CONTEMPORARY MATERIALS SCIENCE

HOW CAN MOLECULAR MACHINES HELP?

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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 molecular 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.

Foresight Team

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- **Allison Duettmann**: Co-Facilitator, Foresight Institute
- **Christine L. Peterson**: Co-Founder, Past President of Foresight Institute
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Executive Summary

Creating better materials is a multiplying factor for making progress on almost everything we care about, from human health to planetary health. Yet, much of the solution space of theoretically possible materials is still unexplored. This competition set out to change this, by seeking proposals that use molecular machines to improve the design, manufacture, and characterization of materials. Following Molecular Machines: From Materials to Nanosystems, it is the second competition in this series, co-chaired by Professor Fraser Stoddart, who was awarded the 2016 Nobel Prize for his breakthrough work on Molecular Machines. We were honored to welcome Foresight Fellow Mélissa Dumartin as co-chair for this competition and are grateful to the International Institute for Nanotechnology for sponsoring the meeting. From September 20th to 21st, 2019, we gathered forty top academics and engineers from across the world to make progress on the challenge “Contemporary Materials Science: How Can Molecular Machines Help?”. Distinguished scientists, spanning fields as diverse as chemistry polymers, supramolecular chemistry, materials sciences, computational science, and physical chemistry collaborated to propose projects that leverage the potential of molecular machines to create better materials. The final project proposals were evaluated by a panel of experts, including Marina Sofos from ARPA-E, Ale Lukaszew from DARPA and Youssry Botros from PanaceaNano. We invite you to watch the video above for the highlights and explore this report for a detailed summary of the state of the art of molecular machines and our winning proposals for how this field can transform materials science. As cherry at the end, we are celebrating our 2019 Feynman Prize winners, which were honored at the meeting for their outstanding achievements in advancing nanotechnologies for the benefit of life. I hope you enjoy this report and join us in the quest for using molecular precision to create more efficient and entirely new materials that can save lives and heal the planet.

Best wishes,
Allison Duettmann
Foresight Institute
Twelve researchers gave their perspectives on artificial molecular machines and their likely progress over the next few years. This section describes the key points of each presentation and allows you to view the presentation by clicking the play icon.

**Molecular Machines Operating in Solution**

Alberto Credi surveyed the capabilities of experimentally demonstrated artificial molecular machines. In these molecules, externally supplied energy leads to large-amplitude movement of some parts of the molecule with respect to others. In principle, such changes can perform useful work. One example is the controlled motion of rotaxanes, i.e., rings on dumbbell-shaped rod-like molecules. With functional groups along the rod, thermal motion tends to move the ring to the group with highest affinity. Changes in the chemical environment or other external stimuli can alter the ring’s affinity for the functional groups, which changes the ring’s preferred position along the rod.

This behavior of rotaxanes is an example of molecular machines rectifying thermal motion, and contrasts with macroscopic machines where the external stimulus directly provides the motive force. This is one of several differences in how the laws of physics act on molecular machines differently than on conventional machinery. Others include use of soft, flexible shapes instead of rigid structures, the
dominance of viscous and surface forces compared to inertia, and rapid dissipation of heat so molecular machines cannot rely on temperature differences as combustion engines do.

Most artificial molecular machines operate in solution. Solutions provide a simple homogeneous environment for the machines and allow controlling the machines by changing solution properties, such as acidity. However, solutions are disordered and don’t allow fixing machines in place, e.g., in ordered arrays to coordinate their activities.

Currently demonstrated molecular machines have limited capabilities. Biology provides examples of more sophisticated machines, including myocin motors in muscles, DNA polymerase, and ATP synthase. Although biological machines operate in solution, they are highly organized, e.g., operating in small compartments or on tracks in cells. Thus, biology provides guides both for molecular machines themselves and how to organize their activities.

**Understanding How Molecular Machines Work**

Dean Astumian described design principles for applying molecular machines to mechanically-driven chemical synthesis. These include designing machines to adjust the free energies of intermediate states and reaction kinetics to favor the desired products, even if they are not favored in equilibrium. These machines are analogous to enzymes in specificity and their ability to enhance reaction rates.

