FORESIGHT INSTITUTE

Designing Molecular Machines Workshop

Foresight Institute
Allison Duettmann
Aaron King

July 10 & 11, IndieBio HQ
San Francisco, CA

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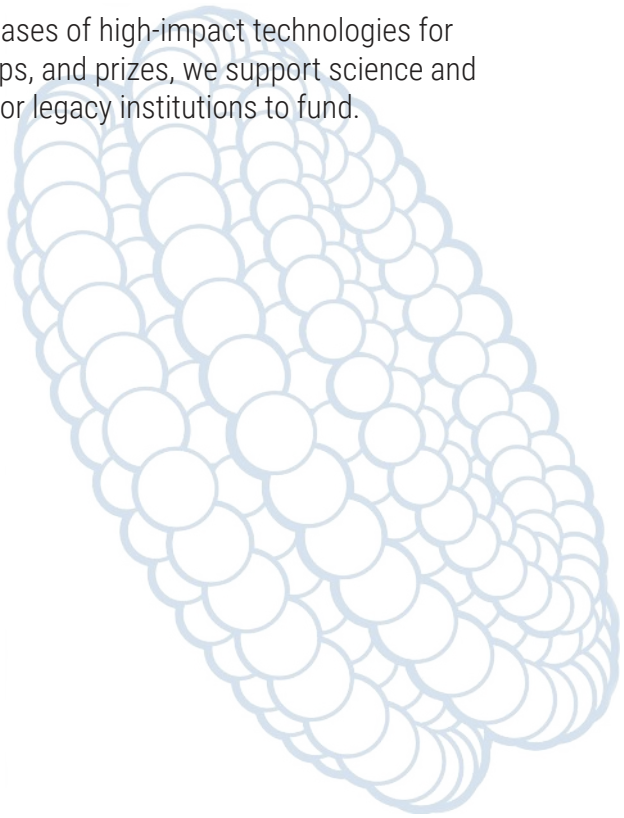
About Foresight

Since 1986, The Foresight Institute has advanced beneficial use cases of high-impact technologies for long-term futures.Through virtual seminars, fellowships, workshops, and prizes, we support science and technology that is too early-stage, interdisciplinary, or ambitious for legacy institutions to fund.

Our focus areas include:
Molecular Machines to better control matter
Biotechnology to reverse aging
Computer Science to secure human AI cooperation
Neurotechnology to support human flourishing
Spacetechnology to further exploration



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Executive Summary

Breakthroughs in molecular machines have the potential to significantly accelerate progress across the board in fields downstream, from biotechnology to materials science, and may reshape our physical reality. Many areas within the molecular machines field could be sped up by progress in design and simulation tooling.

This two-day workshop invited a group of design software specialists to apply their skills to help those tackling the challenges of constructing atomically-precise 3D structures, including pathways using chemistry, applied physics, biochemistry, molecular biology, and engineering. In addition to learning about undervalued opportunities for progress relevant to their field, this workshop was aimed at catalyzing lasting direction and collaboration toward shared long-term goals.

Keynote presentations on open challenges in molecular machines and on advances in software tools were followed by working groups to determine opportunities for progress. This report summarizes the keynotes and resulting project proposals, some of which are now under development.

Congratulations in particular to the top proposals, as voted by our participants:

The third place is shared by Adapt & Evolve, and Light-induced Embedded Dynamics. The second place was awarded to Molecular Additive Manufacturing, and the first place was awarded to Blood Clotting.

Thank you to our sponsors for making this event possible.

Thank you to all participants, and especially our workshop chairs, William Shih, Harvard University, and Benjamin Reinhardt, PARPA, as well as Adam Marblestone, Astera Institute, for making this workshop such a success. You will find their contributions in the introduction.

We encourage you to apply or reach out if you are interested in supporting ongoing progress.

These icons, found throughout the report, link to recordings of each presentation

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Northwestern University

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Introductory Presentations

Allison Duettmann (below left), President of Foresight Institute, gave opening remarks along with **Westley Dang (below right), Principal at Indiebio**. IndieBio, which hosted the Nanotech workshop, invests in human health and planetary health. Upside Meat and The Every Company are two success stories spun out of IndieBio. The workshop presentation process leads to subsequent internal voting using Feynman dollars. These votes distill an informal winner for a small cash bounty to the project with the highest amount of interest.

