, or templated self-assembly. These approaches, however, often require chemically modification of the building blocks to change the size/shape of the self-assembled structures. Here we present a different approach in which magnetic fields are used to control the size of supramolecular self-assemblies in real time. Benzene-tricarboxamide based molecules that assemble with an anti-cooperative mechanism are self-assembled in the presence or absence of a weak magnetic field, which has a large influence on their overall size. We present the analysis of this system by circular dichroism spectroscopy and static/dynamic light scattering, and show that the assemblies can grow or shrink depending on the type of field that is applied. It should be possible to extend our method of controlling the size of supramolecular assemblies to systems with a weaker magnetic moment if stronger fields are used.

References:

Giant vesicles (GVs) are artificial chemical systems largely used as cell models[1], since they are micrometer-sized closed compartments bounded by a semipermeable membrane, which in turn is composed by self-assembling amphiphiles. By opportune engineering the lipid membrane and by entrapping cascade-reaction enzymes inside GVs, it comes possible to design micro-sized reactors where metabolic pathways of biotechnological interest can take place sustained by external substrate feeding[1,2].

Modelling these supramolecular reacting systems is of great interest both to better understand the dynamics of enzymatic reactions in confined space, but also to improve the design and the implementation of new metabolic micro-reactors.

In this contribution two approaches to the modelling of Enzymatic Giant Vesicles (EGVs) will be presented and discussed: the 0D and the 3D approach respectively, that differ in the description level and in the modelling purposes.

The 0D modelling aims to describe the time evolution of a population of EGVs taking into account the size dispersion and the solute concentration distribution. This model allows the investigation of extrinsic stochasticity[3] on the time behavior of the vesicle suspension. The theoretical outcomes of this approach can be contrasted with flow cytometer experimental analysis and can give hints on the vesicle preparation procedure. On the other hand, the 3D approach describes single GVs giving also morphological 3d-space details and allows to take into account explicitly the diffusion of substrates, through the external solution and in the internal vesicle water core, along with molecular transport across the lipid membrane. The theoretical outcomes can be contrasted with confocal microscopy analysis and can be useful in designing communication experiments among GVs.

Both these two approaches have been successfully applied in order to improve the implementation and to elucidate time evolution of enzymatic giant lipid vesicles.

References:
Chemical communication between functional molecules via photocontrolled ions in polymeric nanocapsules

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One key goal of our work is to establish a strategy whereby functional molecules can communicate with one another in solution and in organized, self-assembled media (biotic and abiotic). This represents a first step towards artificial minimal cell units. Natural systems use chemical communication with small molecules and ions to promote transfer of information in different processes. Here we consider rudimentary artificial biomimetic systems integrating photonic and ionic processes, where remote control of ion release from synthetic molecular receptors, and thus the information transfer in aqueous media, is governed by a photonic stimulus in a bottom-up strategy. Fast processes of photoejection and migration of ions are particularly well-suited to studies in real-time via fluorescence. As well as studies in solution, communication between distant sites / molecules considers the use of photoejected ions in nanocapsules and organized media including micron-sized polymersome hosts (Fig 1). Proof-of-principle of compartmental effects in dynamic and non-dynamic nanodomains has recently been demonstrated.[1,2]

Fig 1. Real-time phototriggered ion transfer inside a nanocapsule from confocal fluorescence

References:
Spatiotemporal control in supramolecular polymers in water

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Self-assembly and self-organization in water is obvious for natural systems, but turns out to be much more difficult for artificial systems. In the lecture we will focus on water as the magic solvent for controlling supramolecular architectures. We will present the non-covalent synthesis of a multi-component supramolecular polymer in which chemically distinct monomers spontaneously co-assemble into a dynamic, functional structure in water. We show that a multivalent recruiter is able to bind selectively to one subset of monomers (receptors) and trigger their clustering along the self-assembled polymer; behavior that mimics raft formation in cell membranes. This phenomenon is reversible and affords spatiotemporal control over the monomer distribution inside the supramolecular polymer by super-selective binding of single-strand DNA to positively charged receptors. We will show that super-resolution microscopy and more specifically STORM – stochastic optical reconstruction microscopy – is very useful to get detailed information of the dynamic processes involved.
A core topic of research in prebiotic chemistry is the search for plausible synthetic routes that connect the building blocks of modern life such as sugars, nucleotides, amino acids, and lipids to "molecular food sources" that have likely been abundant on Early Earth. We will present a systematic analysis with a generative chemistry approach for a for the prebiotic chemistry scenario by Albert Eschenmoser, in which he emphasised the importance of catalytic and autocatalytic cycles in establishing such abiotic synthesis pathways.

References:
Observation of protocell dynamic behaviors: Role of the compartmentalization.

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To understand how living cells could emerge from inanimate matter, many designs of minimal self-replicating chemical systems, also called protocell, have been proposed based on the self-assembly and self-organization of molecules, i.e, from the bottom up.

To investigate the dynamic processes taking place during cycles of growth and division (i.e., self-reproduction of the protocells), which are central processes in living systems, a protocell design must be implemented which comprises an information system, a catalytic networks, which is capable of producing its components (compartment building blocks and information polymers) from energy (e.g., light) and precursors available in its environment, and a compartment [1-3].

We are exploring several compartment compositions to determine how the building block nature can affect first compartment self-assembly [4-6] and thereafter catalytic reactions leading to the self-reproduction of protocells.

References:

Bistability in Reversible Peptide Catalysis

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Chemical systems with catalytic features sometimes can rise to interesting behaviors like oscillations, spatio-temporal patterns and bifurcations owing to their non-linear dynamics. Till date, there have been quite a few reports of nonlinear behavior of the systems, though the underlying mechanisms are not yet well-understood. We, thereby, intend to utilize the group’s expertise on peptide chemistry to probe into the nonlinear dynamics of peptide based reversible autocatalytic replication systems. In our lab, we have exploited α-helical peptides[1] and thioester-based depsipeptides[2,3] in order to demonstrate dynamic behavior under kinetic and partial thermodynamic drives. Thus, to exhibit the nonlinear behavior in a comparatively simpler reaction, current research focus has been directed towards novel peptide based systems.

We herein demonstrate the nonlinear dynamics of a closed reversible single-replicator system towards equilibrium. Simulation studies in our group using realistic experimental data have suggested that bistability exists in a closed autocatalytic system for particular concentration regimes. Thus, to find out the validity of the proposed model, an experimental approach has been taken where peptides capable of forming and breaking reversible thioester bond have been allowed to equilibrate. Our experiments deal with a simplistic system made of two peptides, electrophilic thioester fragment E1 and nucleophilic fragment N1, which can form a reversible thioester bond when subjected to appropriate condition and generate R1, a thiodepsipeptide. R1 can dissociate in presence of a proper thiol to regenerate E1 and N1. A dimeric form of the product R1 serves here as an auto-catalyst which introduces nonlinear behavior in the system. The results showed that for the same total concentration, different initial reaction conditions for a reversible peptide replicating system results in bistability, i.e. they reach distinctly different steady state concentrations depending on their history. Furthermore, by changing the initial reaction conditions, we have been able to toggle between two different steady states.

Controlling molecular complexity
Design of bio-inspired materials and catalysts

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In this lecture I will discuss some of our work in the field of bio-inspired complex molecular systems. In the first part I will describe the properties of polyisocyanopeptides, which are rigid protein-like polymers having a helical beta-sheet structure. Our recent efforts to measure the stiffness of these polymers, e.g. by real time single molecule diffusion studies (reptation experiments) will be presented. The stiffness and regular structure of the polymers has been used to prepare materials with complex features. For instance, polyisocyanopeptides with ethylene glycol side chains form gels at extremely low concentrations, displaying properties similar to those of the complex intra- and extra-cellular matrices in nature, e.g. strain stiffening. The possibilities to control the properties of the gels, using the stiffness of the single chains as a design parameter, and their use as matrices for the growth and differentiation of stem cells will be discussed.

The second part of the lecture will deal with catalysis and is inspired by the naturally occurring processive catalytic systems, which can read and process information. I will describe our ideas and efforts to construct a Molecular Turing machine, i.e. a catalytic molecular device that can write information on a polymeric thread following instructions from a tape head. The various requirements for such a machine (information transfer, writing, etc.) will be discussed as well as the first steps to synthesize and study the different components of such a machine.

Acknowledgement
This work was carried out in collaboration with Prof. Alan Rowan, Dr. Paul Kouwer, and Dr. Hans Elemans and supported by the Netherlands Ministry of Education, Culture and Science (Gravitation program “Functional Molecular Systems”) and the European Research Council (ERC Advanced grant “Artificial Life-like Processive Systems”)
Localized Template-driven Functionalization of Nanoparticles Using Dynamic Combinatorial Chemistry

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Although supramolecular interactions are well understood, applying them in selective multivalent recognition still remains a big challenge. Nature has mastered their use for binding between many biomolecules: protein-protein, protein-DNA, protein-RNA. These interactions constitute a promising target for drugs aiming at modifying cell signalling, cell division, gene expression, etc.

We addressed this challenge using aldehyde-functionalized nanoparticles which are capable of learning how to recognize the target biomacromolecule (DNA) from the target itself. This process is performed by a dynamic combinatorial library\[1,2\] of imines formed by aldehyde-modified nanoparticles and amine-functionalized recognition units (see Figure 1). We observed that different DNA sequences can lead to different functionalization patterns, even with very simple building blocks. Importantly, functionalization of the nanoparticle surface takes place only in the direct vicinity of the DNA templates.\[3\]

![Figure 1](image.png)

**Figure 1.** Recognition units assemble under thermodynamic control on the surface of gold nanoparticles, forming patterns complementary to the template biomolecule.

References:

Supramolecular Buffering by Ring-Chain Competition

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Buffering is a well-known term in chemistry and the concept is used in a multitude of varying applications. However, it is striking that, in chemistry, the scope of the buffered molecule is limited mainly to protons. Indeed, the very definition of a buffer - within a chemical context - is “any solution that maintains an approximately constant pH despite small additions of acid or base”.1 Contrastingly, in natural systems the scope of buffering is much broader as biomolecular pathways employ regulation of component concentrations so that important processes become robust to concentration fluctuations. In those pathways, regulation is achieved by various mechanisms such as active negative feedback loops, passive autoinhibition effects or molecular titration.2 These regulatory mechanisms can display similar behavior as compared to ‘classical’ pH buffers. However, a challenge remains for chemists to broaden their definition of buffering and to recreate component regulation in synthetic systems.