One way to control the machines thus is through externally-driven oscillations in properties of the solution around the molecules, e.g., changing their redox potential. A suitable oscillation frequency can tune the rate the machines change to the time constants of the desired reactions. This allows forcing non-equilibrium behavior, dominated by reaction kinetics, rather than relying only on equilibrium behavior, determined by energy differences.

**Molecular Machines Operating in the Solid State**

Miguel Garcia-Garibay discussed the benefits of building molecular machines on solid substrates rather than in solution. By ordering the machines, the substrate offers many opportunities to store and transfer information. Examples are using electric and mechanical coupling to the molecular machines. With solid substrates, we could create ordered machines at multiple scales. An example of this capability
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is 50nm crystals that can grow as large as 20 meters. In addition, the many analytic techniques available for solid state, such as NMR, could improve the evaluation and control of molecular machines.

DNA Nanomachines for Discovery Biology

Yamuna Krishnan discussed DNA-based machines as tools for biological research. For example, DNA machines can map the metabolic status of living cells and evaluate how cells respond to drugs. These measurements include the chemical properties of organelles within the cells, thereby conveying information on how well the organelles are functioning. This functional information accesses the health status of cells more accurately than current measures, which rely on organelle morphology.

To measure organelle function, DNA is connected to existing shuttle proteins that selectively enter the desired organelle. Attached radiometric fluorescent molecules respond to chemicals within the organelle to report the status. An example is measuring chloride in lysosomes. These experiments found higher chloride concentration in lysosomes compared with the rest of the cell. This concentration changes in some diseases. Moreover, these DNA machines found considerable variation in these indicators of lysosome function. This information is a step toward determining a chemical phenotype of cells, and of organelles within those cells. This information could aid precision medicine by identifying which patients are likely to respond to a drug by measuring chemical profile changes of cells exposed to the drug.

These experiments focused on lysosomes. However, using DNA machines to obtain functional information also applies to other organelles, with the exception of mitochondria and the cell nucleus. These exceptions are bound by double membranes, which the machines cannot pass through.
Responsive Nanostructures and/or Catalytic Nanoreactors

Rachel O’Reilly discussed how molecular machines enable precision chemistry across multiple length scales for precise polymer production. Currently, over 90% of commercial polymers are of six types, which are cheap, non-functional, and of low-value. These artificial polymers consist of a single repeated monomer in a mix of variable lengths. By contrast, biology makes polymers with specific sequences of different monomers and with specific lengths. These include nucleotides, proteins, and carbohydrates. The specificity of these polymers provides their functionality. Similarly, we can expect artificial polymers with specific sequences and lengths to have far greater functionality and value than current polymer production. Molecular machines could provide this specificity with programmable polymer synthesis. However, it will be a challenge to scale up from laboratory demonstrations to commercial use.

One appealing application of precise polymer synthesis is sustainability. Specifically, molecular machines could selectively identify and form polymers that naturally degrade over specific time scales. This capability would allow making polymers that last long enough to perform their intended function and then degrade, rather than accumulating in the environment.

Probing Individual Molecular Machines Using Single-Molecule Techniques

Damien Sluysmans discussed experimental tools that quantitatively measure the performance of molecular machines. An important capability is measuring forces on a single molecule. Atomic force microscopy, though mostly used for imaging, can measure forces in the piconewton range. This allows measuring force vs. displacement when pulling on a molecule. An example is determining forces on a single muscle titin protein molecule as an atomic force microscope stretches it. Single-molecule measurements help us
understand fundamental molecular processes, including those of molecular machines. For example, some molecules have different behavior regimes depending on their environment, including applied forces that change their conformation. Single-molecule measurements can identify and quantify these behavioral regimes. This capability contrasts with conventional larger-scale material measurements that only provide ensemble averages over many molecules, in a stochastic mix of regimes.