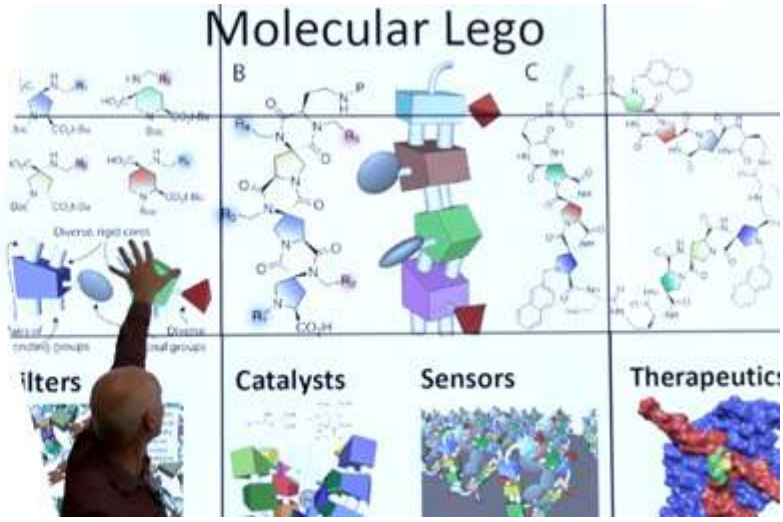
Adam Marblestone (below left), CEO of Convergent Research, spoke about the importance of design tools to the nanotech research and development process. Design tools are necessary to envision what could be built and lower the barrier to entry to get involved in nanotechnology. He believes multiple fields are design tool limited, but that over the past decade we have been making progress on things like DNA and protein design. The design process is complex but he hopes that this workshop could help shed light on how to tackle some longstanding issues.

Benjamin Reinhardt (above right), CEO of PARPA, wants researchers to think about building systems of nanotechnology rather than just isolated components. Most molecular machines are still just simple tools, so how can we combine them together? Proposals for these complex machines are uncommon, and the likely bottleneck is that it is extremely hard to design multi-component systems. Improving engineering designs could bridge the gap between where we are and where we want to be.

Keynote Presentations

Atomically Precise Catalysts

Christian Schafmeister, Professor at Temple University, is interested in building molecules that can do what proteins can do but that can be designed by humans. It's difficult to construct artificial proteins without something like an artificial ribosome, but Schafmeister's lab has been developing cyclic molecules with functional groups that behave similar to proteins. These molecules can be assembled together into macromolecules that act as filters, catalysts, sensors, and therapeutics. He hopes to develop artificial catalysts that can cleave glucosapane bonds in the extracellular matrix of cells, reversing damage caused by sugar in the body.



Building an Integrated Software Environment for DNA/RNA Design

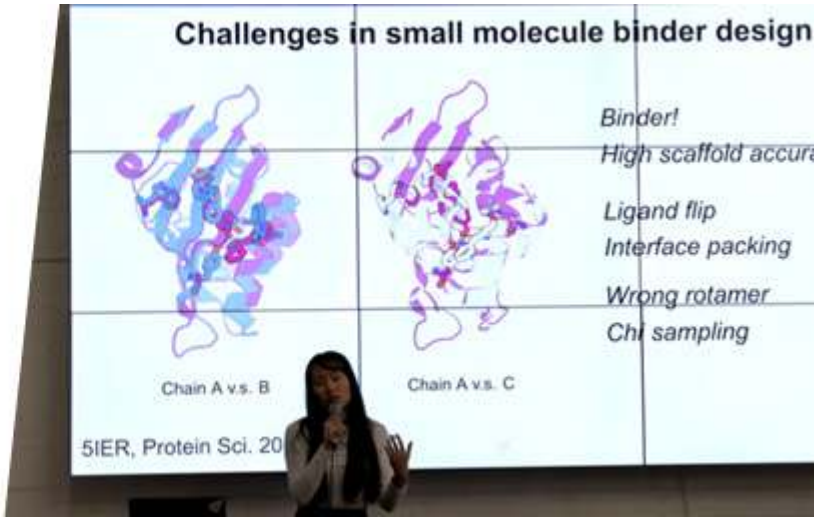
Erik Poppleton, Researcher at Arizona State University, described how computational models can be useful for designing nanotechnology. Modeling can create higher resolution outcomes, give us mechanistic understanding of interactions, and perform experiments that would otherwise be impossible. In short, modeling can make it faster and more efficient to test out nanotechnology designs. Erik has been developing oxView, a visualizer for DNA nanostructures as well as a python library for simulating those nanostructures. The outcome is that the design process has dramatically improved for people who want to see, build, and share their ideas in the field of nanotechnology.

Controlling the Motion of DNA Gliders

Tyler Ross (below right), researcher at Caltech and **Matteo Guareschi (below left), grad student at Caltech** are engineering molecular motors to respond to light. The motors cluster together when light is shined on them, assembling large aggregations of microtubles in the process. Iterating on this concept, he attached the motor proteins to a glass surface and allowed the microtubules to move freely over the surface of motors. The issue now is how to program controlled movement into the process to create gliders. One way to do this is to replace the microtubule glider with DNA, which can be programmed and engineered into highly unique conformations. DNA fabrics, like those being built by William Shih, may be able to be programmed to have complex motion and could unlock new possibilities for this mechanism.

