FORESIGHT INSTITUTE

Integrated Molecular Machines: From Materials to Nanosystems

Co-Chairs
Sir Fraser Stoddart, **2016 Nobel Prize** for Molecular Machines
Jonathan Barnes, Washington University Chemistry Department

May 5-6, 2018
Washington University, Saint Louis

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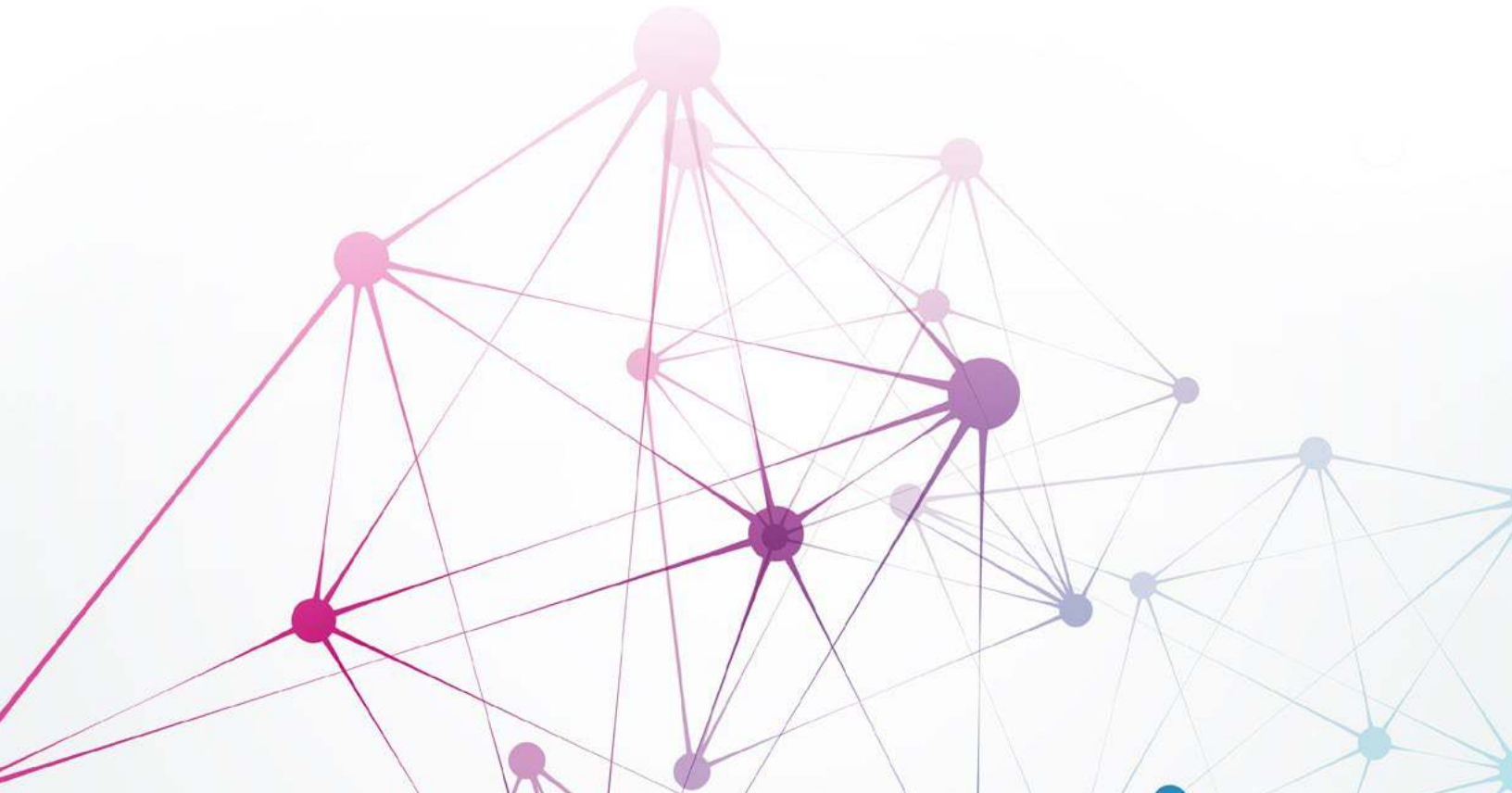


About Foresight

The Foresight Institute steers emerging and world-shaping technologies for beneficial purposes and has done so for more than 30 years. It is our mission to spark innovation across multidisciplinary fields such as synthetic biology, artificial intelligence, and especially nanotechnology. We serve as a nexus for innovation to catalyze research, reward excellence, restrain recklessness, and create community aimed at the long-term flourishing of humanity and the biosphere.