**Systems Chemistry**

Doug Philp took a systems approach to chemistry: instead of focusing on synthesis of a single molecule, he develops methods of designing a large, heterogeneous network of interacting machines. Such networks involve a large number of degrees of freedom and thus offer the possibility of behaviors that are far more complex than individual machines, in analogy with the difference between 2-body and 3-body dynamics in physics. The systems chemistry approach involves distinguishing between chemical genotypes and phenotypes using synthetic replicators. Molecules in such systems can catalyze the production of other molecules, forming complex self-catalyzing networks of chemical reactions. Networks of such reagents and recognition events can generate system level behavior based on kinetic selection of reaction products.

An example is a network of replication templates. These templates recognize their components and increase the rate they react to form another copy of the template. That is, the template holds chemicals in required positions to react, which makes a copy of the template. This process can be indirect where one molecule is a template for creating another that in turn helps create more of the first. Networks of replication templates have been demonstrated with supramolecular polymers that copy themselves. Such networks could improve their precision using molecular machines such as rotaxanes.

In addition to viewing these networks as a set of chemical reactions, they also form an information processing system. For example, adding a particular template to a solution acts as an instruction to the system that then requests the production of more of that template molecule.

Currently, this network behavior is limited to producing fixed points in well-stirred systems. This could generalize to more complex population dynamics, e.g., oscillations or chaotic behavior, by providing a flow of chemicals through the system.
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Machines on the Microscopic Scale

Ayusman Sen presented a ‘Fantastic Voyage: Designing Self-Powered Nano/microbots’ as an illustration of non-biological active materials. This uses free energy to fabricate organized systems far from equilibrium. Information specifying these systems is presented in the form of gradients in their environment, such as chemical or optical gradients. Applications of these materials include motion-based targeting, pumping triggered by specific chemicals, and tuning fluid rheology.

The active particles in these systems harvest energy locally so they can move independently. This contrasts with motion achieved from an applied external field, which makes all particles move in the same way. Independent motion allows the particles to respond to gradients in their local environments. One application is catalytically enhanced diffusion: one enzyme makes a product used by another, which then moves along the gradient of that product to get closer to the first enzyme. If the enzymes are bound to a surface instead of free to move in solution, this process can exert forces on the fluid, which could be used for pumps or sensors that are only active when the enzyme substrate is present.

Slide-Ring Materials and Their Applications

Kohzo Ito showed how rotaxane-based molecular machines improve the robustness of materials. For example, in polymer chains, tensile stress concentrates on short chains, which can lead to cracks. If instead of chemically bound polymers, the material consists of chains linked by sliding rings, the material can adjust to tensile stress by moving the rings in response to that stress. This behavior allows controlling bulk material properties by the choice of how much of the material is composed of this rope-and-pulley-like polymer system. This polymer has been used in a concept car in Japan.
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The behavior of these materials is temperature dependent: higher temperature gives faster sliding and hence faster response. It also depends on the rate of deformation: at slow rates, the sliding rings keep up with the stress, allowing the material to adjust, whereas at high rates, the rings can’t accommodate the stress.

Mounting Mechanically Interlocked Molecules in Metal-Organic Frameworks

Steve Loeb discussed rotaxanes in a metal organic framework rather than in solution. The framework gives a reference frame for the motion of the machines, thereby allowing the manipulation of molecular machines in well-organized solid state rather than randomly oriented and positioned in solution. These structures can have precisely defined shapes and sizes. The solid structure does not alter the machine operation, i.e., the barriers to the motion of the ring along its rod are the same as when these machines are in solution.

How Stereochemistry Can Influence the Operation of Molecular Machines

Steve Goldup showed how stereochemistry affects molecular behavior and could help design stereoisomers for specific machine motions. Stereosomers are molecules with the same atoms that differ in the spatial arrangement of their atoms. Stereochemistry currently provides geometry isomers such as enantiomers, which differ from their mirror versions. Molecular machines provide a new type of isomer: mechanical isomers. For example, when rings on rods move, they change the arrangement of the same atoms. Functionalized structures can alter the speed...
and direction of motion, as well as how the machine responds to changes in its environment. An example of this approach is combining the motions of an array of such molecules bound to a substrate to make a bucket-brigade molecular conveyor belt. Each machine picks up cargo, changes orientation, and deposits cargo within reach of the next machine in the sequence. Extending this idea could make molecular ratchets, pumps, and motors.