Recently, we reported an organocatalytic system in which buffering of the molecular catalyst by supramolecular interactions results in a robust system displaying concentration-independent catalytic activity.3 Here, we demonstrate the design principles of the underlying buffering mechanism using a combined experimental and theoretical approach. Our analysis shows that supramolecular buffering of a molecule is caused by its participation as a chain stopper in supramolecular ring-chain equilibria and we reveal here the influence of various thermodynamic parameters. Model predictions based on independently measured equilibrium constants corroborate experimental data of several molecular systems in which buffering occurs via competition between cyclization, growth of linear chains and end-capping by the chain-stopper. Our analysis reveals that the effective molarity is the critical parameter in optimizing the broadness of the concentration regime in which supramolecular ring-chain buffering occurs as well as the maximum concentration of the buffered molecule. To conclude, a side-by-side comparison of supramolecular ring-chain buffering, pH buffering and molecular titration is presented.

References:

Auto-inductive effects in the asymmetric Cu(I)-catalyzed 1,2-addition of alkyl-Grignard reagents to α,β-unsaturated carbonyl compounds

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Auto-catalysis\(^1\)–\(^3\) and auto-induction\(^4\),\(^5\) take place when the product of a reaction is able to catalyze its own synthesis. In an auto-inductive reaction the product interacts with the pre-existent catalyst and modifies its reactivity. In the case of a chiral catalyst, this interaction can result in a better catalyst and consequently improved asymmetric induction. This kind of behavior has been reported mainly addition reactions catalyzed by chiral alcohol or amine based ligands in the presence of titanium salts. In recent years group developed methodology for highly enantioselective alkylation of carbonyl compounds catalyzed by copper complexes of chiral ferrocenyl diphosphines.\(^6\),\(^7\)

Here we report our recent findings of strong auto-inductive effects in the copper catalyzed addition of Grignard reagents to enones and enals. As a consequence of the auto-induction we observed strong rate acceleration and improvement in the overall asymmetric induction of the reaction affected by the product of the corresponding Grignard addition. This phenomenon has been used as a tool to improve the overall asymmetric efficiency and to gain deeper mechanistic understanding.

References:

Systematic manipulation of DNA functionality by controlled self-assembly and disassembly

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In chromosomes DNA exists in highly organized state, where it is wrapped around histones (structural proteins), forming a composite material called chromatin. Decondensation of the DNA plays an essential role in gene expression. DNA has to be unpacked for the transcription (RNA synthesis) and it arouses interest in understanding underlying electrostatic interaction mechanisms of DNA decompaction.

We unravel the structure and function and monitor the real–time dynamics of the formed self-assemblies of DNA with artificial cationic dendrimers. The high flexibility of microfluidics techniques allows us to control mixing speeds, reaction times, and flow fields. In particular, the laminar flow conditions inside microchannels provide the possibility to investigate interaction processes in a time-resolved manner. Diffusive mixing in microchannels creates tunable reaction conditions with defined changes in local concentrations. Furthermore, we study and emulate by which mechanisms nature deals with locally on/off DNA condensation.

We analyze the dynamics of DNA/artificial histone complexes unpacking by anionic competitor molecules. Here, the negatively charged molecules compete with phosphate groups of DNA to interact with positively charged groups of histone-mimicking dendrimers.

We employ a potent combination of techniques involving microfluidics and small angle X-ray scattering (SAXS) in order to analyze the impact of self-assembly and disassembly on gene functionality.
Role of lipid confinment in symmetry breaking

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Abstract

The origin of biomolecular homochirality is still an open problem, and many scenarios have been suggested [1, 2]. Amphiphilic molecules are renowned for their capability to reorganize themselves in a variety of different morphologies and topologies, and for their capability to partition chemicals in well-defined domains. Self-assembly is governed by the physical-chemical features of the assembly blocks as well as the local confinement. The role of the confinement is assessed via mesoscopic simulation techniques, mainly based on dynamic mean field density functional theory (DDFT) [3, 4].

In this work we will present an extensive investigation of a model system morphologies of a diblock copolymer with and without spatial confinement. To the best of our knowledge, all previous works were focused on the stabilization of the assembled state, or to the kinetics of the assembly. In the present work, we will consider confinement for stabilizing 3D structures or for selecting different morphologies.
Finally, we want to suggest a possible role for amphiphilic molecules inducing symmetry breaking in the framework of the research on origin of life.

References:

Rational design of enzymatic reaction networks showing multiple complex behaviours


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Complex enzymatic networks form the basis of life and give cells the ability to adapt to their environment. If we truly want to understand life and approach synthetic life, we need to design enzymatic networks ourselves. Recently, we published a first example of a rationally designed enzymatic network that shows sustained oscillations in enzymatic activity for over more than 65 hours under conditions of continuous flow.\(^1\) In our system, the endopeptidase trypsin converts inactive trypsinogen into more trypsin, creating a positive feedback loop. The negative feedback loop starts with a carefully designed and optimized small molecule that consists of a trypsin inhibitor inactivated by two coupled amino acid residues. The first amino acid residue is cleaved by trypsin itself, and the subsequently formed molecule is converted into an active inhibitor of trypsin by a second enzyme, aminopeptidase M, closing the negative feedback loop.

A combination of synthesis, rate studies and computational simulations yielded the right molecules and conditions for sustained oscillations to be obtained. The reactions occur in a continuously stirred tank reactor (CSTR) in which reagents are constantly flown in and out to keep the system out of equilibrium. By coupling multiple CSTRs, we were able to amplify and modulate the oscillations, and we coupled our out-of-equilibrium network to a self-assembly process. Our next goals are to increase complexity of the network by exploring new topologies and different enzymes.

Meanwhile, we have been looking at reaction-diffusion systems in which trypsin diffuses through polyacrylamide gels with a fluorogenic substrate to detect enzymatic activity. Initial studies showed that adding an inhibitor to the system affects the trypsin gradient, resulting in ultrasensitivity.\(^2\) A follow-up story increased the complexity of the system by applying multiple gels and again a positive feedback loop to the network. In this case, threshold sensing and pattern recognition were achieved.\(^3\)

Our current work focuses on increasing the complexity of the system, for example by allowing the enzymatic reaction-diffusion network to control the physical properties of the gel it is moving through. Now, we are able to make a hydrogel go through a gel-liquid-gel transition state upon a transient trypsin signal.\(^4\) These steps are the first towards life-like materials that are able to adapt to their environment and may be used as smart medicine.

References:

Transient Signal Generation in a Self-Assembled Nanosystem

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A fundamental difference exists in the way signal generation is dealt with in natural and synthetic systems. Whereas Nature uses the transient activation of signaling pathways to regulate all cellular functions, chemists rely on sensory devices that convert the presence of an analyte into a steady output signal. The development of chemical systems that bear a closer analogy to living ones (i.e. require energy for functioning, are transient in nature and operate out-of-equilibrium) requires a paradigm shift in the design of such systems. Herein, we report a straightforward strategy that enables transient signal generation in a self-assembled system and show that it can be used to mimic key features of natural signaling pathways, which are: control over the output signal intensity and decay rate, the concentration-dependent activation of different signaling pathways and the transient down-regulation of the catalytic activity of nanoparticles.

References:
Self-assembly of achiral amphiphilic porphyrins towards J-aggregates show diastereoselective and enantioselective effects by effect of flows. Further, the effect of the hydrodynamic torque originated by a vortex stirring may select the chiral sign in the spontaneous mirror symmetry breaking that occurs in auto-organization of these systems. This is related to the size and shape of the different mesophorms (mono-, bi- or multilayered, small particles, nanotubes, etc). The mechanochiral reversible effect detected on J-aggregate nanotubes is explained on the basis of chiral exciton coupling effect on the nanotube shape. In spite that these results occur for a specific type of supramolecular structures, they indicate that mechanical torques must be considered to form part of the specific group of chiral fields able to determine the chiral sign in bifurcation scenarios of spontaneous mirror symmetry breaking.
Gel-based phase separation enhances selectivity in dynamic self-replicating systems

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In recent years, the field of systems chemistry\textsuperscript{[1]} has emerged which focuses on complex chemical systems with increased numbers of interacting components, which may result in emergent phenomena. These systems offer a parallel to biological complexity, but are produced from the bottom-up, often utilising ideas of dynamic combinatorial libraries (DCLs), with competitive or cross-catalytic elements that result in increased complexity of the system. The work of many groups involving chemical self-replicating systems have contributed to the birth of this field, notably von Kiedrowski developed the minimal model of self-replication.\textsuperscript{[2,3]}

Here we demonstrate a different approach, by altering the classical replication model (below). This system exhibits greater complexity and by increasing functionality (with the additional recognition element on A), the components of the self-replicators can interact in different ways. There is a subclass of molecules (that play role of component A) that form gels at low wt\%. This phenomenon allows for the creation of dynamic systems with a phase separation, which can be rapidly dissolved upon addition of B, as this starts the replication of T, (thereby consuming A). This addition of phase separation can allow for greater resolution in a DCL, where A is sensitive to only certain components.

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The emergence of life from inanimate material must have involved a phase during which oligomers formed from simple starting materials. It is interesting to ask whether oligoribonucleotides and peptides could have formed simultaneously under the same experimental conditions. Further, it is important to ask what condensing agent(s) could have induced such simultaneous growth of biopolymers. Studying enzyme-free primer extension\(^1\) with unactivated ribonucleotides, we identified conditions that give incorporation of any of the four natural nucleotides (A, C, G, and U) at the terminus of a primer bound to a template strand. We then tested whether the same conditions also induce the formation of dipeptides from amino acid derivatives. From the preliminary results it appears as if this was indeed the case. It appears that likely that somewhat ‘universal’ condensation conditions can be constructed, at least under laboratory conditions. Initial results from a systems chemistry approach to inducing and monitoring simultaneous formation of biopolymers will be presented.

References:

Supramolecular Assembly of Artificial Metalloenzymes based on DNA and Protein Scaffolds

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The catalytic efficiency and high selectivities achieved by natural metalloenzymes are a source of inspiration for the design of novel bio inspired catalysts. An emerging approach for creating artificial metalloenzymes involves incorporating a synthetic transition metal catalysts into a biomolecular scaffold such as a protein or DNA. [1] The biomolecular scaffold then provides the second coordination coordination sphere that imparts enzyme like behaviour on these synthetic catalysts

In DNA-based asymmetric catalysis,[2] a transition metal catalyst is brought in close proximity of the DNA double helix, allowing for transfer of chirality to the catalyzed reaction. This concept has been applied successfully in several important C-C bond forming reactions[3-5] and the first catalytic enantioselective syn-hydration of enones,[6] a reaction for which there is no alternative using conventional homogeneous catalysis. In addition to excellent ee’s, also in many cases significant rate accelerations are achieved due to the biomolecular scaffold. The origins of the enantioselectivity and rate accelerations will be discussed.