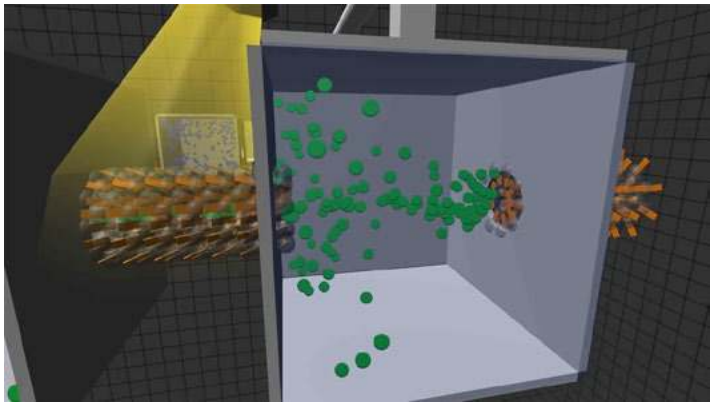
Foreword

Can we build molecular machine systems on a par with what Nature seems to do effortlessly every second of every day?

While Chemistry might seem to be an otherwise mature field, the branch of Molecular Machines is in its infancy, yet has surrounded and inhabited us since Day Zero.

Molecular Machines by purposeful design have the potential to transform our world in concert with those we have been gifted by billions of years of evolution. What will it take for our scientific work to begin to approach the complexity of Nature, by design, for our own purposes?

Dozens of scientists from diverse backgrounds, entrepreneurs, government advisors, and designers gathered together with the 2016 Nobel Prize Winner (and 2007 Foresight Feynman Prize Winner) in Molecular Machines, **Sir Fraser Stoddart**, in order to see what approaches are most likely to bear fruit, and in order to develop workable designs.



Integrated Molecular Machines: From Materials to Nanosystems

See the video

Participants

Joshua Ballard	Director of Research Operations, Indiana University
Jonathan Barnes	Workshop Chair: Chemistry Department, Washington University
Jeremy Barton	Nanofactory Corporation
TJ Brunette	Biochemistry Department, University of Washington
Nate Colley	Chemistry Department, Washington University
Paul Cherukuri	Rice Institute of Biosciences & Bioengineering, Rice University
Abby Delawder	Chemistry Department, Washington University
Alexi Demchenko	Chemistry & Biochemistry Departments, University of Missouri
Tabbetha A. Dobbins	Physics/Astronomy, Biomedical & Translational Sciences Departments, Rowan University
Melissa Dumartin	Chemistry Department, Northwestern University
Martin Edelstein	Co-Founder, Covalent / AguaVia
David Forrest	Technology Manager, Department of Energy
Yuanning Feng	Chemistry Department, Northwestern University
Steve Fowkes	Nanopolymer Systems
Miguel A. Garcia-Garibay	Dean Physical Sciences, University of California Los Angeles
Amine Garci	Chemistry Department, Northwestern University
William A Goddard III	Department of Chemistry, Materials Science & Applied Physics, California Institute of Technology
Angelique Green	Chemistry Department, Washington University
Andreas Heinrich	IBS Center for Quantum Nanoscience, Ewha Womans University
Sergei V. Kalinin	Center for Nanophase Materials Sciences, Oak Ridge National Lab
Troy Kincaid	Chemistry Department, Washington University
Gary Kurek	Get Mobility Solutions
Ruihan Li	Chemistry Department, Washington University
Xueson Li	Chemistry Department, Washington University
Kevin Liles	Chemistry Department, Washington University
Christopher Lutz	IBM Almaden Research Center
Joseph W. Lyding	Electrical and Computer Engineering, University of Illinois at Urbana-Champaign
Michael Marshall	Chemistry & Biochemistry Depts., Georgia Institute of Technology
Thomas McKendree	Engineering Fellow, Intelligence, Information and Services, University of Southern California
Alison Narayan	Life Sciences Institute, University of Michigan