What Does the Future Hold for Molecular Machines?

Ivan Aprahamian inspired participants to consider the many possibilities for improving artificial molecular machines beyond those currently demonstrated. Biology uses many molecular machines to perform a wide variety of tasks in response to environmental changes. These machines are existence-proofs of the range of capabilities artificial molecular machines should one day achieve.

We are currently a long way from this goal. Among the challenges for artificial molecular machines are: managing waste from the reactions, creating molecular clocks, and coordinating the motion of the machines. Designing complete molecular machine systems involves many scales of length and time. In addition to the challenge of building individual machines, there is the complexity of systems level design for coordinating the behavior of a large set of molecular machines, including handling errors. Molecular machine engineering needs better tools to build and characterize molecular machines.
Based on the formal presentations, participants examined promising ways in which molecular machines can improve material development and characterization. After extensive discussions, participants converged on four areas for more extensive evaluation that led to the following project proposals. “An Active Transport Toolbox for Life and Materials Science” was rewarded best project by the judges and additionally received the Public’s Choice Award from participants. A summary of all projects, followed by the judging criteria, can be found below.

**An Active Transport Toolbox for Life and Materials Science**

Most current artificial and biological molecular machines operate in solution. The machines move in response to changes in their environment, such as altered chemical concentration. These machines transform changes in chemical potential into local work, either mechanical or chemical. Autonomously operated machines can harness fluctuations of fields and gradients in field strength or chemical concentration.

Molecular machines in solution are not globally organized, preventing them from providing coordinated, large-scale work. Biological systems address this problem with membranes that compartmentalize and organize reactions, and selectively transport chemicals to or from the reaction. However, embedding artificial molecular machines in membranes to perform active
transport has been difficult to achieve. Thus, artificial molecular machines have not yet demonstrated reliable, controllable transport through membranes.

This project will develop a set of artificial molecular machines that can actively transport specific chemicals across membranes. Such machines could have a variety of applications. For example, many diseases are related to malfunction in ion transport, so new mechanisms for precisely-controlled transport may be helpful for diagnostics or drugs for treatment. Such applications for artificial molecular machines requires creating machines for physical transport, e.g., via shuttles such as rotaxanes, and functional additions that provide controlled change to binding affinity to specifically capture the desired molecule on one side of a membrane and release it on the other side.

Materials science can help design such transporters. In particular, molecular dynamics simulations can quantify force and energy as a molecule moves through a membrane. Such computational studies will help select appropriate molecular designs for further investigation and fabrication.

The first phase of this project will develop a library of small molecule transporters, and characterize their behavior as a guide to scaling up in second phase. This library of validated transporter designs, and experience gained from its construction, will enable synthetic control—spatial and temporal—over cargo delivery through membranes in functional materials.

**Nanofacturing**

Today’s artificial molecular machines are primarily created and operated in solution. This prevents their coordinated operation over large distances. This project addresses this limitation by creating a linked array of precisely positioned molecular machines. Combining both solution and surface chemistry can create an array of rotaxanes and catenanes, i.e., polycatenanes.

Creating this structure starts by making a grid of attachment sites on a silicon substrate in ultrahigh vacuum. Solution chemistry then chemically attaches poles to these surface sites. Decorating the poles with rings, e.g., rotaxanes, and then capping them creates the array of molecular machines.

The attachment of the poles to a surface restricts motion in the plane of the surface while the machines can move precisely perpendicular to the surface. Thus, instead of a large number of randomly oriented molecular machines in solution, the surface array orders the machines to all move in the same direction.

Changes in the machine’s environment causes the rings to move along the poles. Such changes can include chemicals that alter the rings’ affinity for locations along the poles. An application for this behavior is sensing molecules. The structure could also provide tunable nanoplasmonics.
The main technical risks for this project arise from fabrication. These arrays of molecular machines have not yet been made, so there may be unforeseen difficulties in their manufacture, particularly in achieving high yields without defects. Such defects can arise from nonspecific binding to the rotaxanes, so the chemistry used to place the rings requires careful design to avoid nonspecific binding. In addition, the fabrication process may be too slow for practical use if the techniques identified by the project team for fast fabrication do not work.