DNA-based catalytic enantioselective syn-hydration of enones.

In an similar approach we have converted the transcription factor LmrR (Lactococcal multidrug resistance Regulator) into an artificial metalloenzyme. The resulting supramolecular artificial metalloenzyme also proved successful in a variety of catalytic reactions.[7]

References:
DNA circuitry

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DNA success as a molecular programming medium is based on the wide availability of order-made synthetic oligonucleotides, predictable Watson-Crick base-pairing, DNA-to-DNA catalysis, and straightforward interfacing with various physical, chemical or biological signals to be used as inputs, outputs or readouts. These elements can be combined to form in vitro chemical reaction networks, where the topology of the network, together with kinetic laws of the individual reactions, guides the behavior of the whole system. Such molecular systems can be used as a model of biological regulatory circuits, or, in their own rights, as computing elements embedded in wet matter.

I will discuss an experimental exploration of these concepts. We have recently constructed DNA encoded bi- and multi-stable switches, relaxation oscillators or the first predator-prey chemical ecosystem. These networks can in turn be used as modular building blocks to build larger organizations. For example, in a spatially extended reactor, we observe traveling fronts and waves of DNA species; in emulsion of micro-droplets we can directly visualize the full bifurcation diagram of a particular network. The possibility of an evolutionary design process toward robust molecular circuits will also be discussed.

Figure caption: fluorescently barcoded micro-droplets running DNA molecular programs.

References:

Multivalent enzyme kinetics using DNA origami scaffolds

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Cells achieve specificity and efficiency in a complex and crowded environment by spatially organizing enzymes onto scaffolds. The clustering of functionally related enzymes suppresses competing reactions and leads to efficient channeling of intermediates\textsuperscript{[1]}. In this research, we aim to explore the multivalent kinetic effects of such assemblies using DNA origami scaffolds. The DNA origami techniques involves the folding of a ~7,000 nucleotide phage-derived single-stranded DNA into an arbitrary two- or three-dimensional shape using approximately 200 short sequence-designed staple strands\textsuperscript{[2]}. Using this method we were able to construct a 100 × 75 nm\textsuperscript{2} DNA rectangle and confirm its structure by atomic force microscopy. Using short single-stranded handle strands DNA-conjugated enzymes can be incorporated site-specifically and with nanometer precision. As a proof of principle, we site-specifically introduced streptavidin via biotin-labeled DNA strands and visualized single proteins on the DNA origami rectangle (see Figure). As a specific application, we are currently interested in mimicking the structure and function of the apoptosome, a sevenfold symmetric multi-enzyme complex in the apoptotic pathway. The spatial organization of the apoptosome is essential for the activation of caspases, which is thought to require assembly and subsequent di- or oligomerization of inactive caspase monomers\textsuperscript{[3]}. The DNA origami scaffold presented here is perfectly suitable to investigate the stoichiometry and geometry involved in caspase activation and may gain valuable insights in the multivalent enzyme effects in this system and for spatially ordered multi-enzyme complexes in general.

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DNA-templated self-assembly of bisfunctionalized guanidinium compounds

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The design of chiral self-assemblies is an opportunity for building chiroptical materials, which can be used in different applications, such as chiral recognition, chiral memory, multi-responsive materials, and biosensors.1 In this frame, the use of chiral templates with specific binding sites is a promising approach for directing the chiral amplification and self-assembly of a variety of building blocks. Especially, DNA can be used as scaffold with the possibility to organize chromophores in a precise manner, by exploiting the bases recognition.2

Here, we present our recent results on the design of DNA-templated supramolecular systems based on bisfunctionalized guanidinium compounds possessing aromatic side groups.3 By using chiroptical spectroscopy, we study the interplay of the non-covalent interactions (π-stacking, electrostatic interactions, H-bonding) on the self-assembly and supramolecular organization of DNA-templated assemblies, in order to evolve towards complex chemical systems. Importantly, we show that the bisfunctionalized guanidinium compounds self-assemble in aqueous solution with single-stranded DNA through phosphodiester backbone recognition, and the stability of the supramolecular assemblies depends on the temperature, the DNA length, and the presence of competing phosphate ions. Moreover, we highlight the importance of π-stacking interactions in the stabilization of these DNA-templated supramolecular self-assemblies.

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References:
Life requires chemistry making its own dynamic boundaries

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One can try many chemical ‘shortcuts’ to explore the transition from complex reaction mixtures to the hyper-complex set of transformation processes characteristically taking place in any living system (i.e., in any genetically instructed cellular metabolism). However, in order to avoid deviations that may look gorgeous but lead us off track, special care must be taken to keep a wide enough view of the whole puzzle of biogenesis, together with a reasonable hypothesis about the temporal sequence in which the main pieces could fit in. The problem, beyond discovering prebiotically plausible molecular precursors or alternatives for the various functional components of extant biological systems, lies in determining which these components are/were more crucial, and at what specific stage along the transition pathway. So one has to project, from current knowledge in biology, and try to discriminate the necessary from the accessory steps required to reproduce a chem-bio-genic pathway in controlled, laboratory conditions. Under the influence of molecular biology, the standard choice in the field of origins of life has been to focus either on enzyme catalysis or, more commonly, on RNA or DNA replication, as the quintessential biological function(s) to be chemically mimicked. The underlying assumption, especially for the latter option (or a very popular hybrid of the two: the so-called RNA-world hypothesis), is that ‘time’ and ‘natural selection’ will be sufficient to ensure the conversion of these naked polymer chemistries to populations of metabolic cells with LUCA (last universal common ancestor) properties. In my contribution I will suggest that framing the problem of origins in those terms is misleading, for it tends to overlook another fundamental feature of life, the coupling between metabolic networks and membrane compartments, which seems pivotal for the primary organization of all its chemical processes.[1] I will argue that this systemic biological feature (‘reaction network–boundary’ complementary relationship) could be initially implemented through rather simple molecular compounds[2] and, furthermore, that it generates opportunities for emergent chemical behavior that have been hardly investigated to date[3-4] but could be highly relevant for any process of biogenesis.

References:

Speciation and competition in a network of replicators

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The evolution of life on Earth is characterized by spontaneous complexification and diversification, giving rise to the emergence of species. However, the process through which species form remains poorly understood and difficult to investigate. As reproduction is a minimal requirement for the formation of species, networks of self-replicating molecules\textsuperscript{1,2} are suitable systems to capture the fundamental processes behind species formation. In theoretical work in the 1970s Eigen and Schuster introduced\textsuperscript{3} the ‘quasi-species model’ for describing Darwinian evolution of simple self-replicating entities such as molecules and viruses. However, quasi-speciation has never before been observed in an inanimate system. We have been able to monitor the formation of two quasi-species (distributions of closely related replicators produced by errors in their self-replication) in real time in a fully synthetic system of self-replicating molecules that compete for different building blocks. One quasi-species of replicators is the ancestor to a second one, thus capturing a step that is crucial for achieving Darwinian evolution with synthetic replicators. As quasi-speciation in our system takes place on the timescale of weeks and can be investigated at the molecular level this work opens new opportunities for experimentally investigating the process through which species arise in real time and in unparalleled detail. The next step is to observe direct competition between the quasi-species, which could lead to a scenario where the fittest replicators survive and the weakest go extinct. In order to achieve this task we implemented a flow regime to our systems in where the substrates for the quasi-species (food) are flowed in and the bulk of the solution is flowed out resulting in simulated death of the replicators. If one of the replicators is fit enough to overcome the selective pressure of the flow it will be the only one to survive. Our results demonstrate that by incorporating properties such as replication, exchange, mutation and selective pressure into a synthetic system it is possible to observe phenomena previously exclusive to Nature, thus building a bridge between systems chemistry and evolutionary biology.

References:


Topological studies in complex dynamic libraries of pseudopeptides

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In the last years the emergence of dynamic covalent chemistry\(^1\) has provided chemists with a new tool to generate and study complex systems. In water, disulfide oxidation and metathesis have rendered impressive results, with the formation of beautiful linked structures,\(^2\) synthesis of new relevant receptors\(^3\) or even replicators.\(^4\) However, most systems studied are made of dithiols so the structures obtained are always links, even if they are intertwined. We have been studying topologically more complex systems, made of pseudopeptidic building blocks of different ‘valence’ and charge. Thus, although very complex systems can be obtained, mixing the complementary building blocks under the right conditions self-recognition processes appear leading to the formation of stable multicomponent products.\(^5\) We carefully have studied carefully variations in the building blocks and the environment. The lessons learned from these processes will provide with some clues to design better receptors and sensors with improved properties.

References:


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Dissipative self-assembly controlled by enzyme switching

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Over the past decades, bottom-up approaches to self-assemble molecules have resulted in well-ordered and incredibly sophisticated architectures, many of which are able to exert specific functions, as well as change and adapt in response to external stimuli.[1] Nevertheless, we are a far cry from achieving the functional complexity of living self-assembled systems, such as microtubules and biomembranes. This is because nearly all current supramolecular systems are either in thermodynamic equilibrium or kinetically trapped states. On the other hand, living systems operate far-from-equilibrium in so-called dissipative steady states, and continuously consume energy to keep their structure and function.[2][3] Here we report on the preparation of peptide substituted perylene bisimides, whose assembly can be controlled by phosphorylation/dephosphorylation of a serine residue, through distinct enzymatic pathways. The system can be kept far from the equilibrium, in dissipative self-assembled steady states by a continuous influx of adenosine-5'-triphosphate (ATP) as chemical fuel. Using this approach we hope to go beyond switchable supramolecular systems, and make structures that are more like “synthetic microtubules”.

References:

Fluorescent and “incomplete” lipids as useful tools for the study of giant vesicles in “growth and division” experiments

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In the last decade our research was focussed on the preparation of amphiphilic peptidyl-RNA1, 2 being powerful for their nature to be spontaneously compartmented on GVs prepared from different phospholipids and glycolipids.3 Our interest remains on the preparation of combinatorial libraries of peptides 4 that will be combined with RNA for furthers studies on GVs. We recently expanded our research on the preparation of GVs using fully synthetic phospholipids and “incomplete” (not phosphorylated) versions of it. Preparing relevant phospholipids on our own can give us access to classes of molecules not commercially available, for example, racemic mixtures, bearing a different stereochemistry, or differences in chains length and compositions, that can be linked to various fluorophores. GVs prepared from such fluorescent lipids can be used for their vizualisation by fluorescence microscopy.