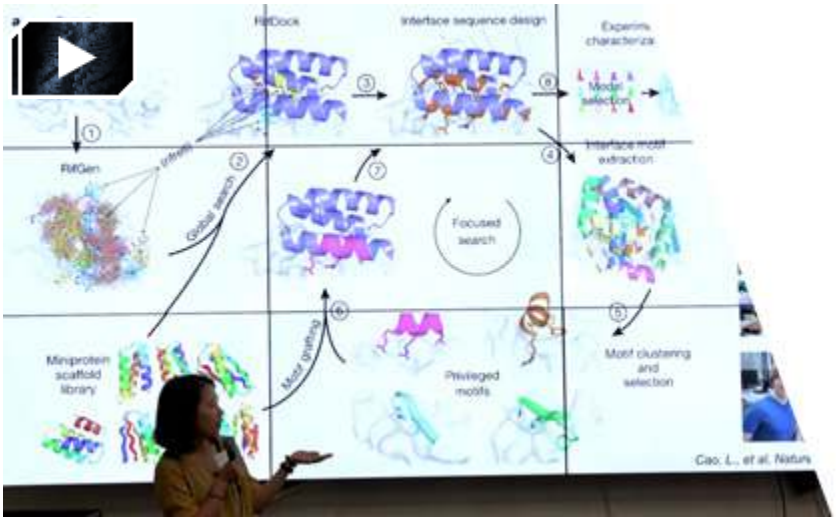
De Novo Design of Small Molecule Binding Proteins

Linna An, postdoc at University of Washington, describes the process of designing small molecules that bind to proteins. The canonical method involved generating scaffolds, designing the ligand docking, designing docks, designing filters, then finally testing in the lab. However, there are difficulties with finding ideal ligand designs because small molecules have such low tolerances. This problem can be solved using deep learning computation to improve every step of the design process. Linna's group is incorporating AlphaFold 2, RosettaFold, and Rosetta to dramatically speed up small molecule discovery.



Design of Receptor Binding Proteins

Xinru Wang, postdoc at University of Washington, stepped in for her colleage to describe the process of designing proteins that bind to receptors. She uses insulin as an example - one of the most useful and widespread prescribed proteins on the market today. Xinru designed an insulin substitute using RifGen and a scaffold library, simulating various motifs for testing via a high-throughput screen. Computational simulation and previously constructed protein libraries are key to rapidly designing and testing protein binding prior to the slower wetlab phase.

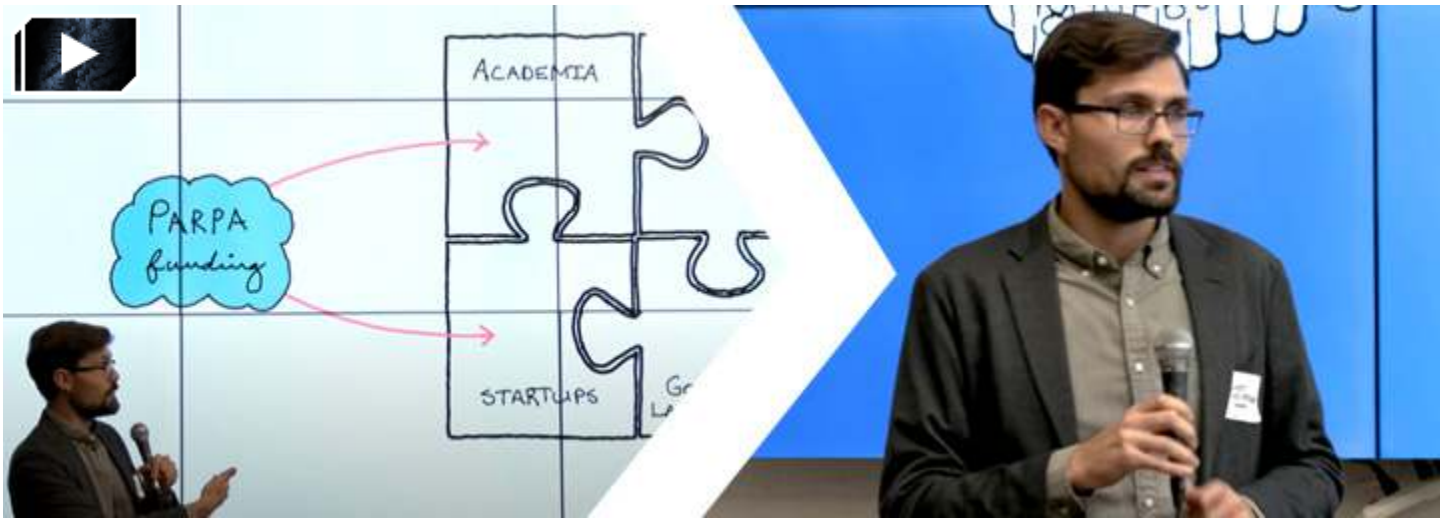


Digitizing Nanoscale Assembly

Oleg Gang, Professor at Columbia University, is working on digital fabrication of complex nanoscale materials. The idea is to convert the nanomaterial construction process into a generic voxel (volumetric pixel) method, that can build anything you want using programmable, self-assembling units. To construct nanomachines this way, we'll need visualization tools, a general purpose 3d printer or self-assembly method, and appropriate modeling software. The applications of such technology would allow us to construct extremely intricate materials and 3d nanohardware, including 3d wiring at the nano scale.

Functional Nanoscale Systems in Bionanotechnology

Chris Wintersinger, Program Manager at PARPA, describes what PARPA does and why it's necessary. The existing structures for invention are ill-equipped to foster development for biomolecular systems. Academia, startups, government, and industry are supposed to work together to create innovation. PARPA addresses inadequacies in Academia and Startup culture. Specifically, the siloed nature of work done in Academia and lack of cross-discipline research.