**Turing-Universal Molecular Machines: Rotaxane Automata**

The density and performance of computational devices have increased tremendously over the past few decades. As features of electronic devices approach the atomic scale, continued performance increases require developing alternate technologies.

One such possibility is tiny general-purpose mechanical computers built from organized molecular machines. This project will create such a computer using rotaxanes to represent states and cellular automata rules to perform logic. This involves a grid structure where links between neighboring sites have movable rotaxanes. The state of each ring affects states of neighboring rings, hence providing logic according to local rules of the cellular automaton.

Light can modify rotaxane affinity along a rod. The computer proposed in this project will exploit this effect by using various wavelengths of light to specify the input, i.e., an initial state for the cellular automaton, by modifying the rotaxane locations. This specificity arises from different functional groups on the machine responding to different wavelengths. Subsequent signal propagation and logic rules are implemented by using different functional groups on rings, e.g., AND vs. OR gates depending on how functional groups on pairs of rings interact. After the propagation through the gates in the grid, the final states form the output of the computation. The output state could be read using a chemical that changes color based on the state. The first generation of the machine will be diffraction limited, i.e., with about 200nm resolution. Subsequent generations could use super-resolution microscopy to achieve resolutions down to 5nm.

An alternative to using light to initialize and read the result of the computation is using chemicals. In this case, specific chemicals would bind to the machine to specify the input state and the output state could release specific chemicals determined by the computation, giving computationally controlled cascades of chemicals.

The time required to transfer the rings limits the computation speed. This speed is low compared to moving electrons in current computers. Thus, applications requiring high speed are not suitable for
this proposal. Instead, it provides computation in small volumes. Suitable applications for embedding these computational devices in materials include complex nano-scale patterning, drug targeting, and dynamic materials responding to changes in their environment.

Instead of speed, metrics for the project are the computational complexity of cell update rules, as well as memory and computational capacity, determined by the grid size that can be fabricated as the project develops.

The logic gates in these computers will likely be probabilistic due to chemistry and thermal noise. That is, errors are a significant concern. As with larger-scale proposals for computing with imperfect components, such as HP’s Teramac computer, this molecular cellular automata machine will handle errors in software using well-established redundant coding methods. This illustrates a general approach to developing computers with molecular machines: their computational capability can compensate, to some extent, for imperfections of early generations of new hardware.

## Rota-Coolers

Large-scale deployment of molecular machines in materials could generate considerable heat as many machines operate in close proximity. Such materials will require active cooling. Cyclic changes in the organization of molecular machines can provide cooling, as an alternative to conventional fluid-based refrigeration. This project will develop a nano-scale cooler based on organizational changes created by molecular machines.

A variety of organizational changes can alter a material’s temperature. These changes could arise mechanically, such as stretching a rubber band (mechanocaloric), or in response to electric (electrocaloric) or magnetic fields (magnetocaloric). Molecular machines could exploit these effects on tiny scales within materials. Currently the electrocaloric effect is found in only a limited range of ceramic materials. Current experience with rotaxanes suggests there is an opportunity for better performance using materials consisting of molecular machines, e.g., rotaxanes.

This project will use dipolar molecular rotor arrays to develop a nanocomposite cooler by taking advantage of the nanoscale electrocaloric effect. This effect involves a spontaneous order-disorder phase transition to assure a very large heat capacity and the greatest possible temperature change. A cycle of this method starts with disordered dipoles. Applying an electric field orients the dipoles. Removing the field causes the system to absorb energy, thereby cooling its environment.

The project will start by characterizing the magnitude of the electrocaloric effect of molecular machines and tune their design to increase its magnitude and operating temperature range. Current studies find
the largest effect around 20K. Specifically, the temperature of the order-disorder transition in response to electric fields determines the useful operating range of these materials. Since this transition depends on the structure of the molecular machines, the addition of suitable functional groups to the rotaxanes allows tuning the temperature range. Thus, better machine designs will provide cooling at a wider range of temperatures, including room temperature.

**Project Evaluations**

**Judges:**

Ale Lukaszew  
(DARPA)  
Marina Sofos  
(ARPA-E)  
Youssry Botros  
(PanaceaNANO)

After the project presentations, the judges suggested how the teams could better meet these evaluation criteria. Project Nanofacturing needed to identify applications and metrics for evaluating the performance with those applications. Project Turing Computing would benefit from more context, including comparing the proposed computer with current efforts in the computer science and engineering communities. In particular, quantifying the capabilities of the proposed molecular cellular automaton with current computers in terms of common metrics such as speed, memory, and error rates. Project Rota Coolers should compare the proposed cooling with current technologies available in the cryogenic community, and identify specific cooling applications where the molecular machines provide an improvement. Project Transport Toolbox needed a clearer risk mitigation plan. This could include a smaller preliminary study of transport by small molecules to identify and address some of the technical risks before starting the full project.

“An Active Transport Toolbox for Life and Materials Science” was awarded best project by the judges and additionally received the Public’s Choice Award from participants.
Conclusion: Molecular Machines and Materials

The discussions and project proposals at this competition identified several promising ways molecular machines could help material science:

- Materials made of molecular machines, such as dynamic metamaterials, provide selective active response to their environment;
- Materials made by molecular machines could produce materials with complex patterns on a molecular scale formed by the evaluation of cellular automata, analogous to the pattern structures of shells made by some biological organisms; and
- Materials characterized by molecular machines, such as single-molecule force measurements, could identify the most significant design improvement areas.

These approaches rely on machines made to molecular precision, but do not necessarily require atomic precision. The capabilities of biological molecular machines indicate the broad scope for improving the artificial machines that have been currently demonstrated.

The competition also discussed the converse question: how materials can aid the development and evaluation of molecular machines. For this, the major suggestion was developing solid materials that could bind and organize molecular machines on larger scales, thereby allowing them to coordinate their activities, in contrast to the current focus on developing artificial molecular machines in solution.

While progress in the field of molecular machines is fast, we are barely scratching the surface of how molecular machines can aid material science and vice versa.

The project proposals developed during this competition illustrate promising directions for how current breakthroughs in molecular machines can be applied in the quest to create ever-better materials that are lighter, faster, cheaper, cleaner, and ultimately may have entirely new properties that can meaningfully impact human and planetary well-being.

Contact Foresight Institute to learn more.
The evening of the technical competition was accommodated by the Award of the 2019 Foresight Institute Feynman Prizes. These are given in two categories, one for Experiment and the other for Theory in nanotechnology/molecular manufacturing. Established in 1993 and named in honor of pioneer physicist Richard Feynman, these prizes honor researchers whose recent work has most advanced the achievement of Feynman’s goal for nanotechnology: the construction of atomically-precise products through the use of productive nanosystems.

In addition, Foresight awarded the prestigious Distinguished Student Prize to recognize a College graduate or undergraduate student whose work is considered most notable in advancing the development and understanding of nanotechnology. Foresight has awarded this Prize annually since 1997.

**Lulu Qian**, Professor of Bioengineering and head of The Qian Lab at the Division of Biology and Biological Engineering at the California Institute of Technology (Caltech), received the 2019 Foresight Institute Feynman Prize for Experimental work.

**Giulia Galli**, Liew Professor of Electronic Strictures and Simulation, Senior Scientist at Argonne National Laboratory, and Head of the Galli Group in the Pritzker School of Molecular Engineering at the University of Chicago received the 2019 Foresight Institute Feynman Prize for Theory.

**Yuxing Yao**, recently of Harvard University in the Aizenberg Biomineralization and Biomimetics Lab and now at the Division of Chemistry and Chemical Engineering at Caltech, received the 2019 Distinguished Student Prize.

Congratulations to Lulu Qian and Giulia Galli, and Yuxing Yao!

"The problems of chemistry and biology can be greatly helped if our ability to see what we are doing, and to do things on an atomic level, is ultimately developed — a development which I think cannot be avoided."

Richard P. Feynman, 1959
Foresight 2019 Workshop on

Contemporary Materials Science: How Can Molecular Machines Help?

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