The aim of our project, carried out in collaboration with the research group of Fabio Mavelli – Bari, b is to explore the potential racemic mixtures of fluorescent phospholipids by, both, confocal microscopy and flow cytometry for the study of the GV’s morphology. 5 The ultimate aim will be to carry out and monitor “growth and division” experiments in which fluorescent GVs are being fed with “incomplete” lipids followed by on-GV phosphorylation reactions. Here we present the first results on the synthesis of racemic mixtures of phospholipids and their use for the preparation of GVs.

References:
Recursive Vesicle-based Protocell Constructed as a Molecular System

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We have constructed a giant vesicle (GV)-based protocell which is highly responsive to the internal and external stimuli available from prebiotic environments on the Earth. When the GV dispersion is subjected to thermal cycles, encapsulated DNA in GV is amplified, and amplified DNA works as a trigger for the budding deformation of GVs, eventually leading to division into daughter GVs when an amphiphilic precursor of the membrane lipid is added\textsuperscript{[1]}. The linkage between self-replication of DNA and self-reproduction of GV is, thus, achieved by virtue of a DNA-complex with cationic membrane lipids and amphiphilic catalyst, formed within the vesicular membrane. The complex works as a pseudo-enzyme to produce the membrane lipid from its precursor. Moreover, ingestion of depleted substrates in daughter GV is achieved by a vesicular fusion with conveyer GVs filled with the substrates. The vesicular fusion is triggered by lowering pH of an exterior water phase\textsuperscript{[2]}. This is because surface charges of these two kinds of GVs become opposite when pH is lowered. We noticed that the recursive loop of self-proliferative GV-based protocell consists of discrete phases (ingestion, replication, maturation, division), resembling four phases in a cell cycle of eukaryotes and that each phase is driven to the next phase specifically by internal and external stimuli. Such a highly stimuli-responsive GV-based protocell emerge from collaboratiot of each component as a molecular system.

An ultimate protocell that can autonomously evolve would develop if a “mutant” appeared during numbers of proliferation cycles, associated with the established correlation between geno-type and pheno-type of GV-based protocell.

A positive feedback loop based on supramolecular ring formation

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Feedback loops provide an important form of control in any network. Here, we report on a novel mechanism of autocatalytic-like behaviour, based on supramolecular ring formation. The ureidopyrimidinone (UPy) motif is well known for its easy accessibility and high dimerization constant (6*10^{-7} M in chloroform). UPy is also able to form heterodimers by binding to the 2,7-diamido-1,8-naphthyridine (NaPy) motif, which is not able to form homodimers. Ditopic UPys have the ability to cyclize, due to the high stability of these UPy cycles their tendency to bind NaPy is lower than for monofunctional UPy compounds (Fig. 1).

![Equilibria between NaPy and mono- and ditopic UPy’s.](image)

In addition, we have reported on the ability of free NaPy to acts as a phase-transfer catalyst for certain Michael additions, via the formation of a complex with K_{2}CO_{3}. This inspired us to develop a system composed of NaPy, and monotopic UPy’s functionalized with either a Michael donor or acceptor (Figurexx). As a result of the high affinity of NaPy for UPy, most of the NaPy will be bound to UPy. The small fraction that is free will however catalyze the Michael addition, resulting in short ditopic UPy’s which are able to cyclize. As a result of the high stability of these cycles, the tendency to bind NaPy will decrease, resulting in an increase in concentration of the catalytically active free NaPy.

![The positive feedback loop based on cycle formation of UPy (blue), catalyzed by NaPy (red).](image)

References:
Complexity in protein containing polymersomes: from light-induced proton pumping to revealing cargo location in compartmentalised polymersomes

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The underlying driver for the work done in our research group is to improve our understanding of supramolecular chemistry and self-assembly to create complex functional system.

A significant part of our work concerns the co-assembly of polymers and proteins in water. Of interest to Systems Chemistry and Origin of Life researchers is that we have recently shown that we can make a photosynthesis-respiration mimic based on a light-controlled proton-pumping enzyme in a polymer-based vesicle.[1] This is important because this allows us to create localised pH gradient that could be used to drive far-from-equilibrium processes.

Recently we also synthesised a thermo-responsive fluorescent-protein-PNIPAM bioconjugate that self-assembles to form polymersomes (vesicles) above 37 °C.[2] Importantly, we showed also that other fluorescent protein and drug molecules can be co-encapsulated (entrapped simultaneously) in these polymersomes and their exact location in the resulting compartmentalised structures revealed via Fluorescent Lifetime Microscopy (FLIM) – Förster Energy Resonance Transfer (FRET) – FLIM-FRET (Figure 1). This work shows that the combination of using fluorescent (protein) building blocks and FLIM-FRET is a very attractive methods to study complex functional systems in compartmentalised space.

Figure 1. A fluorescent (amGFP) protein linked to thermoresponse polymer (PNIPAM) forms polymersomes that can (co)-encapsualte another fluorescent protein (PE545), a fluorescent cancer drug (DOX) or both. FLIM-FRET imaging then reveals the location of the (co)-encapsulated proteins and small molecules.

References:
Self assembly and reactivity in liposomes

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It is widely assumed that the long process from non-biological chemistry to living systems started as mixtures of increasing complex molecules got confined in cell-like compartments afforded by simple lipid molecules. The lipid membrane defined a region of the solution, starting the process of differentiation of what was inside it from the surrounding.[1] In the last years we have been studying the molecular recognition in and around lipid membranes. Here we present a summary of the results that show how lipid membranes modulate molecular recognition and self-assembly and reactivity of molecules associated to the membrane, or simply trapped within the cavity they define.[2] The results illustrate how a more complex, sometimes counterintuitive, behavior of the system arises, due solely to the presence of chemically simple lipid membranes. The implication in regards to both the creation of the novo materials and abiogenesis are considered.

Figure 1.“Ship in a bottle”. Confinement of a few building blocks in a lipid vesicle, leading to the spontaneous assembly and stabilisation of large assemblies upon addition of the necessary missing links.

References:

Morphology control by flow-driven precipitation

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In most chemical reactions used for synthesis, the system is well mixed to create a homogenenous distribution of reactants in order to optimize the rate of reaction. These procedures lack any spatial gradients and hence the associated thermodynamic force, the presence of which would lead to transport processes. By introducing a density gradient and maintaining the arising fluid flow, we have recently been successful in synthesizing the thermodynamically unstable crystalline form of calcium oxalate, the dihydrate, that is otherwise hardly feasible in a well-stirred homogeneous system. Here we show that flow-driven precipitation can result in the selective production of a crystalline structure for calcium carbonate without additives. The experimental results reveal that the local mixing, maintained by the concentration and density gradients, favours the nucleation and growth of high-purity calcite microcrystals identified with Raman microscopy. Under appropriate chemical composition, tubular membrane-like structures develop in the copper-phosphate system. Scanning electron microscopy of the solid structures reveals that the inner and outer surfaces are different. Microflowers and nanorods appear in the inner wall of the tubes on increasing flow. We also demonstrate that the width of copper phosphate bands can be regulated by the pressure-drop of the flow.

In general, these experiments not only demonstrate that transport processes create conditions for selective production of a crystalline form but also may provide insight into natural processes where various gradients play an important role.

References:

Quantitative Imaging of Dynamical Reaction-Diffusion Landscapes in Live Cells by Massively Parallel Fluorescence Correlation Spectroscopy (FCS)

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A new approach to quantitative confocal fluorescence microscopy imaging without scanning via massively parallel fluorescence correlation spectroscopy (FCS) is developed.[1-3] In this system, simultaneous excitation of fluorescent molecules across the specimen is achieved by passing a single laser beam through a diffractive optical element (DOE) that transforms it into a rectangular illumination matrix that consists of 32×32 spots. Fluorescence from 1024 illuminated spots is detected in a confocal arrangement by a matching matrix detector consisting of the same number of single-photon avalanche photodiodes (SPADs). Dedicated software was developed for data acquisition and fast auto- and cross-correlation analysis by parallel signal processing using a graphic processing unit (GPU). This approach enables quantitative characterization of processes in live cells/tissue with a sub-millisecond temporal resolution, presently 21 µs/frame. It retains all advantages of confocal microscopy, including the ability to control depth of field, improved SNR by elimination of out-of-focus light and the capability to produce 3D reconstruction of specimen by optical sectioning. The underlying FCS analysis provides quantitative information about the spatial distribution of molecular numbers and the mobility/trafficking of molecules across the specimen. These information, which cannot be deduced from classical fluorescence microscopy imaging, are essential for understanding the integration of biological molecules in dynamical regulatory and/or signaling networks.

References:


Hybrid structures between a dendronized polymer (denpol) of average degree of polymerization (n), abbreviated as $de$-$PG_2_n$, and two different types of enzymes can be prepared by covalently linking the two enzymes in a defined ratio to one and the same denpol chain via bis-aryl hydrazone (BAH) bonds.\(^1\) Such type of denpol-enzyme conjugates can be used for a stable co-immobilization of two types of enzymes on silicate surfaces, as demonstrated with a conjugate consisting of *Aspergillus* sp. glucose oxidase (GOD) and horseradish peroxidase (HRP), $de$-$PG_2_{1400}$-$BAH$-$\{GOD_{25}$,$HRP_{78}\}$.\(^2\) The same type of conjugate can also be used for the co-localization of different types of enzymes at a desired ratio inside lipid vesicles.\(^3\)
Designing biodegradable protocells via the modular self-assembly of polymers

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Macromolecule-based architectures that resemble structural characteristics of the cell can be created through careful control over molecular structure and the environment in which they are being assembled. Protocellular structures are capable of mimicking the compartmentalization behavior of the cell, whereby various functional components are encapsulated and stabilized within a discrete structure. Polymersomes have been described as a membrane-mimetic protocell, comprised of amphiphilic copolymers in a continuous bilayer. On the other hand, coacervates create a membrane-free protocell model that is capable of actively sequestering small molecules, enzymes and nucleic acids into a viscoelastic liquid that is a kind of proto-cytosol. The design and assembly of such systems from entirely biodegradable materials paves the way towards the generation of protocellular architectures that can be used in vivo, although the limited catalogue of biodegradable materials makes this a challenge. Moreover, the co-assembly of biodegradable coacervates and polymersomes into a hierarchical protocell that comprises the internal structuration of coacervates and the external stabilization imparted by a copolymer membrane is an exciting prospect – a new form of compartmentalized protocell with direct applicability to biomedical technologies.

