THE START OF FMS
and what happened before

BEN FERINGA
Leaving your scientific comfort zone

BIO-INSPIRED MOLECULAR SYSTEMS:
imitating and modulating cellular life
It is a real pleasure to introduce this special magazine of our gravitation program “Functional Molecular Systems”, in which we present our scientists and our science under the banner “FMS en route”. During the writing of the proposal in 2011, we could not have dreamed of the many successes that have followed, with the 2016 Nobel Prize for Chemistry to Ben Feringa the absolute highlight. The many awards received by both our senior and junior scientists clearly illustrate the international standing of the research performed by the molecular chemists in Groningen, Nijmegen and Eindhoven. The myriad of groundbreaking results published in top scientific journals demonstrates our leading international position in the fascinating field of functional molecular systems.

In this “FMS en route”, we showcase our science and scientists and I hope that, while reading, you experience some of the excitement that all our young researchers – master- and PhD-students and visiting postdocs – encounter during their research. Their enthusiasm is key to our success in the education of the next generation of scientists. Right from the start, FMS has invested in reaching out to the general public and many of our scientists and their research are profiled on the freely accessible NEMO Kennislink website and in the beautiful book “Makers van Leven” by Esther Thole.

Next to supporting the most innovative research into the most fascinating aspects of molecular chemistry, FMS stimulates collaboration in a unique and effective manner. Friendly competition goes hand-in-hand with sharing knowledge, experience and infrastructure. Collaborative research projects are stimulated through additional grants.

The many societal challenges for the molecular sciences will direct our research for the future, as is embodied by the title of this magazine: “FMS en route”. Equally important in the coming years will be our contribution to the most profound scientific question: “how did the assembly and organization of a large number of (macro)molecules result in a system that is alive?”

This magazine will give you a glimpse of the passion that drives the FMS scientists.

Bert Meijer
The start of FMS
And what happened before

Say What?

FMS Focal projects

The FMS journey, still on track?

Including FMS Timeline

FMS: future molecular systems!

Involving our international scientific peers

Facts, numbers and awards

Ben Feringa
Leaving your scientific comfort zone

Jos Put
Bringing functional molecules into action

FMS EN ROUTE • 3
Nothing is more difficult to write than a historically correct report of a series of events that took place seven years earlier and where each character in the story contributes a personal impression and perception of what happened. As we are no historians, our story just reflects some thoughts of some of the applicants of the original proposal for a program on Functional Molecular Systems.
In Nijmegen, the initial idea came from Roelof de Wijkerslooth, who at that time was the president of Radboud University. Roeland Nolte was proposed as the person in charge, despite the fact that he already had been retired, while Jan van Hest – at the time in Nijmegen – was asked to help in writing the proposal. Roeland proposed to focus on “Artificial Life-like Systems” based on a report of the American Academy of Science where at that time this topic was selected as one of the five major research topics for the coming years. Partners were needed, and Eindhoven was one of the possible participants as Bert Meijer is a parttime professor in Nijmegen.

At the same time Ben Feringa and Bert Meijer discussed options to apply for an organic chemistry program, instead of being a partner in programs of others as both were asked to join other initiatives (e.g. on materials, catalysis, and nanotechnology). They brought the idea forward to create a consortium from the four universities that are internationally known for their outstanding supramolecular chemistry: Groningen, Eindhoven, Nijmegen and Twente. The latter could not participate as they were forced to be part of a proposal where MSC+ was in the lead. At this point, the two initiatives came together with Nijmegen as the “penvoerder” and Bert Meijer as the main applicant, with Ben Feringa, Roeland Nolte, Sijbren Otto, René Janssen and Jan van Hest as co-applicants. Although all applicants contributed to the text of the proposal, especially Jan van Hest can be credited for the overall editing and writing. For the science proposed, a citation from the abstract of the FMS proposal is most adequate:

The research teams in Organic and Macromolecular Chemistry from the universities of Nijmegen, Groningen and Eindhoven propose a challenging research program in Functional Molecular Systems (FMS) to jointly explore the frontiers of chemical self-assembly. The ultimate goal is to design and synthesize chemical architectures with novel functions and properties emerging from a full control over the molecules in dynamic complex systems. With Nature as a guide, the overall program will eventually address the construction of functional life-like molecular systems, one of the grand challenges in the physical sciences. Individual subprograms will focus on critical research issues like energy conversion, adaptive materials and bio-mimetic catalysis. Where currently most, if not all, molecular and supramolecular systems are made, studied and applied under thermodynamic equilibrium conditions, the objective of the current proposal is – in line with natural systems – to shift the focus to out-of-equilibrium approaches.