Participants

Anu Natraj	Chemistry Department, Washington University
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Cristian Pezatto	Chemistry Department, Northwestern University
Yunyan Qiu	Chemistry Department, Northwestern University
John Randall	Zyvex Labs
Christian Schafmeister	Chemistry Department, Temple University
Damien Sluysmans	Chemistry Department, Northwestern University
Durham Smith	Chemistry Department, University of Stellenbosch
Faheem Solangi	Chemistry Department, Washington University
Mikhail Soutchanski	Computer Science Department, Ryerson University
Sir James Fraser Stoddart	Workshop Honorary Chair, 2016 Nobel Prize in Chemistry, Northwestern University
John Taylor	Chemistry Department, Washington University
Grigory Tikhomirov	Bioengineering Department, California Institute of Technology Institute of Technology
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David Ward	SemQuest, Inc.
Timothy Wencewicz	Chemistry Department, Washington University
Charlie Zannorman	TryVantagePoint
Steven Zimmerman	Chemistry & Biophysics, Quantitative Biology Departments, University of Illinois

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Foresight Team

- **Steve Burgess:** President, Foresight Institute
- **Allison Duettmann:** Co-Facilitator, Foresight Institute
- **Christine L. Peterson:** Co-Founder, Past President: Foresight Institute
- **Marcia Seidler:** Events Coordinator, Foresight Institute
- **Steven Vetter:** Molecular Manufacturing Enterprises, Inc., Foresight Workshop Volunteer
- **Roby Behrens:** Videographer, Lucid Sound And Picture
- **Justin Kelsey:** Videographer, Lucid Sound and Picture
- **Jeff White:** Camera Operator

Introduction to Scientific Fields Discussed at the Workshop

This workshop continued the series of Foresight workshops that develops collaborative projects designed to use atomically precise manufacturing for various application areas. The workshop started with overviews of molecular machines and of government funding for their development. After these introductory presentations, participants broke into groups to identify, create, and present collaborative project proposals. The workshop concluded with each group presenting its proposal and receiving feedback from judges and other attendees.

The workshop covered molecular machines built with organic and inorganic synthesis; objects and devices constructed from DNA, RNA, proteins, or biomimetic polymers; construction via scanning probe microscopes; and other approaches to building molecular machines with increasing complexity and precision from the bottom up, i.e., atomically precise materials.

Presentation 1: **Integrated Molecular Machines** See the video

Jonathan Barnes

The main question is whether we can design and build molecular machines on par with those found in nature. Nature has diverse and dynamic molecular systems that work together to perform a wide variety of functions. Nature far outstrips our current abilities, which effectively are only static systems that operate in one spot and in relative isolation. This begs the question, can we create artificial molecular machines and integrate them in concert to perform design functions?

Since the field of artificial molecular machines is relatively young, there are many opportunities to investigate

its potential. The near term research and findings might not have current applications but could form a set of basic components whose properties are well understood and provide a base for designing more complicated and integrated systems. Once a good base of components has been established it is then key to ask what are the first useful and practically achievable systems we can create from these components? Once we have the ability to create integrated nanoscale systems another set of challenges arises when thinking about how to integrate them with macroscale systems. The factors that will drive the maturation of the field of artificial molecular machines exist in a push-pull state. There is a push from scientists who are creating new components, systems, and techniques and a pull from industry, which can use the new research to solve problems and capture value, leading to more investment in, and maturation of, the research used.

Presentation 2: **Introduction to Atomic Precision** See the video

David Forrest

The Department of Energy is strongly supporting the development of atomically precise manufacturing, with the amount of funding growing from $180k to $20M from 2016-2018. Currently the aim of the program is to produce products with every atom at its designed position and with desired bonds to other atoms. This capability will lead to a dramatic increase in our ability to make and manipulate molecules. Unfortunately the current funding mandate only encompasses physical experimental investigation. However, there are plans to fund computational tools aimed at atomically precise manufacturing in the future.

Atomically precise manufacturing contrasts with the broader term "nanotechnology" defined by the National Nanotechnology Initiative (NNI), a definition that is based on size. Currently we have atomic precision from chemistry assembling molecules - and atom-by-atom positional assembly with atomic force microscopes (AFM). These approaches are limited to creating structures with a small number of atoms. The goal for atomically precise manufacturing is to extend this precision to much larger structures, and with a faster manufacturing rate.

Project Proposals

Five teams developed project proposals during the workshop, and presented their proposals to a panel of distinguished judges. The judges were:

- Fraser Stoddart
- William Goddard
- David Forrest
- Alison Narayan

The judges selected the Molecular Machine Mashup as the project most in line with the workshop's topic.