The figure below illustrates the design methodology employed in this research project: carefully designed copolymers will be used to address the soft coacervate interface in order to assemble a monolayer membrane. The coacervate can be loaded with various biofunctional materials whilst the membrane can be functionalised with membrane proteins and cell-targeting peptides to give specific functions. This research promises to be of interest to a wide range of researchers that are interested in the ability to reproducibly create such functional architectures without using any toxic or harmful components.

References:
Phthalocyanines (Pcs) are macrocyclic aromatic compounds containing 18 π-electron delocalization. They attract considerable attention as advanced materials for a number of high technology applications such as semiconductor devices\cite{1}, liquid crystals\cite{2}, sensors\cite{3}, catalysts\cite{4}, photosensitizer in photodynamic anticancer therapy\cite{5}, and dye-sensitized solar cells\cite{6}. This popularity which arises from their unique physical and chemical properties encourages many researchers to work on design and synthesis of novel pcs to improve the physicochemical properties and organization capabilities for intended application. The most common approach to improve the physicochemical properties of pcs is the covalently functionalisation of these macrocycles with appropriate substituents and centre metal atom. With this aim, many phthalocyanines are being synthesized that have different substituents and central metal atoms.

In our laboratory, the syntheses and characterizations of novel phthalocyanine derivatives for several applications have been achieved, and their physicochemical, liquid-crystalline, and conductivity properties have been investigated.

Our studies were supported by the TUBITAK-Scientific and Technological Research Council of Turkey (Project No: 108M500, 108T063, 112T213, 111T689 and 114Z463).

References:

When hydrated, most phospholipids spontaneously self-assemble into lamellar closed containers, i.e. liposomes. Such vesicles are approved delivery vehicles that transport encapsulated drug molecules through the blood stream. Current research is focusing on i) targeting specific sites in the human body and ii) releasing the liposomal cargo upon the application of an exogenous trigger (light, heat, pH, etc.). However, such a system is lacking for the immediate treatment of heart attack patients who need to have a blocked piece of artery reopened in order to allow blood to pass again and to reperfuse the heart with oxygen. The common bolus injections of nitroglycerin can lead to vasodilation of all blood vessels and concomitantly to a dangerous drop in blood pressure.

Here, we summarize our work on mechanosensitive liposomes. These vesicles are tight in the resting state but release their cargo when submitted to elevated shear stresses. Such high wall-shear stresses are found when blood is passing from open blood vessels into stenosed blood vessels. Standard targeted drug delivery of an atherosclerotic plaque would not be possible because of the lack of specific biomarkers in a stenosis. The purely physics-based targeting using mechanosensitive liposomes therefore represents a fresh approach in drug delivery.

The work is based on artificial bis-amido phospholipids. An efficient, convergent synthesis of the molecules is presented together with straightforward purification protocol. All molecules were characterized biophysically using various monolayer and bilayer characterization tools. The results show a significant stabilization of the phospholipid bilayer when compared to the corresponding monolayer, induced by a membrane leaflet interdigitation. This leads to a type II lamellar membrane with a high lateral membrane stiffness and therefore a faceted liposome morphology, as shown by cryo transition electron microscopy. Finally, the characterizations are enhanced by complementary studies on additional artificial phospholipids that were designed in order to answer specific question concerning the forces at play in mechanosensitive liposomes.

References
Poster Abstracts
Adaptive peptide-metal complexes towards Fabrication of Nanometer Scale Structures

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The generation of well-defined and stable macroscopic structures is an emerging field in the bio- and nanotechnology world. In a "bottom-up" approach, simple building blocks spontaneously arrange themselves and self-assemble to form highly organized one-, two-, and three-dimensional nanostructures and macroscopic objects with nano-scale order. The process of molecular self-assembly as a fabrication tool has a significant impact in all biological systems; it has implication for certain disease states and applications in biotechnology and nanotechnology. In this regard, the most ubiquitous and simplest self-assembly protein system is the α-helical coiled-coil.

Here we present the fabrication of new adaptive nanometer scale structures through self-assembly processes, for which the building blocks include the coiled-coil peptides modified with metal-binding sites. Thus, the first step toward fabrication of such nanometer scale structures is to explore the factors that dictate the complexation between peptide-ligand conjugates and different metal ions and to characterize such systems. I have designed, and characterized nanometer scale building blocks composed of antiparallel coiled coil peptides modified with dipicolinic acid as the metal binding site using thiol-thioester exchange experiments, and Circular dichroism. Then this system have been explored upon addition of different metal ions such as Eu(III), Tb(III) and Cu(II), using different technique such as fluorescence, UV-VIS, CD and TEM. These measurements suggest that upon addition of different metal ions to the antiparallel coiled coil peptides various structures could be obtained.
In the Search of Bigger Replicators from Dynamic Combinatorial Libraries

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One of the most fundamental questions at the interface between biology and chemistry is what constitutes the minimal molecular basis of life. There is a big gap in our knowledge considering the early steps of the formation of evolvable life. Systems chemistry, and dynamic combinatorial chemistry in particular, is a promising approach to address this intriguing question.

Figure 1. Schematic representation of self-replication in a dynamic combinatorial library.

Self-replicating systems constructed by β-sheet prone peptide building blocks, reported up to day, formed hexamers and heptamers as the largest macrocycle size. Recent studies in our group showed that decreasing the hydrophobicity of the building blocks leads to formation of larger macrocycles consisting of 8 building blocks. This study aims to further extend the set of building blocks that can give rise to replicators having even larger macrocycle size, consisting of 9, 10 or more building blocks. Among all the parameters, an investigation of the hydrophobicity/hydrophilicity of the building blocks was chosen to explore the size limits of replicating systems. If the β-sheet type interactions between the building blocks are weakened, macrocycles having a larger number of building blocks will be favoured to compensate this effect. In order to weaken the intermolecular interactions, the hydrophobicity of the building blocks was decreased by incorporating more hydrophilic amino acids (such as Asn, Thr) and phosphorylated amino acids. Furthermore, the C-termini of the peptide building blocks were decorated with an amide functionality. The resulting new sequences were synthesized and the replication behaviour of the dynamic combinatorial libraries made from these building blocks is being investigated.

References:

Novel Donor-Acceptor Systems

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Macrocyclic compounds have been in use as synthetic dyes. Phthalocyanines (Pcs), one of the known macrocyclic compounds, have been used as blue and green colorants for decades.[1] Pcs exhibits a great structural variability with different substituents and metals in Pc core.[2] These structural variability makes their use in different applications such as optical, electronic and photoelectronic devices.[2]

Recently we have focused on designing and synthesis of novel Pc derivatives as an absorber and photo-conductor in organic solar cells. Hence, we have prepared donor-acceptor systems including Pc core as donor and perylene group as acceptor.

Acknowledgements:

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References:

Towards Self-Replicating Molecules Capable of Forming Compartments

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The idea that life on Earth originated from inanimate matter via a series of chemical steps of increasing molecular complexity and functionality has been widely accepted in scientific community. However, the transition from non-living to living state is hard to conceive both from experimental and conceptual point of view. The important step in this direction is to design a chemical system in which essential requirements for life (replication, metabolism and compartmentalization) are integrated.

Investigating the emergence of compartments (compartmentalization) made from self-replicating molecules (replication) from a network of interconverting molecules (a primitive form of metabolism) is a way to fabricate such a chemical system. Such network can be created by the Dynamic Combinatorial Chemistry (DCC) approach where reversible covalent reactions are used to link building blocks together, forming libraries of compounds whose product distribution is under thermodynamic control. Addition of a template results in the shift of the equilibrium, amplifying those library members that are stabilized by the template. Amplification may also occur in the absence of a template: if one or more species in the library can self-assemble, the library composition will favor those species that can form the most stable aggregates. When the self-assembled species are further amplified by the self-replication and they consist of compartments, the system in which compartmentalization is driven by self-replication is achieved.

Figure 1. Different combinations of superchemical though infrabiological subsystems, inspired by Ganti’s general scheme of the chemoton, based on three coupled autocatalytic cycles: template (T), metabolic (M), and boundary (B) subsystems. The TMB ternary supersystem would already meet all the requirements for life.

References:

Anionic ligands for Lanthanide emission

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A series of ligands for lanthanide complexes have been constructed based on a 1,2,4-triazole core. 1,2,4 triazoles offer a versatile synthetic platform for ligands and have been employed in binding Fe, Ru, Os, Rh, Pd, Ir and B. The complexation behavior has been studied using spectrophotometric titrations of all ligands with Tb(NO$_3$)$_3$·5H$_2$O and Eu(NO$_3$)$_3$·5H$_2$O in methanol which revealed the formation of a mixture of different ligand to lanthanide stoichiometries. Time dependent emission spectra of the different stoichiometries showed lifetimes ranging from 1.6 to 2 ms for Tb and 0.8 to 2.6 ms for Eu. The optimal lifetime showed quantum yields of 24 to 35% for Tb and 1.5% to 5% for Eu. In this presentation ligand design strategies will be discussed.

References:

Dynamic Combinatorial Chemistry (DCC)\(^1\) has emerged as a powerful strategy to identify ligands for biological targets.\(^2\) It allows the formation of Dynamic Combinatorial Libraries (DCLs) by connecting building blocks through reversible covalent bonds. Upon addition of a target, one or more members are bound, thereby leading to selection and amplification of the strongest binders from the DCL.\(^3\) The imine formation/exchange is a suitable covalent bond to perform DCLs, because the reaction is reversible and the equilibrium can be shifted to adapt to the presence of the target. Moreover, further reduction of the imine bond would freeze the equilibrium, allowing the isolation of the amplified species.

In this work, we have designed a library of potential modulators of protein-protein interactions generated from two diamines and five aromatic aldehydes, and used DCC to identify the best binder(s) to control the Semaphorin 3A-Neuropilin 1 (Sema3A-Nrp1). The scaffolds were selected from a preliminary docking study of potential binders at the Sema3A-Nrp-1 interphase. After addition of Sema-3A to the mixtures, we characterized the protein-bound library member(s) by UPLC-HRMS (High Resolution Mass Spectrometry). From the 30 possible compounds, 7 potential binders were identified by the DCC methodology and their interaction with Sema-3A was confirmed by Saturation Transfer Difference (STD) NMR.