The proposal was submitted in April 2012 and after receiving six very positive referee reports, the proposal was successfully defended for an international committee. For the latter we prepared ourselves well and organized a special training session in Amsterdam on the evening before the defense. This turned out to be a highly successful exercise because many questions we had anticipated, indeed were asked. Eventually, our proposal was granted and we received the plaque from the Minister of Education in a special session in The Hague at the beginning of 2013.

“...The ultimate goal is to design and synthesize chemical architectures with novel functions and properties emerging from a full control over the molecules in dynamic complex systems.”

Fast-forward to 2018. At present, Ben Feringa, Bert Meijer and Wilhelm Huck are taking care of the daily business of FMS and great support is enjoyed from Marta Comellas-Aragonès at the start, followed by Olga Goor and now from Ghislaine Vantomme.

Handover of the Gravitation plaque to the representatives of the FMS program (January 2013) - Bert Meijer was unable to be present.
We successfully passed our mid-term evaluation; time to take the next steps. In spite of the large number of achievements, there will be many challenges ahead of us in this exciting research field. Three co-applicants, Jan van Hest, René Janssen and Sijbren Otto, elaborate on their FMS journey. They put the various research themes into perspective and reflect on the impact of these topics on the overall field of functional molecular systems.
Within this subtheme of the FMS program, we aim to explore how far we can push molecular self-assembly into mimicking living cells, and how we can integrate supramolecular chemistry and biology to modulate cellular function.

Living cells can be considered as highly sophisticated molecular assemblies with intricately directed interactions between the different molecular components. It is therefore our firm belief that to truly understand how a living cell operates, a bottom-up molecular approach should be followed. Furthermore, by considering the cell as a supramolecular complex, it seems very reasonable to introduce novel cellular functions through the integration of synthetic supramolecular structures.

Over the years, the bio-inspired molecular systems program has shown progress at three different levels. Looking at the results obtained so far, it is fair to say that we are still well on track to achieve our initial goals.

Firstly, compartmentalization has been successfully explored to create platforms that mimic elements of the living cell. Microfluidic water-in-oil systems, polymer vesicles and complex coacervates have all been used as synthetic cell systems, and they have been endowed with a range of life-like properties, such as self-regulated metabolic pathways with out-of-equilibrium behavior, cell-mimetic shape changes and fission processes and communicative potential.

Secondly, synthetic elements have been integrated with living cells. These elements include artificial organelles, which have been used to correct dysfunctional biological processes, and supramolecular assemblies that, due to their dynamic and multivalent character, were able to be selectively incorporated in living cells.

Finally, catalytic species based on single polymer nanoparticles and protein scaffolds have been developed. These species exhibit enzymatic properties, but also bio-orthogonal reactivity. This next generation of so-called synzymes is highly promising for unusual living cell catalysis, for example for the production of antibiotic derivatives.

Overall, we have achieved a number of elegant conceptual approaches. Now, the main challenge is how to move towards truly functional and applicable life-like systems that demonstrate the unique added value of our molecular approach.

A cell-mimetic platform based on complex coacervates stabilized with a polymer membrane and loaded with three different dye-labeled proteins (Mason et al. J. Am. Chem. Soc. 2017, 139, 17309)
Nanoscopically structured functional materials

Functional molecular materials that enable the conversion of light and the production of electrical power or chemical energy, or that can be used in retinal prostheses have advanced beyond our initial expectations. A strong reinforcement of our paradigm: from molecule to device.