Additionally, there was a popular vote by the workshop participants. The people's choice was "The Dark Side of Molecular Motors".

Project 1: **Molecular Machine Mashup** See the video

Team: Jonathan Barnes (Presenter), Michael (Shawn) Marshall (Second Presenter), Martin Edelstein, Angelique Green, Melissa Dumartin, Damien Sluysmans, Amine Garci

Existing molecular motors have a variety of motions. As examples, catenanes rotate relative to one another to give rocking and bending motions; rotors spin unidirectionally; and rotaxanes slide a macrocycle along a rod. This project proposes to incorporate all of these structures into a single material and selectively activate each motion using a different wavelength of light in an integrated system. Each of these molecular motors will be incorporated into a gel of polymers that can be activated by light to either contract or expand. The choice of gel polymer determines the density of the machines.

There are many potential applications this technology would have. Examples include:

(1) Creating thin films of molecular machines embedded in gel polymer networks and then manipulating the size of the pores in them, creating membranes with different size exclusion characteristics.

(2) Building components for soft robotics to create tools to create actuation at the nanoscale.

(3) Manipulating focal lengths for active optics. Defect correction for lenses could be achieved by manipulating the materials after construction to give it the correct properties.

(4) Modifying quantum dots band gap properties in a way similar to how static organic structures are currently used.

The fundamental science question for this project is the degrees of contraction and rates of contraction that can be obtained from each of these individual building blocks. Building these machines could likely be done in three years at a cost of $500K.

Project 2: **The Dark Side of Molecular Motors: Harnessing & Storing Solar Energy** See the video

Team: Abby Delawder (Presenter), Alexei Demchenko, Mark Nosiglia, Tim Wencewicz, John-Stephen Taylor, Xuesong Li, Paul Cherukuri, Steven Zimmerman

This project proposes to store light or chemical energy as mechanical energy by using Feringa molecular motors to apply torsional stress on a pair of polymers locked to the rotor by a disulfide bridge. A reductive process breaking the bridge would release the energy. This energy could then be used to power molecular machines in vivo and in vitro. The polymers could be polyethylene glycol-based, or they could be could be polyamine-based, in which case adding protons would change the molecular architecture. Thus the molecular motor is to be an integrated component of a larger microfluidic system including polymers and rotaxanes, and perhaps arrayed on a surface. An important issue is how to characterize the system, e.g., how fast the motor spins and their efficiency for energy storage. The performance of the system could be assessed either by microcalorimetry to measure heat released, or by using FRET pairs to measure changes in molecular separation. One implementation would use stored torsional energy to spin a magnet.

Project 3: **Integrated Molecular Machines** See the video

Team: Tabbetha Dobbins (Presenter), Joshua Ballard, Nate Colley (Second Presenter), Yuanning Feng (Third presenter), Miguel Garcia-Garibay, Steve Fowkes, Yunyan Qui

This project combines photo-switchable molecular motors with microfluidic channels to produce integrated systems of

molecular machines. Current microfluidic channels allow for the manipulation of channel length, however they do not have any kind of control system to help the fluid flow better. To provide the missing ingredient for such integrated systems, this project proposes 5- to 20-nanometer channels with fluid control provided by Feringa motors. The hypothesis behind the idea is that given the small channel size functionalizing the inside of the channel with direction-specific Feringa motors would allow the photo illumination to drive the Feringa motors to rotate and shuttle the fluid down the channel. Azobenzene molecular switches, which can be switched between cis- and trans- conformations upon photo illumination, will be placed underneath the Feringa motors to control the direction of fluid flow.

Design choices to be considered are what the channels should be made of. Possibilities include anodic alumina or metal organic frameworks, the former being appropriate for sizes around 20nm and the latter for channel sizes around 5nm. Challenges include how to ensure all motors are aligned in the same direction, and their synchronization. For control over the alignment, two different linker molecules could be used to anchor the molecules and an electric field used to selectively place the linkers down. Another option could be having asymmetry in the linkers themselves or to manipulate equilibrium constants between the binding of themselves.

Interesting questions to be answered for the maturation of this idea are what constitutes a good substrate, determination of geometry and motor alignment, linker, and motor synthesis, and number of motors per unit channel length. A preliminary design uses two molecules to anchor a Feringa motor to a quartz surface. Could such systems be reduced in size to gate single molecules by active diffusion?

Project 4: **Longorami** See the video

Team: Bill Goddard, Sergei Kalinin, Chris Lutz, Joe Lyding (Presenter), Tom McKendree, John Randall, Greg Tikhomirov, Steve Vetter, David Ward

This project will increase the amount of atomically precise product that can be fabricated from a minimal amount of atomic precision patterning by combining atomically precise lithography with DNA origami. In essence, a scanning probe microscope is used to remove hydrogens from a silicon surface in ultra-high vacuum (UHV). From there two atoms are placed, with atomic precision, that serve as template with attachment points for a million atoms of atomically precise DNA origami structures. The templated silicone can then be removed from UHV and solution and the DNA origami would then self-assemble onto it. This allows a technologically feasible near term approach for atomically precise manufacturing since two atoms of patterning can give millions of atoms of precise positioning while being a low cost approach.

This would allow the development or improvement of tunable plasmonics, photonic circuitry, 3D DNA Origami with actuators, quantum dot structures and focal plane arrays.

Challenges to overcome include improving lithography to make atomically precise binding sites for linker molecules, implementing long range atomically precise spacing of binding sites, correcting creep and hysteresis,

perfecting lattice recognition, obtaining large terraces, and dealing with step edges.

Further work that could be investigated is the building of libraries of DNA origami structures that can be made using this technology and their functionalities. One might also investigate the integration of electric wires into the structures so that electric fields and biasing could be applied to structures that have been made. This type of manufacturing could also be extended to other classes of molecules such as molecular legos.

Project 5: **Modular Polymer Catalysts** See the video

Team: Chris Schafmeister (Presenter)

This project proposes to assemble enzyme-like pockets from five to six one-kilodalton synthetic modules, which in turn are assembled from three or four protein-like molecular building blocks. The building blocks proposed for use are bis-peptides, which are linear conformationally restricted and, functionalizable molecules. The ends of these building blocks would be linked together through pairs of amide bonds at one end. At the other end they are joined by the linking of a diene and dienophile. These would normally be unreactive but because they are held in close proximity to each other, due to their linkage at the other end, a Diels-Alder reaction can take place. Each bis-peptide building block has two stereocenters and can be functionalized with one of hundreds of different aldehydes to form metal binding sites, or with bulky hydrophobic groups, small alkyl groups, alcohols, or a variety of other groups. Such catalytic structures would hold their shape in organic solvents or at high temperatures, would be immune to proteases, and nearly invisible to the immune system.

By manipulating the functional groups and stereocenter the enzyme-like pocket could be changed. Arrays of these enzyme-like structures could be placed on a surface via positional assembly. Mixtures of compounds of interest could then be passed over them and their catalytic ability could be measured via techniques such as florescence, heat detection via a thermal camera, or a sipper fed to mass spectrometry, then tested to see how well they perform. What is learnt from one round of catalysis could be used to better design the next set of catalysts.

Once catalysts of interest are found, the backside of the bis-peptide building blocks could be functionalized and attached to surfaces. Additionally, metal binding groups or molecular machines could be used to control the folding of catalyst structure to switch the potential catalyst on and off.

Conclusion

Atomically precise manufacturing of molecular machinery is still in its infancy, but holds enormous promise. The incredible functional diversity of nature's atomically precise systems support this conclusion. While nature has had billions of years of evolution to refine its atomically precise systems, we want to develop artificial molecular machines much more rapidly. This requires employing a more systematic approach to the design of artificial systems able to perform desired functions.

To accomplish this goal, researchers need to develop fundamental units which can be used as components in atomically precise manufacturing. They then need to understand the properties of these units and develop a framework for using them to create systems with desired properties and functions. Interfacing these systems with the macroscopic world also provides significant challenges. Furthermore there is the question of how to scale up the synthesis of atomically precise systems to viable mass production in order to see their widespread adoption.

Adding to the complexity of this task are the many paradigms for creating atomically precise systems. While it is too soon to know if a single technology will dominate the manufacturing of large-scale atomically precise systems, it seems unlikely that this will be the case. Thus developers of this technology need to be aware of a variety of approaches. This will allow them to draw inspiration and lessons from a broad community, while also providing opportunities to merge different methods of creating atomically precise systems to create new and unique functionality that is greater than the sum of its parts. The Foresight Institute workshops and community provide a good model for what this type of collaboration would look like.

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