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14-3-3 proteins as a scaffold for small-molecule controlled signaling platforms


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Designing a synthetic cell requires tightly controlled signaling networks. Engineered protein scaffolds can be used as key regulators for signal transduction in artificial signal transduction cascades where they can regulate in- and output of the network. In this research a 14-3-3 protein scaffold is developed which induces dimerization of proteins mediated by the small molecule stabilizer fusicoccin. As proof of principle caspase 9 is used to constitute proximity induced dimerization, leading to activation of the caspase cascade involved in the programmed cell death pathway. Caspase 9 does not naturally bind to 14-3-3 proteins, therefore the caspase 9 monomer is conjugated to a 14-3-3 binding motif which is known to bind with high affinity in the binding grooves of a 14-3-3 dimer and this interaction is stabilized by the small molecule fusicoccin. Dimerization of the caspases is shown by analyzing the caspase activity using a synthetic substrate which becomes fluorescent upon caspase specific cleavage. Results show that addition of 14-3-3 protein alone to the caspase construct does not lead to enhancement of caspase activity compared to caspase background activity. Upon titrations of stabilizer fusicoccin caspase activity is enhanced up to 45 fold, meaning that fusicoccin is essential for inducement of caspase dimerization and subsequent activation. Additionally, the activated caspase 9 is also able to cleave its natural substrate caspase 3. In future experiments the dimerization capabilities of the 14-3-3 scaffold will be tested in vivo. Thereafter the scaffold properties of 14-3-3 proteins can be further exploited in the incorporation of a synthetic signaling network.
Molecular hydrogel catalysis of three component cascade reactions

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Molecular hydrogels are formed by non-covalent intermolecular interactions of low molecular weight compounds in water. These intermolecular interactions, mainly hydrogen bonding and hydrophobic effect, are acting in a preferred direction leading to elongated aggregates that evolve into nanometer to micrometer-sized fibers. Molecular gels with selected functionalities may produce smart materials.[1]

L-proline derived hydrogelators have been use recently to catalyze aldol additions,[2] and there are also some examples of metallogels used to catalyze organic reactions.[3] In the present work we plan to use an interpenetrating catalytic network of two components, a Cu(I) complex of the triazolium-based hydrogelator (Figure 1, top) with an L-proline derived hydrogelator (Figure 1, bottom), in order to catalyze a click and an aldol reactions respectively.

Can we do a “one-pot” of two reactions with the coaggregated catalyst?

Figure 1

References:
An in vitro gene expression platform to study far from equilibrium synthetic gene networks
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From a physico-chemical point of view, cells can be seen as out-of-equilibrium microreactors able to sustain a large set of reactions all in the same time, some of these reactions adopting complex behaviours such as oscillations. Oscillations can be found at a genetic level, where a delayed negative feedback in a genetic network leads to periodic synthesis of regulating or catalytic elements, which is a key element for cell regulation.

In vitro synthetic biology tends to reproduce these complex cellular behaviours by bringing together a set of building blocks, one combination or one minimal set of building blocks generating one complex behaviour. Therefore, in vitro synthetic biology can be used as a tool for demonstrations in biology, as well as a platform to design new biological functions.

This project aims to create a simple in vitro gene expression platform, where almost every kinetic parameter or precursor concentration can be tuned to allow the emergence of complex behaviours such as oscillations in synthetic gene networks.
By combining an E.coli cytosolic extract with exogeneous RNA polymerase (RNAP) such as T7 RNAP and various genetic templates, and by coupling this reaction mixture to a long-term feeding system providing substrates for transcription and translation, it is possible to perform multiple protein expressions following a designed scheme on a large timescale.
Nanotubes vs layered structures: The effect of hydrodynamic forces on the size and shape of J-aggregate particles of self-assembled amphiphilic porphyrins

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The different mesoscopic particles of the J-aggregates of amphiphilic porphyrins of *meso*-aryl substituted porphyrins are studied by PFM and Cryo-TEM techniques. The contradictory previous reports on the detection of monolayered nanotubes, bilayered, and multilayered particles depend on the observation method, but the reported structures also are different mesoscopic forms of the J-aggregates. All types of particles show similar electronic absorption spectra but different resonance light scattering and optical polarization properties. All studied J-aggregates were chiral, as observed by CD determined by Mueller matrix polarimetry, as a consequence of the intrinsically chiral structure of the primordial aggregation sheet that yields the different mesoscopic forms but that is not translated to nano- or micro-chiral shapes. Hydrodynamic forces may destroy nanotubes in viscous solutions but not in diluted solutions, and slow repairing effects were also observed. Diastereochemistry (tacticity) of the resulting J-aggregates has dramatic consequences in the structure and stability of the nanotubes.
Molecular recognition of ConA and mannose on liposome surface

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Multivalent glycolipid derivatives are a new class of compounds which may be of interest for glycosylation of liposome surfaces and targeted drug delivery¹,². For a selective transport to the target immunocompetent cells, these compounds comprise mannose molecules in their structure which bind specifically to C-Type Lectin Receptors. The design and synthesis of multivalent glycocluster requires the conjugation of biologically relevant carbohydrate epitopes functionalized with linker arms to multivalent core scaffolds. In order to study the influence of multivalency of the carbohydrate part of glycolipid molecule to the affinity and recognition of the targeted receptors, the mono-, di- and tetra-mannosyl lipoconjugates were synthesized. The synthesized compounds were easily incorporated into liposomes and the mannosylated liposome were characterized by DLS and AFM, Spectrofotometric³ and carbohydrate liposomal quartz microbalance based assays⁴ have been established for studying carbohydrate–lectin binding. It was demonstrated that liposomes with incorporated mannosyl-lipoconjugates were effectively recognized by the Con A. It was shown that lectine affinity increases with the increase of the number of molecules of mannose in glycolipid conjugates.

Also, it was demonstrated that the mannosylated liposomes can be a useful model for investigation of specific interactions with lectin receptors.

Biofunctionalized supramolecular hydrogels for intestinal organoid expansion


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A single Lgr5-CBC stem cell from the bottom of the crypts of the intestine can be cultured in vitro into three-dimensional intestinal organoids, which have the capability to reconstruct the crypts of a de-epithelialized wound bed.\textsuperscript{[1]} Intestinal organoids together with colonic organoids can be used to grow human epithelia for the treatment of gastrointestinal tract diseases.\textsuperscript{[2]} However, the current culture medium Matrigel is derived from tumor cells, and its composition is not well defined leading to a batch-to-batch variation. As a result it is attractive to find a promising candidate to replace Matrigel.

One of the most important guides for scaffold designs is the extracellular matrix (ECM), since it provides the mechanical framework for natural tissues and is responsible for many biological functionalities of the cells embedded in it. The most abundant components of the ECM are the collagen fibers, which provide tensile strength to the surrounding tissue; laminin for cell attachment via integrin binding; the proteoglycan perlecan, which binds to other ECM components and growth factors; and nidogen connecting the collagen fibers to laminin.\textsuperscript{[3]} In order to mimic the extremely complex environment of the ECM, cells need to be instructed by the environment to transmit signals in order to adhere, migrate, proliferate and/or differentiate. These signals can be divided into insoluble cues (like laminin), which offer anchoring points for cell attachment, and soluble cues, like growth factors, that bind to transmembrane receptors resulting in cell growth, proliferation, differentiation or migration.\textsuperscript{[4]}

We aim to build functionalized supramolecular hydrogels by incorporating laminin derived peptides for cell attachment and sulfated peptides for growth factor binding to our supramolecular system. Either ureidopyrimidinone or 1,3,5-benzenecarboxamide functionalized monomers are used, which are known to stack into fibers.\textsuperscript{[5]} Due to the dynamicity of these stacks, the bioactive peptide sequences can cluster into a specific binding domain for the cell, which might result in an improved cell attachment and subsequent cell expansion.

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Two Replicators Competing for a Common Building Block

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We recently reported the emergence of replicators from dynamic combinatorial libraries (DCLs) made from peptide building blocks bearing thiol-functionalities. 1,2 The oxidation of an aqueous building block solution gives rise to a continuously exchanging pool of disulfide macrocycles. Initially, cyclic trimers and tetramers dominate but, upon agitation, self-replicating hexamers emerge, which self-assemble into fibres, due β-sheet type interactions and eventually become the major product in solution. Until now the hexamer was found to be the only self-replicating species in this system but we found that in some cases the trimer can also forms fibres. We have been able to prove that this trimer is also a self-replicator.

Fig 1: Trimer and a hexamer replicators from the same building block, emerging from DCL under different conditions. How will they compete against each other under different conditions?

With two different replicators emerging from the same building block, we were able to perform competition experiments under agitated and non-agitated conditions but also in flow-experiments to figure out which replicator is the fittest replicator under given conditions.

References:
Redox controlled emission in a novel D-A-D polymer film

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Over the past decades smart materials, materials that respond to external stimuli such as light, redox chemistry and heat, have gained an increasing amount of interest. Organic conducting polymers in particular have so as they possess tunable HOMO-LUMO band gaps and optical properties and also can be used after easy processing and in foldable devices. Here, an amino-phenyl carbazole naphthalene diimide (APC-NDI), a novel oligoimide, has been synthesized. This compound, which possesses a Donor-acceptor-donor (D-A-D) design, can undergo electrochemical polymerization through the carbazole units. The optical and electrochemical properties of the monomer, polymer film and the electrode-solution interface have been investigated using UV/vis, IR, Raman and emission spectroscopy, cyclic voltammetry, confocal microscopy and several spectroelectrochemical techniques: in situ UV/vis and emission spectroscopy, SERS and resonance Raman. Similar D-A-D oligoimides find applications in high-performance nonvolatile memory devices, logic gates, non-linear optical materials and sensing devices. In the present contribution we show that the current D-A-D arrangement shows signs of switchable photo induced electron transfer rates, thereby able to modulate fluorescence. Several of such systems have already been developed, but to the best of our knowledge this is the first of its kind to regulate fluorescence by reduction instead of oxidation, opening up to more possible applications.


Adaptive processes in a topologically diverse dynamic library of pseudopeptides

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The Dynamic Combinatorial Chemistry\(^1\) proposes the creation of a mixture of compounds (Dynamic Combinatorial Library, DCL) inter-connected through reversible chemical processes. The changes of concentration of species in a DCL contain valuable information about changes in stability, with the corresponding implications in the recently emerged topic of Systems Chemistry\(^2\) and the concept of molecular evolution.\(^3\) One of the most widely used chemical connections to generate DCLs is the disulphide bond,\(^4\) mainly from molecules with two reacting sites (bipodal), and thus directed towards the generation and interconversion of cyclic oligomers.\(^5\)

In this work, we studied the effect of combining mono-, di- and trithiols in the same DCL\(^6\) in order to expand the structural and topological diversity. We will show how the reaction mixture evolves from a complex combination of compounds to the almost exclusive formation of a major species through error-check and correction processes. This adaptation proceeds by delicate non-covalent intramolecular interactions, which are sensitive to structural and environmental effects.