Organic solar cells

Monitoring morphology formation in real time, combined with detailed electron microscopy, X-ray diffraction studies and theoretical modeling have provided the framework for the understanding of nanoscopic morphology formation of donor-acceptor blends in organic solar cells. Together with the development of advanced organic semiconducting materials to reduce photon energy loss and optical light management, organic solar cells continue to increase their efficiency. Progress in multi-junction devices has recently resulted in a first demonstration of a quadruple-junction polymer solar cell, featuring four different band gap materials. This unique device represents one of the most complex semiconducting polymer devices ever made, but it can still be fabricated by simple solution processing.

Photosynthesis and artificial retina

Organic multi-junction cells have been successfully employed in artificial leaves for photo-electrochemical water splitting, achieving solar-to-hydrogen energy efficiencies close to 6%. Research efforts are now directed to the more challenging photo-electrochemical CO2 reduction, where Faradaic efficiencies of 80% for CO have been obtained. To fuel the future development of high-resolution retinal prostheses, tandem organic photodiodes sensitive to near-infrared light have been developed. The electrical charge photo-generated by these tandem micropixels reach neural stimulation levels with short light pulses at physiologically safe intensities.

Perovskites

Hybrid lead halide perovskites are revolutionizing photovoltaic research. Power conversion efficiencies close to 20% have been achieved by controlling crystallization, grain boundaries, defects, developing organic charge transport layers and device layouts. The opportunity to change the optical band over the relevant solar spectral range using organic cations and halide substitution opens opportunities to increase efficiencies to 30% or more in tandem cells in the near future.

Artificial organic leaf under illumination based on a triple-junction organic solar, with catalytic electrodes for hydrogen (right) and oxygen (left) evolution.
It is now five years since the bottles of champagne were uncorked, to celebrate that our application for a new research center on Functional Molecular Systems was approved. While the bottles have long been empty, the FMS activities are still in full swing. We are now approximately halfway into our program, which is a good moment to take stock and survey the road ahead.

FMS is already very successful in intensifying the ties between leading supramolecular chemistry groups in the Netherlands. While already a closely knit community at the level of the group leaders, the many activities of FMS have also fueled a community spirit among the (PhD) students and postdocs. From what I have seen and heard at the FMS meetings, the scientific quality of this young community is exceptional. It is the highest I have seen worldwide in the area of supramolecular chemistry and it is increasingly also recognized as such internationally. Something to be proud of!

Collaborative efforts are starting to bear fruit, and these should be further intensified. Part of the challenge here is that many of the FMS groups have comparable expertise and are used to being rather self-sufficient. Yet, there is definitely also a great deal of complementary expertise that we can, and should, exploit.

One of the aspects of FMS that I really appreciate is that it supports fundamental science in a climate that is increasingly doing the opposite. Fundamental science is under pressure everywhere. Indeed, many of our international colleagues envy the opportunities provided by FMS for exploring topics of fundamental importance. We are in a privileged position. Whereas funding requirements push researchers in countries like the USA more and more towards short-term applications, we can now lay the foundations of the science of the future. The FMS efforts directed towards out-of-equilibrium systems are a good example. I just returned from the inaugural Systems Chemistry Gordon Conference. The importance of this topic was evident from many of the talks there, which also made clear that there are still great challenges ahead. Within FMS, we are ideally placed to make an impact here. We are already actively training our young researchers in this topic and I am looking forward to the new findings and insights that will undoubtedly come out of our various research themes.

All in all, with the resources and expertise that has been brought together within FMS, we have all it takes to further strengthen the Netherlands as the international powerhouse of supramolecular (systems) chemistry. Let’s do it together!
Ben Feringa
interviewed by Esther Thole
Leaving your scientific comfort zone
Building molecules. That is what chemists do. And it is what they do best. Over the years, the chemical community has gathered and developed a huge body of knowledge on molecular design and synthesis. However, despite our skill in making the most complex molecules you can think of, we are still rather primitive when it comes to creating systems, even very simple ones, in which different molecules come together to collaborate and generate function.

Mother Nature
But we know that such systems are everywhere. Mother Nature offers proof, as well as inspiration. After all, living organisms are not more than complex molecular systems with multiple integrated functions. So, it can be done. Functional molecular systems are not a scientific vision for the future, they are a reality. They are all around us and we ourselves are functional molecular systems as well. Creating such a system from scratch - that is what we want to achieve. Our common goal is to not only build all the molecules needed, but somehow create the conditions in which these molecules start working among themselves in a coordinated and functional manner. And I think our Research Center for Functional Molecular Systems is well positioned to push this effort in the right direction. Why? Because of all the people that together make up the FMS. Researchers with various backgrounds that bring a wealth of expertise to the program; we have experts on networks, replicators, supramolecular interactions, catalysis, synthesis, compartments, dynamic molecules, self-assembly, modeling and many other essential aspects of complex systems.

“Dare to be curious.
But it takes a true community to do that.”

FMS Community
The FMS community not only offers a large variety of chemical knowledge, it is also an attractive mix of people at different stages of their careers. We have established international leaders, upcoming stars that are carving out their own research line and a large group of motivated PhD students and postdocs. These young researchers from all over the world bring a wealth of fresh ideas and insights that form the fuel of scientific progress. However, even though variety is essential, what all these researchers share is perhaps even more valuable. And that is the willingness to step out of your comfort zone. To explore new and unfamiliar territories. To take a leap into the unknown and accept the risk of failure and disappointment. That is what you need to really push the frontiers of our knowledge further ahead. Dare to be curious. But it takes a true community to do that. Collaboration can only flourish when they are based on trust and respect. That is what I see within FMS and that is why we are all comfortable to ask new questions and try new ideas. To create room for crazy ideas and wild initiatives. The freedom to be curious, to fail and to try again is at the heart of science. I am very happy that FMS has succeeded in creating an environment where dreaming is allowed and curiosity is rewarded. And I sincerely hope that we can create such freedom for all future scientific endeavors as well.

The Functional Molecular Systems program is granted by the Ministry of Education, Culture and Science of the Netherlands (Gravitation Program 024.001.035).

On Saturday December 10, 2016, Ben Feringa received the Nobel Prize for Chemistry in Stockholm, Sweden. Ben Feringa is accompanied by Betty Feringa and Bert Meijer.
“The most profound challenge is to acquire the fundamental insights that allow precision engineering of the materials of the future. FMS offers the perfect environment as it is a vibrant hub for ground-breaking cross-disciplinary science.”

Ilja Voets

“This concept ‘functional molecular systems’ opens a universe of possibilities to explore reactivity in molecular based systems. FMS hasn’t tried to draw lines and borders that limit the possible and this makes it unique in creating a network where our scientific ambitions can take full flight.”

Wesley Browne

“Synthetic biomaterials, naturally! Future innovation in biomaterials science lies in mimicking natural systems in a synthetic way.”

Patricia Dankers

“We are getting more and more control over the scientific fundamentals of protein-protein interactions, such as their thermodynamics, and over conceptual approaches for chemical modulation. This is the basis for functional molecular systems based on protein assemblies ranging from novel drugs to the synthetic cell.”

Luc Brunsveld

“As an organic chemist, being involved in FMS and seeing what is happening in other research areas, has inspired me to think more broadly about my own research and allowed me to come up with new ideas and directions. It has enabled me to connect my research in catalysis to new synthetic pathways aimed at the design of new functional materials by mimicking and building on the properties of biological systems. Starting to apply these new insights to the rapidly evolving frontier of life-like systems is an exciting prospect that I hope to play an active role in during the coming years.”

Syuzanna Harutyunyan
“FMS enables me to do groundbreaking research in collaboration with top level colleagues. Meeting ambitious peers stimulates me to aim high and set challenging goals.”

Rint Sijbesma

“Living cells are like bustling bars: crowded and vibrant, yet tightly organized. If we understand the molecular rules of this organization, we might one day discover where life came from.”

Evan Spruijt

“The beauty of understanding molecular systems is that we can use them to establish functional behavior at much larger length scales, even visible to the naked eye.”

Peter Korevaar

“FMS has allowed me to work together with scientists in the Netherlands on exciting and challenging projects which would have been difficult to achieve otherwise.”

Tom de Greef

“As the world becomes more and more complex, the need for interdisciplinary research increases. The FMS brings together in depth knowledge spanning different fields, and hereby offers outstanding opportunities to all members to find synergistic relationships. This way, complex questions that cannot be answered in a monodisciplinary manner, such as finding bio-orthogonal procedures for non-natural reactions in complex media, can be addressed, and hopefully robust answers will be found.”

Anja Palmans

“What if we could randomize the outcome of a chemical reaction or process so that, let’s say, it has some resemblance to decision-making in our brain. The experiment will never be accepted since the results are irreproducible.”

Sander Wezenberg
Wilhelm Huck

FMS: future molecular systems!
Chemistry is a creating (and creative) science par excellence. Over many decades we have mastered the synthesis of incredibly complex molecules, as well as their assembly into a wide range of large and intricate structures.

However, even Ben Feringa’s beautiful nanomachines, which rightly earned him the Nobel Prize, pale in comparison to the complexity we encounter in living systems. Complexity not in the structure of a molecule, but in the networks that are formed as a result of molecules interacting with one another. The properties of these networks give living systems their unique capabilities such as self-healing, adaptation to the environment, homeostasis, and the conversion of chemical energy into motion, growth and division. Creating such complex functional molecular systems is not only one of the dreams of modern chemistry, it is also the goal of our program.

With the FMS program approximately halfway, we are beginning to see the emergence of an exciting future. We are learning the rules that govern the dynamics of these networks and we are able to create ever more complex networks. We are now developing a new ‘programming language’ that is modular and scalable, thereby providing a systematic approach to the newly emerging field of systems chemistry. To be successful, we need to closely look at the underlying design principles of living systems: out-of-equilibrium, functionality emerging from reaction networks, and compartmentalization. Incorporating these principles can be achieved in multiple ways, for example using programmable DNA networks, as Tom de Greef in Eindhoven is demonstrating so elegantly, or by using enzymes, as we do in Nijmegen, or by involving supramolecular stacks as pioneered by Sijbren Otto in Groningen.

What does the future hold, when we are successful in creating systems with life-like properties? I predict that these will represent a paradigm shift in how we think about materials, devices, or synthetic systems in general. Initially, we will aim to introduce functionalities that we are familiar with in living systems, such as self-healing, information processing, or ‘computing’ at the molecular scale. However, as we learn to construct ever more complex systems, I foresee a transition point where these life-inspired systems also become self-learning and self-improving. Such ‘evolving’ systems or materials would truly lead us into a completely new world. Our consortium is paving the way for that transition.
Wilhelm Huck (Nijmegen) and Tom de Greef (Eindhoven)
Towards ‘Living Materials’ – Pattern Formation and Motility in Preprogrammed Hydrogels

Gerard Roelfes (Groningen) and Anja Palmans (Eindhoven)
A Hybrid Metabolic System

Ben Feringa (Groningen) and Bert Meijer (Eindhoven)
Supramolecular Highways for Marching Nanocars

Paul Kouwer (Nijmegen) and Patricia Dankers (Eindhoven)
Control of Alignment in Supramolecular Biomaterials; towards Complex Hierarchy in Synthetic Extracellular Matrices

Syuzanna Harutyunyan (Groningen)
Daniela Wilson (Nijmegen) and Ilja Voets (Eindhoven)
Compartmentalized Catalytic Systems for Autonomous Movement
Involving our international scientific peers

The international Scientific Advisory Board (SAB) plays several roles in the FMS program. As colleague scientists they actively follow the developments in the program, both the scientific and organizational aspects.

During individual visits, including lectures and workshops, to the participating groups there is the important personal contact with group leaders, staff and students. This allows the board members to witness the continuous process towards a growing cohesion and integration of the individual groups. The board stimulates collaboration, to create opportunities for the younger generation, and to set goals of high scientific ambition.

In that respect the board has advised to create growth opportunities in the areas of out-of-equilibrium systems and adaptive nanosystems, as it sees the FMS program primarily as science-driven. Of course when there are opportunities for high tech applications these should be actively pursued as in the areas of bio-inspired systems and nanostructured materials.

In addition to its role as discussion partner, the SAB has been involved in the (pre-)evaluation process that has led to the successful extension of the FMS program with another 5 years. The SAB is extremely pleased that in this second phase the integration is growing further as well is the scientific level and output. In the field of chemistry this combination of supramolecular chemistry and nanotechnology is unique in the world.
**FACTS**

- **Royal Honor** Wilhelm Huck (2018)
- **Commander in the Order of the Netherlands Lion** Ben Feringa (2016)
- **FMS in KNAW Faces of Sciences** Dowine de Bruijn (2016-2018)
- **Exposition in NEMO Science Museum Amsterdam** (2017-present)
- **Book – ‘Makers van Leven’** by Esther Thole (2018)
- **FMS was a sponsor of the NextGenChem** (2016, 2017, 2018)
- **5 Focal projects within FMS granted** (2017)
- **FMS started a collaboration with Kennislink** (2013)
- **FMS present at the NWO stand at CHAINS** (2015, 2016, 2017)

**NUMBERS**

- **53** PhD students hired
- **19** Postdoctoral researchers hired
- **1** FMS tenure track position assigned
- **20** Research groups within FMS
- **6** Members in our International Scientific Advisory Board
- **4** Members in our Industrial Advisory Board
- **5** Members in the financial support team
- **2** FMS Board meetings each year
- **1** FMS PI meeting each year
- **3** Participating universities
- **>700** Publications
- **214** Publications for the general public on NEMO Kennislink website
FMS established the Netherlands Award for Supramolecular Chemistry for scientists that contributed significantly in the field of supramolecular chemistry. We are proud of our award winners and we are looking forward to expanding the awardee list in the years to come.
Jos Put
Chair of the FMS Industrial Advisory Board

Bringing functional molecules into action
Recently, synthetic chemistry has made a surprising leap. The convergence of biological and molecular engineering has led not only to a better understanding of biological systems, but also to the creation of (semi-)synthetic functional molecular systems, which mimic their biological sources of inspiration.

The Research Center on Functional Molecular Systems is dedicated to the further development of this field.

During the past decade, research was mainly focused on developing and optimizing synthetic techniques. However, in the coming decade, the focus will have to move to directing the functionality of these systems towards well defined applications. There has been a lot of speculation on potential applications, but at present there is still a large gap between academic research into functional molecular systems and their practical use. This is not surprising for such a disruptive approach. As Nobel Prize winner Jean-Marie Lehn already stated in his book on Supramolecular Chemistry: “The novel features that appear at a higher level of complexity do not and even cannot conceptually exist at the level below”. In other words, there is a fundamental difficulty in predicting the possibilities that will pop up while developing these new complex molecular systems. As such, these systems are not (yet) designed with a particular application in mind. But eventually their potential will surprise us.

At present, the interest of the Dutch industry in this new area of chemistry is limited. Companies are facing a sustainability transition that might turn the whole industry upside down and there is no clear vision yet on how the new chemistries could contribute these challenges. However, it might well turn out that realistic solutions emerge from these new ways of performing chemistry.
FMS event October 2017
Building life with molecules - NEMO Science Museum Amsterdam
EDITORIAL

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EVENTS

Within FMS we organize many events and courses to strengthen our knowledge in the field of functional molecular systems and invite renowned and inspiring (inter)national speakers.

A glimpse of the FMS events:

- Annual meeting
- Biannual Supramolecular Chemistry Course (2015, 2017)
- Biannual Out-of-Equilibrium Course (2016, 2018)
- Electrochemistry Course (2018)
- Symposium on H2O (2015)
- Topical seminar on Viral Particles (2014)
- Topical seminar on Supramolecular Hydrogels (2015)
- Topical seminar on Catalysis in Living Cells (2015)
- KNAW Academic Symposium (2016)
- Co-organization of the pre-conference on Molecular Systems Engineering (Basel, 2017)