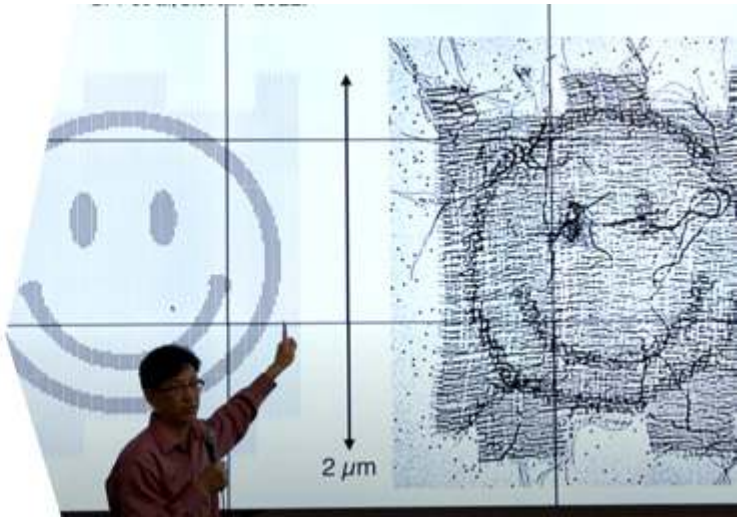


MSEP: What, Why, and How?

Erik Drexler, Cofounder of Foresight Institute, spoke about the Molecular Systems Engineering Platform (MSEP), his vision for a nanotechnology development organization that will accelerate progress in the field. Since 1992, complex molecular machines have been designed and yet have not been constructed. The foundation of the organization rests on a new wave of emerging design software. Gamifying the design process and spreading it out through the community would enable many people to get directly engaged with nanotechnology concepts in a fun way, pulling more people into the field and growing the network. It has recently received funding, and he is looking for dedicated and intelligent people to help make this project a reality.

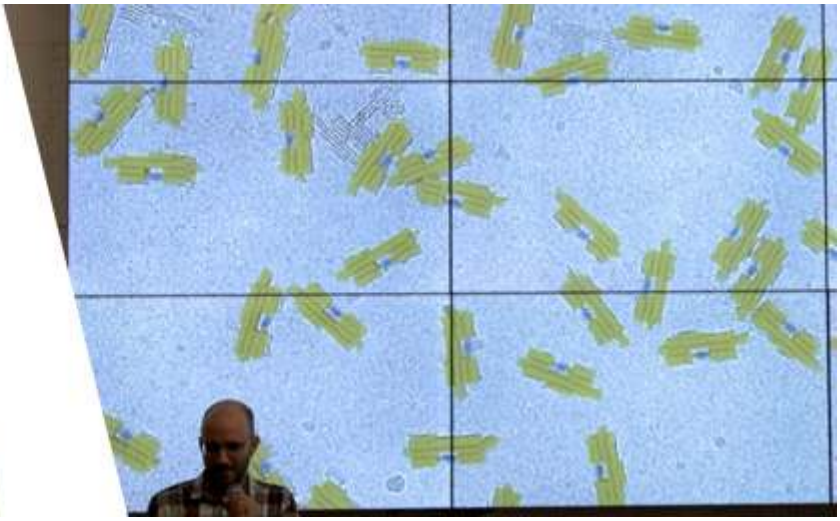
Multi-Micron Crisscross Structures Grown from DNA-Origami Slats

William Shih, Harvard Professor, is developing massive DNA origami structures. DNA origami refers to the practice of constructing physical structures out of DNA, typically using bundles of DNA bonded together to form a strong physical structure that can be used as rods. Will's group is building self-assembling fabric structures, larger than 2 micrometers, from DNA origami which have fully addressable surfaces. Essentially, he can attach unique molecules to the surface to change the color or chemistry of the fabrics. These fabrics have the potential to be readable/writable nanoscale surfaces.



Nanoscale Instruments for Visualizing Small Proteins

Shawn Douglas, Professor at University of California San Francisco, is developing a better way of identifying proteins. A common method for identifying proteins is Cryo-EM. This process freezes proteins in place in varying orientations, takes pictures of the protein silhouettes, and then combines many silhouette images to reconstruct the 3d shape of the protein. If the protein is too small, this method becomes very difficult. Shawn constructed a scaffold - a molecular goniometer - to hold the protein in place and rotate it on its axis by a set angle, making it much easier to use Cryo-EM to identify the structure of small proteins.

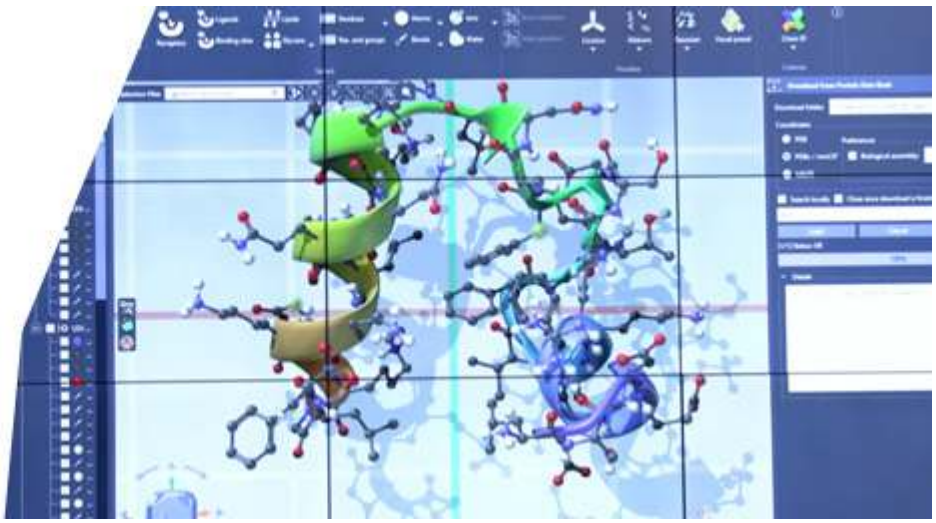


Nanoscale Machinery from DNA

Erik Benson, researcher at Oxford University, presented a brief overview of DNA origami mechanisms. His primary project is the construction of a simple 2D printer built out of DNA origami. Three structures - rails, a print head, and a print sheet were built. He was able to get movement and writing of the print head to work, and produced patterning which was visualized by fluorescence. The structure itself was quite soft, so the next steps are to use software simulation to come up with improved designs to increase rigidity.

SAMSON Connect

Stephane Redon, CEO of OneAngstrom, demonstrated his integrated software platform for molecular design. SAMSON can do visualization, animation, simulation, and construction of complex molecules. It's been stated before that simulation software for DNA/protein hybrids is lacking. This software is attempting to integrate DNA, proteins, small molecules - basically any nanostructure - together in a single unified simulation and visualization environment.

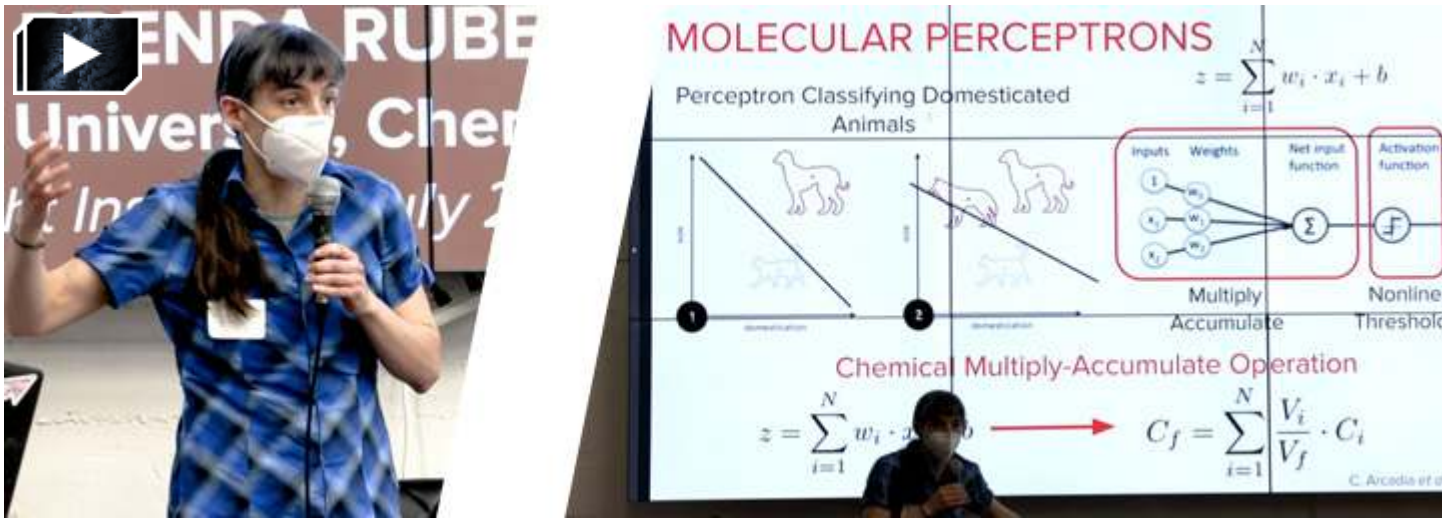


Software-Facilitated Design Atomically Precise Manufacture

Andrew Turberfield, Oxford Professor, spoke about the necessity of in-silico experimental design as part of the broader experimental process. He has been using in-silico design to develop a very small nanoprinter that uses DNA origami as the structural component to read and write to a DNA nanofabric. Eventually he hopes to increase the accuracy of the machine and extend its ability to operate in three dimensions. Andrew is also working on an artificial ribosome to perform programmed, sequence controlled polymer synthesis.

The Indispensible Missing Link: Molecular Wiring

Brenda Rubenstein, Professor at Brown University, works with small molecules to store information as mixtures rather than polymers. Bits are encoded in the presence or absence of a solution, then interpreted by machine learning algorithm. Brenda is able to store data in molecules, but also wants to compute data using this system as well. In order to do computation, a type of molecular 'wire' must be developed. Not an actual physical wire but rather a wire in an abstract sense - the ability to direct information between specific molecules at a distance. Creating molecular wiring in this context would open up the field of chemical computation and possibly enable a much more dense form of computation than is currently possible.

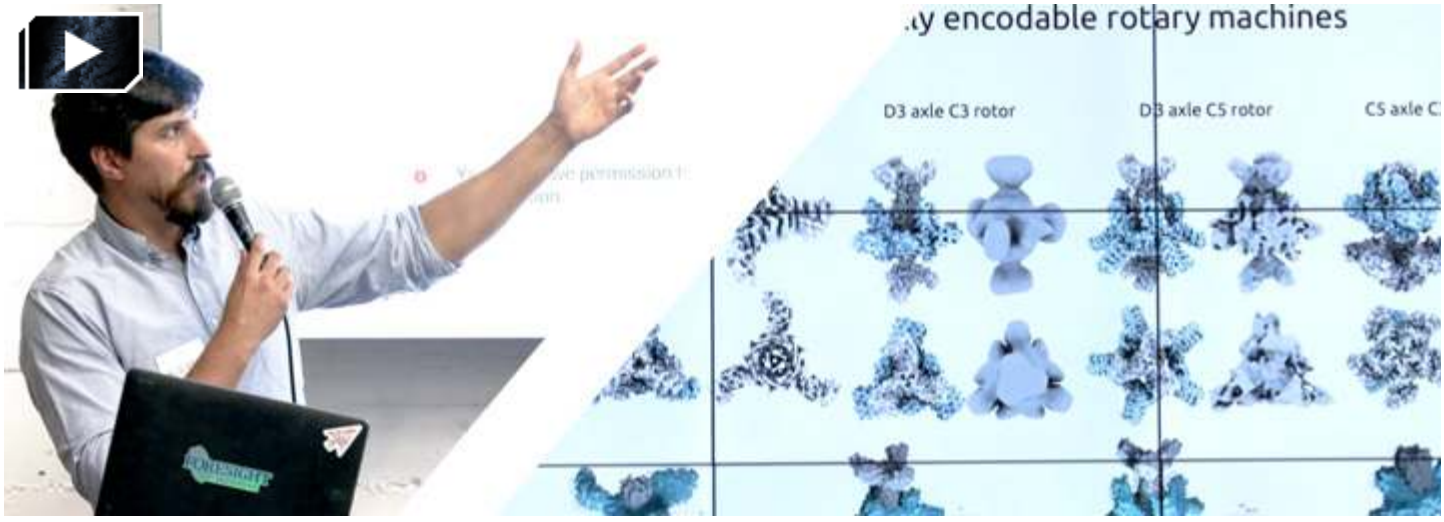


There's Plenty of Room in the Middle

Jacob Swett, previously a scientist at Arizona State University, claims that the top-down and bottom-up processes of nanofabrication and protein design can 'meet in the middle', around the 5-50 nanometer range. There are opportunities here for scaleable manufacturing that doesn't run into the problems experienced at either extreme. Specifically, he uses the example of protein conductance and using proteins as wires. Interfacing electronics with proteins is the kind of midrange technology that is not quite atomic level precision manufacturing, but still seems very accessible and does count as nanotech.

Computational Design of Genetically Encodable Nanomachines

Alexis Courbet, researcher at University of Washington, described computational protein design and it's emergent possibilities. A design pipeline is emerging where first a structure or combination of structures is proposed based off of a mechanical concept, then corresponding proteins are generated that match with each section of the structure. Alexis presented a large library of computationally designed protein rotors and motors, and hopes to use deep learning to improve on those designs and create more complex machines in the future.



Project Presentations

MSEP

Hein-Pieter van Braam, Prehensile Tales
JJ, Ben-Joseph, InQTel
Eric Drexler, University of Oxford

What are you trying to do?
We want to design a user-friendly nanotechnology design system that includes beautiful visualization and molecular dynamics.

How is it done today?
No similar system exists today.

What is new in your approach?
We have a well-funded project with an experienced project manager who has experience in visualization and game design that can gather a team. We have known interest from people with experience in Python/machine learning.

If you are successful, what difference will it make?
Encourage the advancement of nanotechnology R&D by making it accessible to the general public and citizen scientists.

Cost and Timeline?
It will cost $200k-300k for a minimal viable product, with a full version (continuous maintenance) requiring $1m per year. The time for first demo - four to six months. Actual implementation must start Aug 1, 2022. Final version will be ongoing.

What are the midterm and final exams to check for completeness?
Midterm (create a demo; demo oriented development): Build a way to take existing components that dense covalent structures Eric Drexler made in the 90s and make them well simulated and understood. Allow people to create more complex machines and have an accurate simulation as if you could build it. Simulate it in close-real time. It shouldn't be a rehash of what people have already seen. The final exam will be the ongoing maintenance of the project.

Self-driving Gliders for Programmable Routing of Microscopic Cargo

William Shih, Harvard University
Ayush Noori, 50 Years Capital
Serena Zhang, 50 Years Capital
Ricardo Ruiz, Lawrence Berkeley National Laboratory
Nikhil Lyles, Wayfinder Biosciences

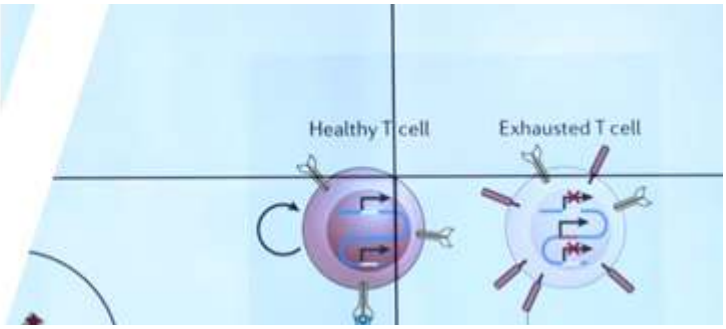
What are you trying to do?
We propose self-driving gliders for programmable routing of microscopic cargo on surfaces patterned with dynein motors. We'll initially focus on two applications: (1) sorting of CAR-T cells to enrich for metabolic fitness and avidity to peptide-MHC targets; (2) DNA-sequence encoded assembly of informational polymers ("makeshift synthetic ribosome") and subsequent multi-objective evaluation and annotation of functional performance ("Molecular Ninja Warrior").

How is it done today?
Current cell sorting methods are limited by the assay of choice. The dominant sorting paradigm is FACS; limitations of FACS include the high cost, medium throughput, and limited capability to assay only for staining efficiency.

What is new in your approach?
"Molecular Ninja Warrior": Gliders enable annotation of library members with transit time through each reaction chamber, which could be a proxy for a rich range of functionally interesting behaviors

If you are successful, what difference will it make?
The ability to assess the anti-tumor activity of specific CAR-T variants would facilitate the development of more effective CAR-T immunotherapies to improve patient outcomes. "Molecular Ninja Warrior": Small molecule compounds can be assembled with specific activity profiles based on time-tracked performance in sequential reaction chambers. Compounds with desired activity profiles can be identified via high-throughput sequencing for personalized medicine. For example, chemotherapeutics with activity profiles that match the mutational profile of a patient tumor can be selected to prevent drug resistance.

Cost and timeline?
CAR-T cell sorter ($500k per year total cost): Years 1–2 proof-of-principle to demonstrate genotype-specific, DNA-tape-annotated transit times of gliders; Years 3–4 prototyping performance with CAR-T cells; Molecular Ninja Warrior ($500k per year total cost): Years 1–2 proof-of-principle to demonstrate control of genotype-specific routing of gliders for split and combine synthesis; Years 3–4 prototype device for demonstrating library synthesis and functional evaluation.



Platform for 3D Manufacturing

Oleg Gang, Columbia University and Brookhaven National Laboratory
Yonggang Ke, Georgia Tech
Erik Benson, Oxford University
Kunyu Wang, University of Texas
Stacy Copp, UCI
Michael Matthies, Arizona State University
Stephane Redon, OneAngstrom

What are you proposing to do?
We want to establish a 3D nanofabrication platform for massively parallel manufacturing of designed functional nanoscale materials/devices.

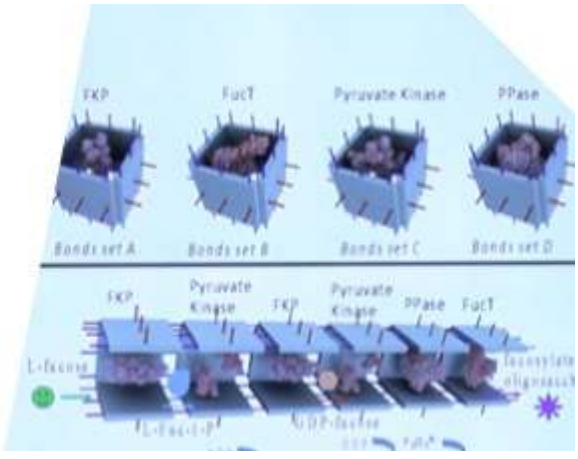
How is it done today?
Current top-down approaches such as nano-lithography are inherently planar and suffer from limited throughput and restricted material options. 3D printing struggles to achieve high resolution and offers a limited material choice and throughput. Molecular beam epitaxy is exceedingly slow and works with a limited material repertoire.

What is new in your approach?
We will be reverse engineering self-assembled architectures to create the desired function, and decoupling the assembly process from the nature of the component. We will also encode functional nanocomponents and encode a connectivity of nanoscale modules.

If you are successful, what difference will it make?
We can create optically active materials which are required to bridge nanoscale-photonic systems. We could enable negative refraction index material, metamaterials, modular nanoreactors and factories, and optical computing.

Cost and timeline?
We expect it to take $10M over 4 years.

What are the midterm and final "exams" to check for success?
In the midterm, we only need to see a prototype structure. For the final exam, we would have a coarse grained model block with a computational design workflow.



Programmable Blood Clotting

Shelley Wickham, University of Sydney
Grigory Tikhomirov, UC Berkeley
XinRu Wang, University of Washington
Siddharth Agarwal, UCLA

What are you trying to do?
We want to build a system for external control of local activation and deactivation of blood clotting using magnetic fields.

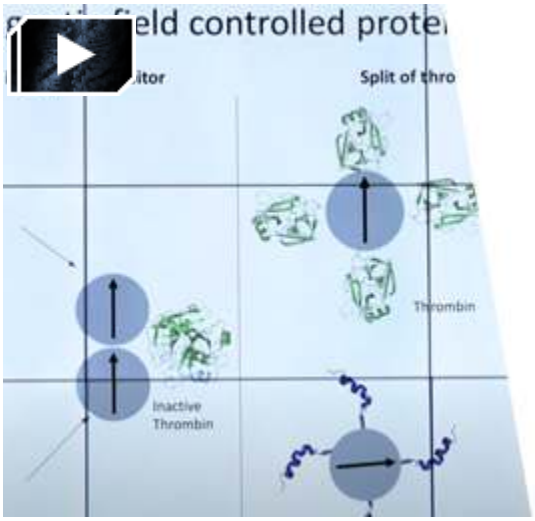
How is it done today?
The current solution is to systemically administer blood thinners, which leads to bleeding and buildup of resistance. There are also physical 'temporary tourniquet' options.

What is new in your approach?
Using nanobots to actuate blood coagulation based on magnetic fields is absolutely not being done by anyone else. The novel features are reversability and precise control.

If you are successful, what difference will it make?
The immediate impact is in the emergency room; for stroke, embolism, covid patient, and premature babies survival. It could prevent >1M deaths annually in the US.

Cost and timeline?
$1M and 2 years for in vitro proof-of-concept, 5 years + $$ for in vivo animal model.

What are the mid-term and final exams to check for completeness?
The milestones of progress can be measured by demonstration in-vitro, in drawn blood, in mice, in pigs, and finally in humans.



Adapting and Evolving Materials

Lee Cronin, University of Glasgow
Ayusman Sen, Pennsylvania State University
Giulio Ragazzon, University of Strasbourg
Brenda M. Rubenstein, Brown University
Shucong Li, Harvard University

What is the group doing?
The group wants to build a materials system that works by adapting to the work requirement, or better yet that evolves to optimize its performance. We want to subject the systems to energy sources and engineer how materials adapt to the influx of energy; thus, evolving by adaptation. For example, we can think of libraries of peptides that can adapt in the presence of different environmental cues, in presence of an energy supply such as ATP. Or we can observe the synthetic protocells that will be able to pass the Turing test and act as translators between different living species.

What is new in your approach?
We will focus on controlling constraints (kinetics, time scales, length scales), which we see as memory, either short-term or long-term, depending on process kinetics. In particular, we will try to understand the energy flow and how information content affects behavior.

How is it done today? If you are successful, what difference will it make?
Currently, adaptation is mostly limited to synthetic biology, or in silico systems. Essentially, it is never from scratch. If we succeed, everyone in functional materials will be engaged. We would unlock systems that can optimize themselves and can work together. For example, this would mean that a single material system would be able to optimize its performance towards four different tasks.

Cost and timeline?
We aim at a multidisciplinary consortium of 16 postdocs/grad. students/years encompassing synthetic chemists, physical chemists, algorithm development – including modelers – chemical engineers, material scientists, and biologists. It will take 4-5 years, with a good deal of luck.

What are the midterm and final exams to check for completeness?
Midterm: one out-of-equilibrium system that adapts to different tasks.
Final: 1st generation materials that can evolve through adaptation to 2nd generation materials that give better performance.

Universal Constructor

Alexis Courbet, University of Washington
James Arthur Cooper, University of Reading
Linna An, University of Washington
Charlie McTernan, Francis Crick Institute
Jacob Majikes, NIST
Sara Walker, Arizona State University

What is the group doing?
We want to build a universal constructor for 3D structure of polymers, adaptable to any chemistry.

What is new in your approach?
Our approaches will create the first-ever technology that can make sequence-polymer structures for non-natural polymers, which will provide a new language to unlock a vast design landscape of possible 3D polymers that is currently completely inaccessible.

What is new in your approach?
Biology invented a molecular architecture that can 3D 'print' any protein. We want to build an architecture that can do the same for any possible polymer system. We will start with building a simpler ribosome, since the sequence to 3D structure map is worked out and chemistry known. We will use those design insights, iteratively from computational design to evolution, to expand to other possible polymers, building the first system that can program 3D structure into any variety of polymer.

How is it done today? If you are successful, what difference will it make?
Natural ribosomes are extremely complex as well as not reengineerable, not transferable, and necessitate complex cellular machinery. They cannot generalize to polymers outside of the key macromolecules biological life uses. Meanwhile solid state synthesis of peptides are inherently limited (length, speed, scalability). If we succeed, we will be able to program sequence-to-structure for polymers that were not biologically evolved, allowing significant expansion of the capabilities of macromolecular chemistry.

Cost and timeline?
Initial funding should focus on the 'minimal ribosome' project, with the idea that the key output is not just the artificial ribosome functionality, but a design platform transferable to other polymer types.
Design and filtering in silico -> wet lab expression and prototyping (~months - 1 year of postdoc time standard computational resources), successfully tape copying experimental evidence, with iterative design-evolution-testing (translation of mRNA into protein of target structure) (~2 years postdoc time, standard biochemical ressources)