![Diagram](image)


References:


Bio-orthogonal metalloporphyrin catalysts for *in vivo* chemistry

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In recent years the development of synthetic metal complexes for *in vivo* chemical transformations has received much attention, using these complexes as catalyst for non-biological reactions [1]. Whereas these metal complexes were used for the labelling of biomolecules by cross-coupling or protecting group cleavage [2,3], they could also be employed for *in vivo* synthesis. By adding a new reaction to the ‘toolbox’ already available to nature, new pathways could be opened and new chemical structures can be obtained from biosynthesis.

A range of metal complexes, for example metalloporphyrins, can be used for *in vivo* transformations. Porphyrins have been shown to be biocompatible and their localization in cells can be controlled [4].

![Figure 1](image)

In this project, metalloporphyrins will be synthesized and employed in catalysis of cyclopropanations and aziridinations of dehydroalanine in living cells (*Figure 1*).

References:

Morphological diversity emerged by complexation between DNA and catalysts in vesicle-based protocell

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According to the constructive approach, we have synthesized a self-reproductive giant vesicle (GV)-based protocell in which the GV division takes place associated with the replication of DNA: The self-reproduction of the protocell with amplified DNA occurred much faster than that with non-amplified DNA. The collaborative dynamics between self-replication of DNA and self-reproduction of GV was presumably induced by the complex formed by the DNA and catalysts in the vesicular membrane1.

The complexation was substantiated by the energy transfer experiment using the BODIPY-tagged catalyst as a donor and the Texas Red-tagged DNA as an acceptor under the presence of TEMPOL which is a water soluble quencher of Texas Red. The complex turned out to serve as an active site for production of the membrane lipid from its precursor by monitoring the decomposition reaction of the precursor using UV-Vis spectrometry.

We observed two deformation modes, the budding and the multi-tubulation of the protocell composed of POPC, POPG, cationic membrane lipid, catalyst, cholesterol (35:39:12:9:5 mol%). The ratio of the budding to the multi-tubulation decreased when the incubation time of protocells with amplified DNA becomes longer. This result implies the complexation progresses over the time and the status of the complex influences the mode of deformation.

When the amount of additional membrane precursors decreased, the ratio of the budding to the multi-tubulation increased. These results indicate that the production rate of the membrane lipids depends on the degree of the complexation, leading to the diversity of deformation modes. This peculiar transition of the morphological change from the budding to the multi-tubulation will be interpreted in terms of the competition between the production of membrane lipids and Laplace pressure.

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Effectively regulating downstream DNA-based processes while reducing retroactivity

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The de novo construction of complex biomolecular reaction networks with unique functionality is one of the main challenges for the development of bottom-up synthetic biology. Due to the reduced number of components, these simplified biochemical networks in vitro are more amenable to systematic design and quantitative analysis than circuits constructed within cells. However, inside cells biochemical circuits with specific functionality regulate downstream processes creating higher order complex biomolecular networks. Interestingly, while these downstream processes act as a load, the upstream biochemical circuits maintain their specific functionality. Here we demonstrate in vitro a two-input enzymatic DNA-based bistable network driving downstream processes such as a DNA tweezer or DNA-directed control of an enzyme-inhibitor complex. Specifically, we propose a DNA-based insulator which effectively regulates downstream processes while reducing retroactivity.

![Two-input switchable DNA network](image)

Figure 1. Previously designed and constructed two-input enzymatic DNA-based bistable network, which can be switched to state $\alpha$ and state $\beta$ by Input 1 and Input 2 respectively. Single stranded DNA strand $\alpha$ is used to produce single stranded DNA strand SD which in turn regulates a downstream process, e.g. a DNA tweezer.

References:

Selective Functionalized Iron Oxide Nanoparticles’ Surface Based on Dynamic Imine Chemistry in The Presence of Biotemplate

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Molecular recognition plays a quite important role in biological systems such as receptor-ligand recognition, antigen-antibody recognition, and RNA-ribosome. With these accurate recognition processes, organisms can live and develop exquisite function, adaption and evolution, etc. Unlike the molecular recognition in synthetic systems, most of molecular recognition in biological systems involve macromolecular interactions. Currently, research is increasingly focusing on the interaction and recognition between biological functional macromolecule such as protein-protein interactions (PPI). Some new insights into processes central to life can be obtained through these studies, it also can contribute to find new lead compounds in the process of drug discovery.

Dynamic Combinatorial Chemistry (DCC) is an excellent method for achieving molecular recognition. DCC is a method of generating new molecules by reversible reaction of simple building blocks under thermodynamic control[1]. Here, DCC will be used for the surface functionalization of nanoparticles aiming at the recognition of the surface of biomacromolecules, such as DNA[2] and protein. Aldehyde groups will be introduced on the iron oxide nanoparticles which are reacted with amines to produces a dynamic combinatorial nanoparticles surface through reversible imine bond formation in water solution. In the presence of biomacromolecules, surface functionalization should be selective for those amines that have affinity for the biomacromolecules. The labile imine bonds may then be reduced to stable amines, resulting in nanoparticles which have a surface complementary to the biomacromolecules. Such nanoparticles should then be able to interfere with protein-protein interactions in biological systems and may become useful tools for biochemical studies and may even have therapeutic potential.

References:
Compartmentalized catabolic network leads to autonomous movement on natural substrates

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In the discipline of bottom-up synthetic biology, compartmentalized nanoreactors that resemble bacterial microcompartments and eukaryotic organelles are required to bridge the gap between table-top chemistry and autonomous functioning artificial cells. In addition, bio-applicability of the nanoreactors is a prerequisite for the development of autonomous devices that can perform multiple functions such as sensing and the transport of cargo in response to external stimuli such as substrate, cofactor or biomarkers. Here we address this by designing and constructing a supramolecular assembly of a nanoreactor containing an enzymatic metabolic network that is capable to propel the artificial cellular organelle in multiple fuels such as glucose and lactate at low and biological relevant concentrations as well in human blood serum. By engineering a signal-amplification step in the enzymatic pathway, a sensitive signal transduction involving propulsion behavior is created and shows that the compartment is able to sense and convert different exogenous biochemical signals into kinetic energy. Movement on natural substrates, allows the nanoreactors to move while simultaneously perform a task or series of tasks.

References:

Evolving Single Chain Polymeric Nanoparticles for Cooperative Folding

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During the last decades, fundamental studies on protein folding have attracted significant attention in scientific research. Since proteins can perform highly selective functions, e.g. specifically catalyze only one reaction out of several hundreds of possibilities, it follows that their three-dimensional structure should be limited to only a few different functional conformations. Thus, the majority of proteins directly derive their function via their three-dimensional organization of structure.

A central question in protein folding research has been how proteins only fold into those specific conformations. While the structure of a folded protein is described by a primary, secondary, tertiary and quaternary structure, it is the primary structure - the sequence of residues - which is ultimately responsible for the conformations in which the protein can fold. Indeed, simulations of simple amphiphilic polymer chains have shown that there exists a specific subset of sequences, so called ‘protein-like’ sequences, that display cooperative folding and a globular folded structure.\(^1\) In contrast, both random and random-block copolymers are predicted to have a non-cooperative folding process resulting in an elongated asymmetric shape (cigar shaped). These simulation results have been verified experimentally by comparing two polypeptoids of the same length and with the same overall composition, but different sequences.\(^2\) Scattering data showed that the protein-like polypeptoid both has a lower radius of gyration in the folded state, and that the unfolding transition is more cooperative.

The single chain polymeric nanoparticles (SCPNs) that have been produced in our group have either random or block sequences. Thus, in light of the theoretical work, it is perhaps not surprising that folding studies have shown that the polymers fold non-cooperatively\(^3\) and that the structure in solution is elongated.\(^4,5\) Therefore, in order to create cooperatively folding SCPNs, the challenge becomes to obtain some level of control over the primary sequence of the polymers. However, while significant advances in sequence control have been made, it is not yet at a level of total control.\(^6\) Thus, we propose to use an intrinsic property of the protein-like folded state of an amphiphilic copolymer: its lower energy state, as compared to random or random-block sequences. The manner in which we will use this energy difference is by performing dynamic covalent chemistry (DCC) using a polymer backbone and exchangeable side groups. The idea is that the side groups will reshuffle into a primary sequence that is energetically more favorable.

References:

Communication pathways among liposomes encapsulating a chemical oscillatory reaction

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The propagation of chemical signals is an important phenomenon, stemming from the interplay of different mechanisms, which is vital to biological cell signalling and have applications in fields ranging from information technology to molecular computing. Chemical oscillators are an example of molecular signal emitters which, if confined in micro-domains, they can be used to model complex processes such as cell communication. In this context, a major prerequisite to mimic biological cell structure is to elaborate aqueous micro compartments surrounded by phospholipid membranes. In turn, these compartments must hold a well-defined chemical reaction whose progression is governed by concentration fluctuations of individual species, e.g. an autocatalytic system. One such system is the Belousov-Zhabotinsky (BZ) reaction\cite{1}, a robust chemical oscillator in which an organic substrate (malonic acid, MA) is oxidized by bromate in the presence of a redox catalyst, such as ferroin, Fe(o-phen)$_3^{3+}$. Recently, we reported for the first time the successful encapsulation of the BZ reaction inside giant liposomes and emulsions obtained with microfluidics.\cite{2,3} Engineering stable and communicating liposomes encapsulating the BZ reaction requires a fine-tuning of the physico-chemical properties of the confining membranes, such as lamellarity and permeability. This is possible by modifying the membrane composition. We carried out the structural characterization of membranes with different composition in the presence of BZ reagents using small angle X-ray scattering (SAXS). In addition, we investigated the effect of membrane composition on the BZ oscillatory behaviour using UV-Visible absorption spectroscopy. The aim of this work is thus to obtain insight into the BZ-phospholipid membrane interaction which, in turn, will be beneficial for engineering stable liposomes which encapsulate the BZ oscillator for the study of chemical communication.

References:

\[2\] R. Tomasi *et al.*, *Chemical Science*, 2014, **5**, 1854.
Dynamic combinatorial libraries operated far from-equilibrium: toward dissipative molecular networks

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Dissipative, far-from-equilibrium systems are very common in the biological world but are still an exception in chemistry. The behavior of far-from-equilibrium systems is probably a lot richer than that of equilibrium systems but has yet to be explored. Therefore, we are trying to develop conditions where the components of dynamic combinatorial libraries (DCLs) based on disulfide chemistry are continuously cleaved and reformed via reduction and oxidation processes. These conditions can be named “recycling conditions” since the material is permanently part of a cycle of breakdown/reformation. In order to allow these redox reactions to take place, oxidizing and reducing agents are continuously added to the media. This is the source of energy that drives the systems far from equilibrium and thus should enable us to observe new states that cannot be reached in absence of this continuous flow of energy. In order to ensure that the global oxidation level of the system remains constant, an automated setup is being developed. The oxidation level is continuously monitored in situ with an UV/Vis probe and an algorithm controls the flow of oxidant and reducing agent added at any time to the system (Figure 1.).

Figure 1. Schematic representation of the automated setup developed to maintain the global oxidation level of the system constant

Our first experiments clearly demonstrated that a detailed understanding of the kinetics of all steps in the system processes is essential to achieve the desired conditions. In the conditions we initially used (neutral pH, ≈ 80 % oxidation...), reorganization (equilibration via exchange reactions) was found to be too fast to be influenced by the imposed redox reactions. Thus, we have turned to an investigation of the separate redox and exchange rates under a broad range of conditions with the intent, aided by computational modeling, that once conditions are found where oxidation and reduction are faster than exchange processes we will apply them first to DCLs based on building blocks developed in our laboratory, expecting to observe a template effect. Then, these “far-from-equilibrium” conditions will be applied to self-replicators emerging from DCLs, where the recycling conditions will allow us to observe evolution in artificial self-replicating systems.
The folding process of a single polymer chain with a chiral internal secondary structure


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Abstract: The intramolecular folding of chiral single polymeric chains into single-chain polymeric nanoparticles (SCPNs) via \( \pi \)-stacking was investigated. To this end, hydrophilic polymers grafted with structuring, chiral 3,3'-bis(acylamino)-2,2'-bipyridine substituted benzene-1,3,5-tricarboxamides (BiPy-BTAs) units were prepared via ring-opening metathesis polymerization (ROMP). A combination of spectroscopic and scattering techniques was employed to obtain a better understanding of the folding behavior and the chiral internal structure of these systems. Circular dichroism spectroscopy showed that the folding of the polymer is highly dependent on the solvent quality and temperature. The folding process in water was fine-tuned via the addition of a good co-solvent (tetrahydrofuran – THF), resulting in an optimal balance between the conformational freedom of the polymer’s backbone and the stability of the \( \pi \)-stacked units. Small-angle X-ray scattering (SAXS) experiments showed that the shape of the SCPNs is controlled by the formation of a chiral internal secondary structure.
Design and Length Control of Mixed Block Co-fibers From Dynamic Combinatorial Libraries

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Self-replicating systems play a very important role both in origin of life and material science in which the assembly process strongly affects the resulting properties of the material[1]. In such supramolecular assemblies it is very challenging to precisely control the structure and dimensions of resulting self-synthesizing material that grows on nuclei. Very recently, in our group, it has been shown that, controlled self-assembly with homogeneous seeds having certain lengths help to achieve a control over resulting fiber lengths with the living property of nucleation-growth process[2].

In this study, it has been tried to extend the scope of living nature of peptide replicators through the formation of B-A-B type triblock co-fibers with controlled length. In order to achieve this, two different hexamer forming peptide replicators have chosen for the block compositions. The food mixture (3mer/4mer of outer blocks) has been seeded with hexamer seeds of the inner block. Formation of the supramolecular assemblies has been confirmed by partially reducing the fiber ends and sample composition is followed on UPLC as the amount of reducing agent is gradually changed.

References:
Fragment Linking of Inhibitors of the Aspartic Protease Endothiapepsin Facilitated by Protein-Templated Click Chemistry

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Fragment-based design (FBD)¹ enables the design of bioactive compounds. Whereas there are numerous reports on FBD using optimization of a hit by fragment growing/optimization, fragment linking is rarely used.² Protein-catalyzed click chemistry is a hit-identification strategy, in which azides and alkynes are assembled irreversibly to the corresponding triazoles.³

We have demonstrated that fragment linking and protein-templated click chemistry constitutes an efficient hit-identification strategy. Using co-crystal structures of the aspartic protease endothiapepsin and fragments,⁴ we have designed a library of inhibitors generated from alkynes and azides and used protein-catalyzed click chemistry to identify potent inhibitors, which were characterized by UPLC-TOF/SIM.

References:

Developing a Self-replicating System Based on 2-Arylidene Indandione

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In Dynamic Covalent Chemistry (DCC), a network of interconverting compounds under thermodynamic control is created called a Dynamic Covalent Library (DCL)\(^1\). Library members from the DCL can be amplified in different ways, one of which is by coupling the library to a self-replicating system. A self-replicating system is based on a molecule that is able to catalyze the formation of another copy of itself.\(^2,3\) It does this through association of the building blocks through molecular recognition in a ternary complex and bringing the reactive sites in close proximity. Self-replication is important to consider in the context of pre-biotic chemistry since self-replicating entities are hypothesized to have emerged on pre-biotic earth prior to the emergence of life.\(^1\) In our laboratory, we have developed self-replicating systems in which the bond forming reaction is a cycloaddition involving a maleimide,\(^2\) which can be coupled to a DCL to amplify one library member selectively.\(^4\)

A functionalized arylidene-indandione can also be used as dipolarophile in a reaction with a nitrone and hence a new self-replicating system can be constructed. In contrast with the maleimide, the cycloaddition between the indandione and the nitrone is reversible. When the indandione-based self-replicating system is coupled to a DCL, a library member can be amplified reversibly. This reversibility presents the opportunity to regenerate the library member by changing the conditions and to use it in the kinetically controlled maleimide-based self-replicating system. The aim is to exploit the reversible nature of the indandione-based self-replicator in order to create increasingly more complex chemical systems.

References:
Active materials fueled by a chemical reaction

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Dissipative self-assembly of natural macromolecular building blocks is at the basis of many essential processes in living organisms, including cellular transport, cell dynamics, and morphogenesis. Driven by the conversion of chemical fuels, structures such as microtubules are sustained far from thermodynamic equilibrium, leading to localized, transient assembly of architectures with adjustable dynamics. Characteristically, these active materials are maintained only for as long as useful energy is available to the system.

Recently developed synthetic materials that are obtained under kinetically-controlled conditions, exhibit a rich structural diversity and new functionality compared to equilibrium-processed materials. Nevertheless, they still reside at (local) thermodynamic minimum and lack the dynamic character of natural out-of-equilibrium materials.

Here, we explore the potential of synthetic active materials using the dissipative self-assembly of a surfactant system fueled by a chemical reaction. General design principles are used to develop our current example, which contains the (de)activation of NAD-based surfactants, which operates in water at room temperature, on timescales of hours. The interesting dynamic properties of this system are investigated using several techniques, such as absorption and dynamic light scattering spectroscopy, NMR and electron microscopy.

We observe a fuel dependent self-healing assembly of the surfactants. Furthermore, the self-assembly process can be tuned by the catalyst concentration. Additionally, the architecture of the both the equilibrium as the transient state can be tuned by varying the micelle packing parameter.

Our work shows a new approach to materials that are formed far from equilibrium, with properties that are related to the chemical reaction conditions. The observed fuel and catalyst dependent redox and self-assembly behavior of the surfactants are key developments towards more complex synthetic active materials.
Selective recognition via imprinting of multivalent supramolecular polymers


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Here, we propose to use the dynamic nature of supramolecular polymers of water soluble benzene-1,3,5-tricarboxamide derivatives (BTAs) for the selective recognition of biological targets such as double stranded DNA (dsDNA).

Multivalent super-selective recognition plays an important role in many biological processes like signal transduction and the immune response. Synthetic systems capable of super selective recognition are extremely interesting for biomedical applications like the inhibition of viruses and the targeting of diseased cells.\(^1\)\(^2\)\(^3\)

Previous research shows that polymers provide a great platform for multivalent recognition via several methods of imprinting.\(^2\) These methods predominantly use covalent polymer backbones which can be functionalized via supramolecular or dynamic covalent bonds. By using the highly dynamic nature of the BTA polymers we like to introduce supramolecular chemistry to the field of polymer imprinting and super-selective recognition. Figure 1 shows the proposed steps towards a highly selective binder for a specific DNA sequence based on the imprinting of functionalized BTA polymers.

A dsDNA template is mixed with supramolecular polymers of BTA’s containing monomers functionalized with sequence-specific DNA-binders. Due to the multivalent interactions between the fiber and the dsDNA, the dsDNA-binding monomers are rearranged and clustered for an optimal binding to the specific DNA sequence. After crosslinking the polymer, the DNA template is removed which leaves a structure with a high binding affinity specifically for the imprinted dsDNA sequence.

![Figure 1](image)

**Figure 1:** Schematic overview of the proposed imprinting of the supramolecular polymer. First, the polymers are formed containing a fraction of DNA-binding monomers. After DNA is added, the supramolecular polymers allow the functionalized monomers to rearrange which results in the formation of a cluster. By covalently crosslinking the stack and removing the template, a highly specific DNA binding system is obtained.

The first steps in this research are the functionalization of BTAs with DNA-binders and determining the binding properties of these binders when incorporated in the polymers. For this, the fluorescent DNA intercalator thiazole orange (TO) is coupled to the BTAs with different linker lengths and types. TO provides an great read-out for DNA binding due the increase in its fluorescent intensity upon intercalation. With this, we want to investigate the linker dependent binding affinity of the functionalized supramolecular polymers to dsDNA and the subsequent clustering of functionalized monomers in the polymers.

\(^3\) C. S. Mahon, Nature Chemistry, 2014, 6, 665-672
Chiral phosphorus-based ligands are probably one of the most important types of ligands in transition-metal-catalyzed asymmetric reactions.\cite{1} To date, numerous chiral phosphine ligands with huge structural diversity have been developed and successfully applied to various metal catalyzed asymmetric reactions. Chiral overcrowded alkenes which act as molecular motor can convert the energy provided by UV-light and heat into unidirectional rotation around the central double bond. During this cycle, two cis-states of opposite helicity are accessible. Based on our previous molecular motor-based organocatalyst,\cite{2} new photoresponsive multistate chiral ligands were designed and synthesized. It is shown that light-induced changes in geometry and helicity of the switchable ligand enable excellent selectivity toward the racemic or individual enantiomers of the product in a Pd-catalysed desymmetrization reaction.\cite{3}

Figure 1. a. Traditional C\(_2\)-symmetric privileged ligands: (S)-Binap and Trost ligand. b. Crystal structure of the parent molecular motor,\cite{4} left: (S,S)-(M,M)-trans isomer, right: (R,R)-(P,P)-cis isomer. c. Novel three-state photoresponsive phosphine ligand based on unidirectional molecular motor. d. Switchable asymmetric catalysis.

References: