FORESIGHT INSTITUTE

Foresight Institute 2023 Workshop

Molecular Manufacturing Architectures Report

THE INSTITUTE, SAN FRANCISCO, CA, USA

11 & 12 September, 2023

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Executive Summary

Could complex molecular machines system design be sped up by integrating emerging approaches and software advancements? Some possible avenues for progress were highlighted in our 2022 Molecular Machines Workshop, some are newly emerging.

Our 2023 Molecular Machines Systems Designs Workshop invited leading researchers, entrepreneurs, and funders to put the pieces together and focus on the original vision of nanotechnology: creating reprogrammable tools that can create individually specified chemical bonds at scale.

In the first workshop phase, workshop co-chairs Benjamin Reinhardt from SpecTech and Adam Marblestone from Convergent Research highlighted possible architectures for reprogrammable molecular machine tools, before selected researchers presented emerging approaches that could potentially be leveraged to develop them.

The workshop group shortlisted a few architecture proposals to focus on, such as a molecular 3D printer, a molecular breadboard, molecular legos, assembly with STM or AFM, and combining self-assembly and positional manufacturing. Collaborative project groups were established to explore how emerging scientific approaches could be leveraged, scaled, and combined to create building blocks of the shortlisted architectures.

The first part of this report focuses on the resulting architectures, summarized by Tad Hogg of the Institute for Molecular Manufacturing, while the second part of the report provides context on the final architectures by giving overviews of the introductory presentations. By clicking on the play icons next to the written outlines, you can view the corresponding presentation recordings. In addition, each molecular machine architecture proposal includes an animation video illustrating its mechanisms, courtesy of Roen Hogg.

Finally, for an interactive overview of the molecular field, including major needed technical capabilities, existing actors, and outstanding challenges, please see Foresight Institute's molecular machine technology tree.

I would like to extend my heartfelt gratitude to our workshop participants for their excellent contributions and to our generous sponsors, Schmidt Futures and Moore Foundation. Without their support, this workshop would not have been possible.

We look forward to building up on these efforts in our 2024 workshop. In the meantime, we welcome those interested in cooperating on long-term goals in the Molecular Machine space to reach out to us.

Best regards,

Allison Duettmann
PRESIDENT, FORESIGHT INSTITUTE
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About Foresight Institute

Foresight Institute is a research organization and non-profit fostering the beneficial development of transformative technologies. Since our founding in 1987 on a vision of guiding powerful technologies, we have expanded our focus to various cutting-edge fields that are too ambitious for legacy institutions to support. This includes molecular nanotechnology, health and life extension, improving cognition via neurotechnology, space exploration, and Intelligent Cooperation in AI. By gathering leading minds across these areas, we seek to advance research and work towards flourishing futures.

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Adam Marblestone

CONVERGENT RESEARCH

Adam Marblestone is the CEO of Convergent Research, where he collaborates with a vast network to devise a strategic roadmap for future FROs. Beyond this, he serves on the boards of nonprofits like Norn Group and New Science, focusing on novel methods of scientific research funding and organization. Additionally, he participates as an interviewer for the Hertz Foundation. Previously, Marblestone held roles as a Schmidt Futures Innovation Fellow, a Fellow with the Federation of American Scientists (FAS), a research scientist at Google DeepMind and MIT, and Chief Strategy Officer at Kernel. He pursued his PhD in biophysics at Harvard under George Church and studied theoretical physics at Yale. His entrepreneurial efforts include co-founding BioBright, and he has advised institutions like Open Philanthropy.

Allison Duettmann

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Allison Duettmann is the president and CEO of Foresight Institute. She directs an array of programs such as Intelligent Cooperation, Molecular Machines, Biotech & Health Extension, Neurotech, and Space, along with Fellowships, Prizes, and Tech Trees, and shares this work with the public. She founded Existentialhope.com, co-edited Superintelligence: Coordination & Strategy, co-authored Gaming the Future, and co-initiated The Longevity Prize. She advises companies and organizations, such as the Consortium for Space Health, and is on the Executive Committee of the Biomarker Consortium. She holds an MS in Philosophy & Public Policy from the London School of Economics, focusing on AI Safety.

Benjamin Reinhardt

SPECULATIVE TECHNOLOGIES

Ben Reinhardt is the founder of Speculative Technologies, a nonprofit research organization dedicated to pioneering materials and manufacturing technologies overlooked by other institutions. Previously, Reinhardt facilitated company formations in Singapore, engaged in various roles in Silicon Valley—including at a unicorn startup, a VC firm, and his own startup—and served at NASA. He holds a PhD in Space Robotics.

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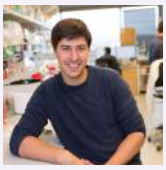

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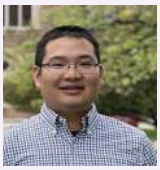

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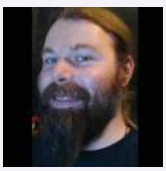

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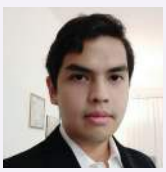

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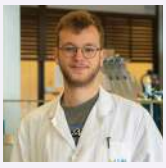

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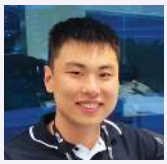

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What's missing:
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Molecular Manufacturing Architecture Proposals

INTRODUCTION

Early discussions of molecular manufacturing proposed an assembly tool that could precisely position individual atoms [Drexler 1992]. This tool could bond atoms at specific locations in a structure and prevent the atom from reacting at other locations in the structure. If necessary, the tool could apply force to overcome kinetic barriers to the reactions, analogous to the behavior of enzymes. This proposal for manufacturing by precisely manipulating individual atoms remains unrealized several decades later.

Another approach to atomically precise structures, self-assembly of molecular structures in solution, has advanced considerably in the past few decades, e.g., producing DNA-based [Ke et al., 2018] and other machines [Peplow 2015]. However, self-assembly is difficult to scale up to larger and more complex machines since the final structure must be encoded in the specificity of interactions among the building blocks. Extending self-assembly to build larger structures while maintaining atomic precision thus requires increasingly complex design and synthesis of the blocks, and methods to detect and correct errors.

To avoid the challenges of manipulating individual atoms and scaling up self-assembly, most of the atomically-precise manufacturing architectures proposed at this workshop combine positioning and self-assembly to exploit their complementary capabilities. First, self-assembly creates a variety of molecular building blocks with specific binding sites that match those on other blocks. The blocks are then positioned at precise locations where they link with other blocks to form a larger, atomically precise structure. Architecture 3 (Molecular legos) is an exception in only using self-assembly.

The building blocks in these proposals are a few nanometers in size. The blocks contain enough atoms to allow designing their

interactions with other parts. This designability contrasts with that of individual atoms, whose reactions with other atoms cannot be modified to facilitate assembly. Blocks with designable interactions makes them simpler to use with positional tools than is the case for positioning individual atoms. For example, blocks can be designed to only react with other blocks so they can be positioned while in solution rather than requiring high vacuum. In addition, due to their larger size, molecular building blocks do not require as precise positioning as individual atoms do. This means the positioning can tolerate larger thermal motion so the assembly process can proceed at room temperature instead of requiring cryogenic temperatures.

Delivering building blocks to the workspace in solution avoids another challenge of working in vacuum: obtaining the building blocks. In a vacuum process, the positioning device must find each building block, e.g., at locations where they are attached to a surface of feedstock components, bind strongly enough to the block to pull it off the surface, but not hold it so tightly that the block can't then be delivered to the structure under construction and removed from the positioning device. Continually moving from the location of feedstock to the specific location to add each retrieved component is challenging since it requires repeated motions over relatively large distances (compared to the size of the feedstock components) and at the same time high precision to find each new component and then bring it to the desired location in the structure under construction.

The architectures proposed at the workshop differ in their choice of building block and positioning method. The building blocks are matched to the positioning mechanism. However, with suitable modification of the blocks' binding sites, blocks in one architecture could also be positioned by methods of other architectures. Thus these proposals are not mutually exclusive.

Due to their combination of self-assembly and positioning, the architectures have similar performance measures for building complex molecular machines. These include:

- yield of molecular building blocks from precursor chemicals, i.e., fraction of those chemicals that self-assemble into the desired blocks
- yield of machines from the self-assembled building blocks, i.e., the fraction of blocks that go into the assembled product
- error rates: the fraction of missing or incorrectly placed molecular building blocks in the final product
- error detection and recovery: whether addressed during manufacture to allow closed-loop control and possibly recovery from errors, or testing afterwards to discard incorrectly assembled structures
- production rate: accounting for both the rate of self-assembling building blocks and their subsequent positioning to build the final product
- production cost, including cost of feedstock to make the blocks and the assembly process
- power and heat dissipation: programmable synthesis is energetically demanding so the

system design must specify where the energy will come from, how it will be transduced, and how it will be dissipated

- design cost for both the blocks and the sequence of positioning operations to place them into the final product
- the complexity of structures that can be built, including whether limited to 2D structures on a surface or general 3D structures
- whether limited to passive structures, such as atomically precise membranes, or can also build active machines, such as molecular motors [Astumian and Hanggi 2002, Drexler 1992], that can exert forces in controllable directions to perform work on other components of the structure and its environment, in the presence of large random forces from thermal fluctuations

Estimating these performance measures can compare the potential of the proposed architectures.

Open questions for the architectures include:

- Each architecture can make atomically precise bonded structures. Are those structures limited to static structures, such as membranes with pores and binding sites? Or can they also be machines that perform work in controlled ways, e.g., gears and motors [Drexler 1992, section 11.6.4]?
- What is the rate limiting step in the construction process? Possibilities include the time required to synthesize the building blocks, position each block to the structure, and wait in position until they bind?
- How does the architecture detect and deal with errors? What is the expected yield of desired products after handling errors?
- What are expected design and production costs of products?

ARCHITECTURE 1: A MOLECULAR PRINTER

Adam Braunschweig, CUNY Advanced Science Research Center; Boris Fain, Stanford University; Christian Schafmeister, Temple University; Jonathan Ackley, University of Amsterdam; Lillian Chong, University of Pittsburgh; and Tad Hogg, Institute for Molecular Manufacturing

A molecular printer uses prefabricated molecular blocks and a probe that ensures each block only binds to a desired location in a structure constructed on a surface. This procedure can assemble structures in solution at room temperature.

The group discussed two ways to use the probe:

- 1A: the probe binds to and positions each block in its desired location until it covalently bonds to the structure.
- 1B: the probe activates a specific location on the structure, so that blocks only bond near that location.

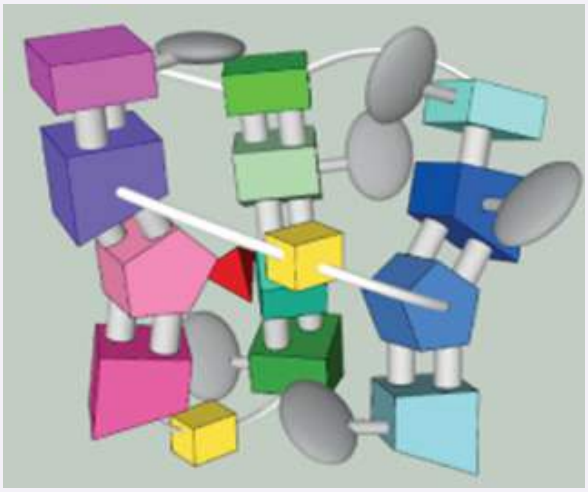
Architecture 1A: Positionally assemble molecular blocks

This molecular printer builds atomically precise structures on a surface using a probe to position prefabricated molecular blocks designed to have complementary reactivity with specific other blocks already in the structure.

These blocks are spiroligomer nanostructures shown schematically in the figure. They can be made using synthetic organic chemistry and designed with CANDO software [Schafmeister 2016] to have desired bindings.

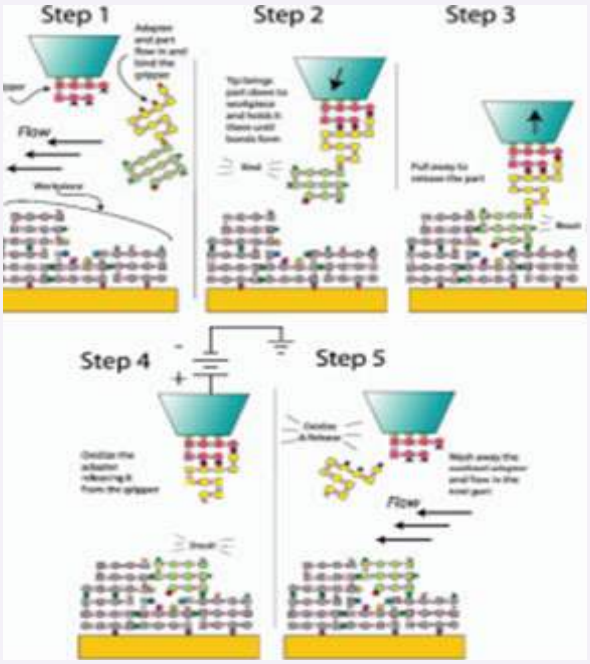
The manufacturing process for adding one block consists of the following steps. First, a solution containing many copies of that block, attached to an adapter, flows past the probe tip. When one of those blocks reaches the tip, it attaches to the tip via its adapter. The probe then moves to the location in the structure where the block belongs and holds it there until it forms covalent bonds with blocks already in the structure. Meanwhile the solution with the blocks is flushed out of the

microfluidic device. Pulling the probe away, breaks the connection between the adapter and block, i.e., the adapter is more strongly bound to the probe than to the block. Applying a voltage to the tip weakens the binding between probe and adapter so the adapter releases from the probe and is washed away in the solution. The process repeats with a solution containing the next block to add to the structure.



This image shows the sequence of operations for adding one block to the structure on the surface. For details see [Schafmeister 2007, Fig. 11].

Software to design the molecular blocks [Shafmeister 2016] searches through spiroligomer chemical space to find spiroligomer sequences that organize chemically reactive groups on the surface of the block to mate with groups on other specific blocks. This process is analogous to that of Rosetta Design searching through protein sequence space



The blocks are large enough that it is possible to add molecular adapters to link them to the probe tip in a desired 3D orientation. Thus, the probe need only be positioned with 3 degrees of freedom, rather than also needing to control its orientation (for a total of 6 degrees of freedom). This feature of adapters avoids the engineering complexity of requiring that the probe orient the block into the correct position for addition to the structure, e.g., by building a Stewart platform on the tip [Drexler 1992, p.476].

Next steps toward building this architecture are to demonstrate the synthesis and positioning of blocks. This requires a team that designs and synthesizes blocks connected to adapters. They must also make an AFM-like probe with a tip that is designed and synthesized

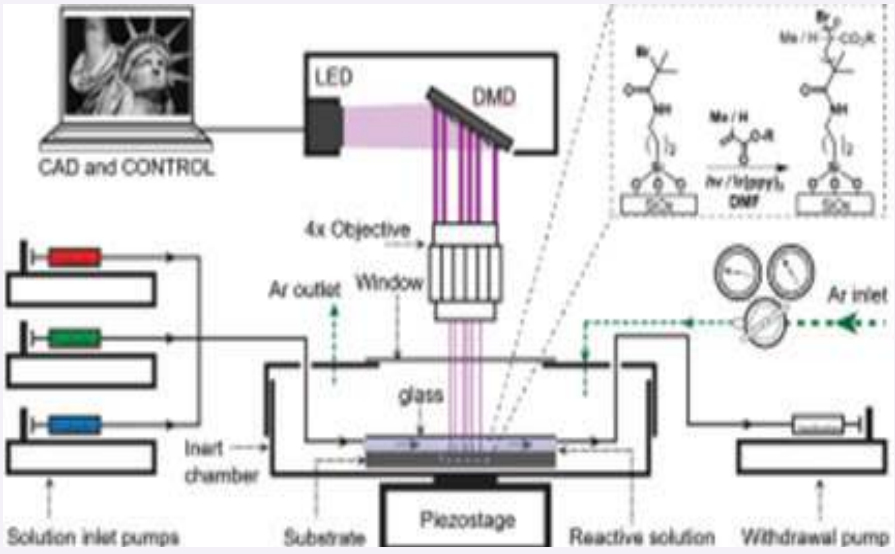
like the other blocks that can reversibly and under control of light, force, heat, or electrical potential, capture an adapter-block combination. The probe must have the positional control to bring the block to the surface, attach the block and pull away, breaking the connection between the adapter and the block and then release the adapter from the tip.

Open questions:

- Molecular printers were proposed in [Schafmeister 2007]. What's changed since the proposal to make this approach feasible now when it wasn't before? E.g., is it due to the demonstrated ability to synthesize the blocks?
- How does the probe's operator know when the probe has attached to a block in solution, so the probe is ready to move to the location in the structure where that block is inserted? Is there a detectable change in the probe? Or is it sufficient to wait long enough that there's a high probability that one of the blocks in solution has bound to the probe, and handle any missing cases via an error protocol?

Architecture 1B: Hypersurface Lithography by Selective Activation of Reaction Sites

This molecular printer uses building blocks whose activation energy for bonding to each other is much higher than that available from thermal energy. This means that any blocks diffusing to the surface under construction will not bond to it. To place one of the blocks into the structure, the probe adds energy to a specific location on the surface to lower the activation energy, allowing bonding of a block that diffuses to the surface at that location. The probe can supply energy in a variety of forms, such as light, force, heat or electric potential to achieve this precise localized chemistry.



The probe only acts on the built structure and does not need to find, bind or deliver parts to the structure, nor does the probe need to detach from the bonded block without damaging it, thereby simplifying the design of the building blocks.

The figure illustrates this proposal. The molecular printing occurs on the indicated substrate on the piezostage at the bottom of the figure.

A similar architecture with tip arrays has already been demonstrated [C. Carbonell et al. 2018, C. Carbonell et al. 2020]. Thus the proposed molecular printing could build on this prior work with the addition of suitable molecular building blocks.

Next steps toward building this architecture are to create a team of tip-based lithography people together with organic chemists to explore how to localize energy to do site-specific synthesis with molecular resolution.

Open questions

- What is the significance of the term "hypersurface" to describe the construction surface in this proposal? Is it different from the surface used in the other version of molecular printing? E.g., does the term refer to a type of surface structure whose chemical activation can be altered in a specific way by the addition of energy, which is provided by the probe in this case?
- When the probe delivers energy to the desired binding location on the surface, how does it avoid blocking building blocks from diffusing to the surface at that location? Does the surface activation remain long enough after the probe's removal to allow binding? Or does the probe have only a minor effect on reducing diffusion rate to the correct site on the structure, i.e., blocks rapidly diffuse around the probe.
- How does the probe's operator know how long to keep the probe activating the surface location? I.e., long enough that a block in solution diffuses to the activated location on the structure. Is this similar to the situation in version A, of waiting several times the average reaction time to ensure high likelihood of binding?
- How large an area does the probe activate on the surface? Is it just the size of a single block on the structure? Or, if it activates several nearby blocks, does this require that neighboring blocks in the built structure are sufficiently different that only the target block among those neighbors reacts with the next block arriving from solution?

Discussion

Both variations of the molecular printer add one block at a time to the structure. Thus, building a large structure requires many iterations of switching solutions of building blocks and adding one of the blocks in the solution to the structure, while the other blocks pass through the device unused. Thus many more blocks must be synthesized than are used in the final assembled structure.

Unused blocks could be recycled for subsequent steps if the structure requires the addition of another of the same block at a different location, or to build additional copies of the same structure. Alternatively, recirculated flows of a few blocks as a dilute solution could avoid the need to synthesize a large number of each block, but blocks in a dilute solution will take longer to reach the probe (variation 1A) or the activated portion of the surface (variation 1B).

The tip needs to remain in place long enough to ensure a high probability the block binds to the structure. In the first variation, the tip-adapter-block combination has to be held in place for tens of reaction half-lives. In the second variation, the activation energy from the tip must be supplied long enough to ensure a block diffuses to the desired location on the structure and has time to react before the energy dissipates throughout the structure and surrounding solution.

Both the serial building process and the need for the tip to remain at the structure limit the rate at which molecular printers can produce large structures. To achieve faster growth and more complex designs, the molecular printer could be a hierarchy of machines, where machines at each level use blocks created by one or more lower-level printers. In this hierarchical approach, first-level printers assemble larger super-blocks from primitive blocks, second-level printers

assemble these super-blocks, and so on. This process could increase build rate, but also requires more complex design for blocks at each level of the hierarchy. In such a system, it may be advantageous to print linear polymers that fold into 3D shapes for the first-level printers (since positional control on the smallest scale is the most difficult), and shift to 2D or 3D for higher level printers.

The printing process is subject to errors: a block may bind to the wrong location in the structure or not bind at all. The rate of such errors determines how large a structure can be made, with high yield, without error correction. Beyond that size, errors must be detected and corrected.

Suitable design of the blocks and limiting the error in probe position can reduce the chance of binding in the wrong position. One approach to reducing positioning error is to use ratchet mechanisms that rectify Brownian motion [Astumian and Hanggi 2002].

For blocks that don't bind, molecular printers can implement error correction by alternating blocks that add to the growing structure and "imaging probes" that attach to the tip and are used to image the block that was placed in position. If the block wasn't successfully attached then it can be flowed back in and the addition step can be attempted again.

Structures to build with Architecture 1

- Nanopore DNA sequencing. One properly designed pore could sequence a lot of DNA
- Printing cells or other hierarchical biological systems atom-by-atom or molecule-by-molecule
- Combinatorial glycan synthesis
- Quantum circuitry
- Manufacturing soft architectures that are incompatible with clean room processes
- Bioelectronic circuits – wires integrated 3D within gels
- Mechanical computers
- Prototyping of complex molecular devices

ARCHITECTURE 2: A MOLECULAR BREADBOARD

Anastasia Ershova, Harvard University; Fei Zhang, Rutgers University; Jacob Majikes, National Institute of Standards and Technology; Mandal N; Shucong Li, MIT; Si-ping Han, Switch Theraputics; and William Shih, Harvard University

In this system, a programmable breadboard structure precisely positions molecular blocks for bonding to form a precise structure. The programming occurs through the design of selective bonding locations on the breadboard and the building blocks.

The breadboard starts in an open configuration. This allows building blocks in solution to bind to matching locations on the breadboard, which holds them far enough apart that they don't react.

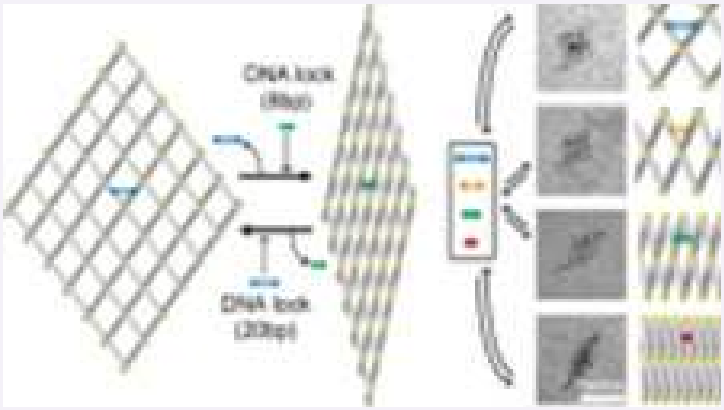
Once the blocks are bound to the breadboard, the breadboard is made to fold. In the folded form, the building blocks are in a precise 3D arrangement with neighboring blocks close together. Blocks then react to bind to their neighbors at designed connection points. After bonding, the breadboard is made to unfold. The bonds between the blocks are strong enough to keep the structure together as the breadboard unfolds, so the built structure pops off the breadboard as a separate structure in the solution.

Suitable breadboard structures include a collapsable gridiron structure [Han et al. 2013], reconfigurable DNA accordion rack [Choi et al. 2018], programmable DNA origami [Wang et al. 2021] and icosahedral shells [Sigl et al. 2021].

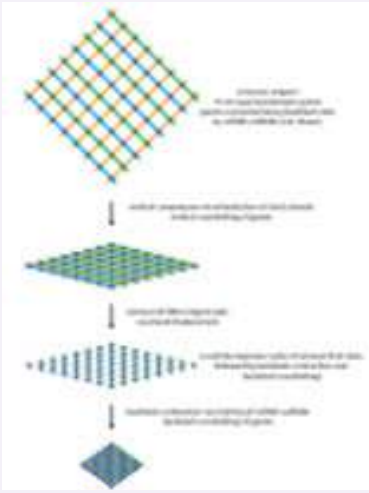
One possible breadboard is a crisscross structure made from DNA with 14nm spacing between individually addressable binding sites at the cross points, as illustrated in this diagram:

Assembling a DNA breadboard takes minutes to hours. However, self-assembly in solution is scalable: trillions of building blocks could assemble in parallel on multiple breadboards. Thus while the overall cycle time is fairly long, each cycle could produce structures from large numbers of building blocks.

Once building blocks are bound to the open DNA breadboard, it can be folded via, for example, an accordion fold as shown in this figure [Choi et al. 2018]:

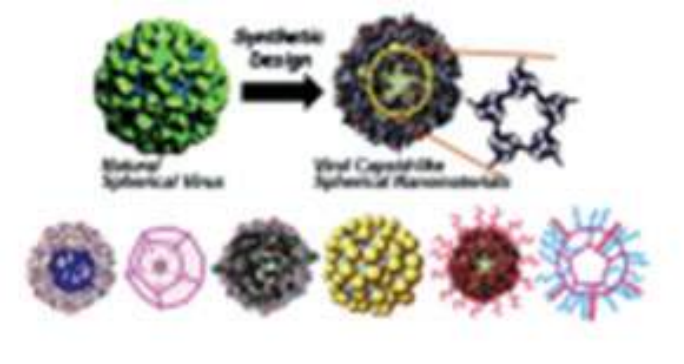


This diagram illustrates the steps of the manufacturing process:

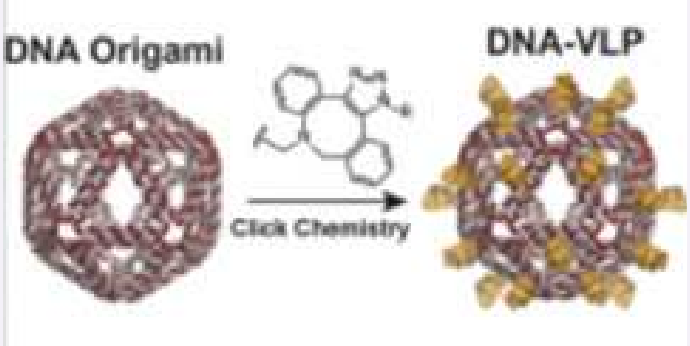


Another possible breadboard is a hierarchically assembled addressable breadboard, e.g. using crisscross cooperative assembly [Wintersinger et al. 2023], illustrated in this figure:

The building blocks can be viral capsid-like spherical nanomaterials, such as shown in these figures:



[Matsuura 2018]

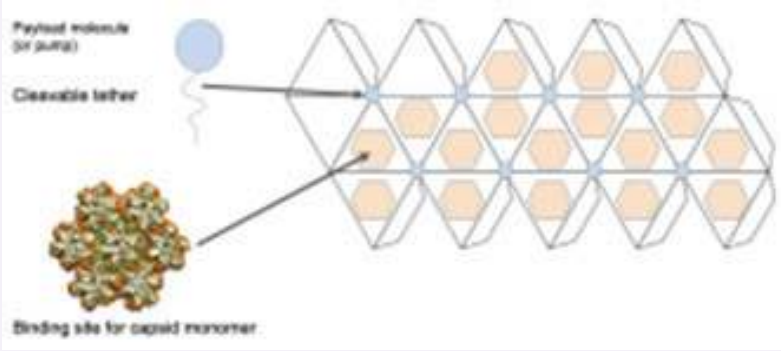


[Knappe et al. 2021]

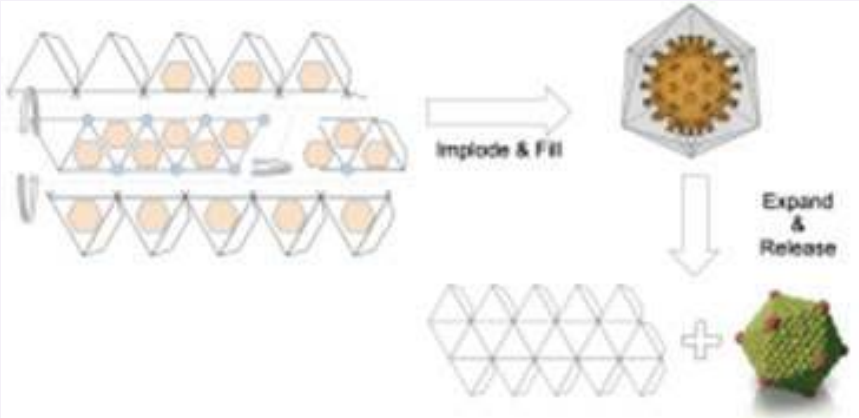
The breadboard approach could also use molecular building blocks discussed with the other architectures in this report, such as proteins tagged with DNA.

Breadboards provide additional flexibility of local control over the degree of compaction [Han et al. 2013, Wang et al. 2021]. This could allow creating structures via a sequence of neighbor bonding reactions, possibly involving different distances between blocks.

The DNA breadboard shown above is a contractible 2D structure. Alternate breadboards could provide more complex 3D geometries in which to bond the building blocks. A conceptual design for 3D folding is shown in this diagram:



After building blocks attach to binding sites in the breadboard, it folds, creates the 3D structure and releases it:



Next steps need to develop breadboards, the chemistry for linking blocks to the breadboard and methods to purify and recycle the breadboard. The breadboard must be rigid enough to ensure addressability for binding blocks from solution, and foldable via some change in the solution. It is also important to identify cost-effective applications, i.e., where the value of the product greatly exceeds the cost of the DNA used in the breadboard, and the structure cannot be made by self-assembly of the blocks in solution, i.e., construction requires the positional control provided by the folded breadboard.

If reactions between building blocks are not sufficiently selective, the blocks could be created in cages to prevent inter-block interaction during assembly of the pegboard, and uncaged after completion of binding to the breadboard.

Open questions:

- For the crisscross breadboard, how are building blocks bonded in the direction perpendicular to the contraction (shown as compressing in the vertical direction), since blocks remain far apart in that direction after the contraction? Is the structure released from the breadboard after the first contraction direction, and then the perpendicular contraction happens spontaneously due to stresses introduced with crosslinks, once the structure is released from the folded breadboard? Or does the breadboard continue holding the building blocks during the perpendicular contraction?
- What mechanism releases the bound building blocks from the folded structure? Is it from the design of the bonding strengths: blocks bound more strongly to their neighbors than to the breadboard, so when the breadboard expands, bonds between blocks and breadboard are the ones that break?

- After building blocks bind to the breadboard, are remaining unbound building blocks removed? If so, how? E.g., flushing with new solution will not only remove unbound building blocks but also the breadboards: in contrast to Architectures 1, 3 and 4 where the built structure is attached to a solid surface so that flushing with new solution does not remove them.
- If unbound building blocks are not removed, do they start attaching to the breadboard once it expands, after contracting and releasing the product? Thereby starting a new construction.
- After the product structure is released from the breadboard, how is it separated from the breadboard, and any remaining building blocks? Is the product filtered from the solution by size? Or does each product require a purification step specific to that product?

Structures to build with Architecture 2

- Compartments with pressurized cargo with controlled stoichiometry and logic-gated release
- Signal scaffolds
- Logic gates
- Woven nanofabric extruded from surface and topologically interwound structures. The precise bonding can create nanofabrics with extreme mechanical properties, e.g., mechanical metamaterials with molecular precision.

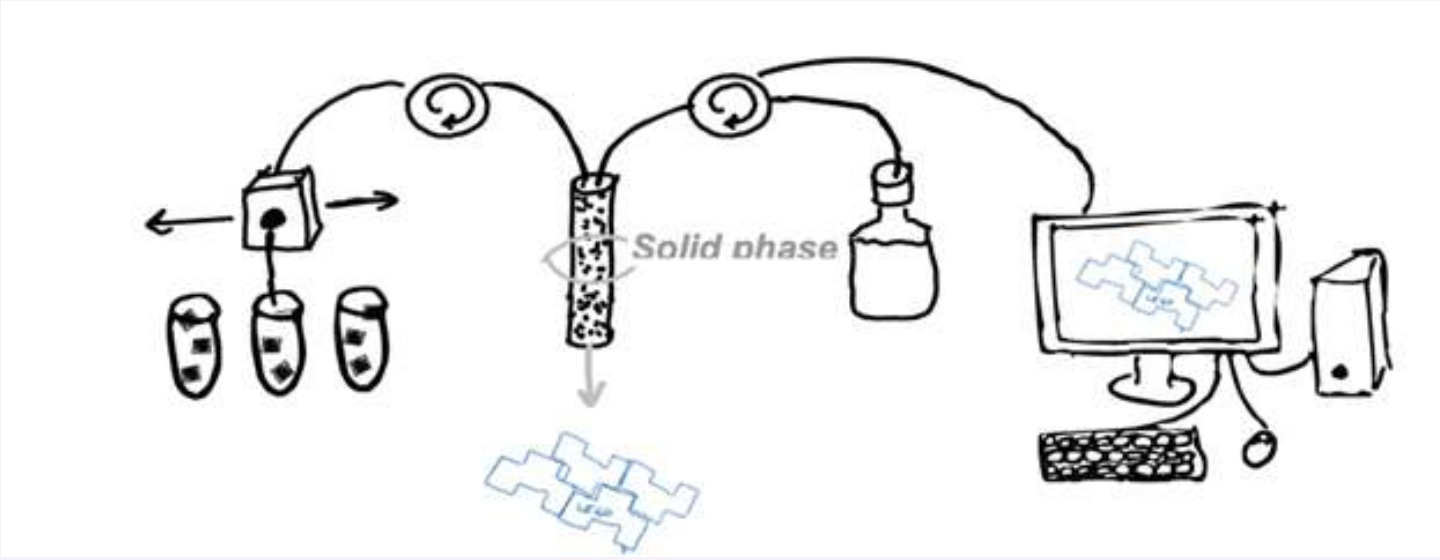
ARCHITECTURE 3: MOLECULAR LEGOS: SEQUENTIAL SOLID SURFACE TEMPLATING OF MOLECULAR MACHINES

Bill Efcavitch, Molecular Assemblies; Caleb Meredith,Chromatir; Chris Wintersinger, Speculative Technologies; David Forrest; Jonathan Ackley, University of Amsterdam; and Rachel Shi, Johns Hopkins University.

The molecular legos architecture assembles protein lego blocks on a functionalized solid surface using a sequential microfluidically-controlled process. Deterministic links between blocks are used to assemble blocks through computationally engineered non-covalent and covalent interactions. Additional inputs, such as light, solutes, or external fields may be used during assembly to unmask lego blocks and sites on the growing structure, and to remove the final structure from the surface.

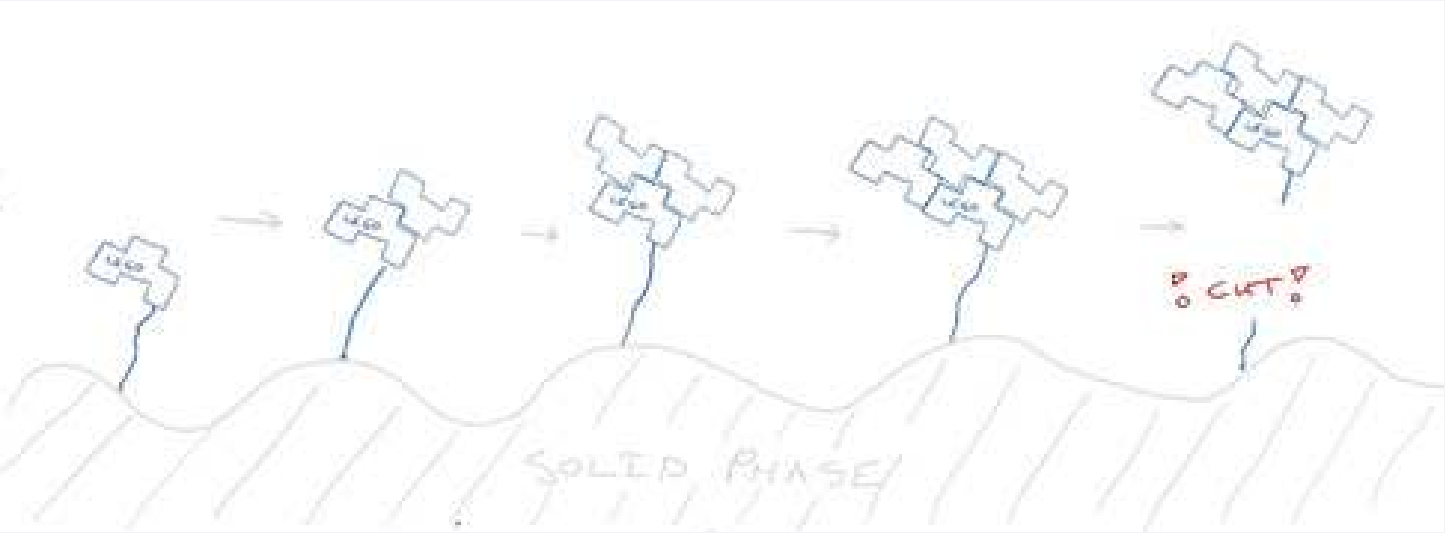
The primary information content input to the system is encoded in the 3D structure and affinity of the building blocks. This allows leveraging existing protein design tools to create blocks with the necessary functional groups to reliably assemble and link in the appropriate structural configuration at the growing surface as they are introduced through the solution phase.

A schematic of the overall process:



At each step of the construction, a solution containing the next building block is sent through the microfluidic channel for enough time that it is very likely one of those blocks has reached, and bound to, its matching position in the structure. Then the solution of remaining unbound blocks are flushed out and a solution with the next block is sent in.

This schematic illustrates successive steps in the process at one location on the surface (shown here with each step horizontally shifted from the prior step):



Building structures on a surface with sequential introduction of blocks with designed bindings is similar to the procedure of Molecular printing (architecture #1). However, the Molecular legos proposal does not need a probe to position or activate the surface, so avoids the complexity of fabricating the probe tip. Instead, the entire process is via self-assembly of the blocks bonding to specific locations in the growing structure predetermined by the ordered addition of the blocks and their precisely engineered amino acid sequence and folded structure.

The lack of positioning control means the final structure is determined by the block bindings and the order of their introduction via the solution. The design of the blocks is challenging since they must avoid binding to undesired locations in the structure. Nevertheless, this self sequential assembly design offers greater control than self-assembly in a solution containing all the components at the same time. By holding the structure at a solid surface, the solution can be washed out without removing the partially constructed structure. This allows introducing building blocks sequentially. Thus, for instance, a block that would erroneously bind to a location exposed at an early step in the construction could not be introduced until that location was covered by subsequent blocks.

The schematic of the construction process shows lego-block structures with fixed final shapes. However, hinged building blocks could be included in construction to produce structures that can change shape, e.g., in response to changing conditions in the solution.

The required reaction time for assembly is determined by the mean free path for diffusion of the blocks to reach the surface as well as rate of binding kinetics which may depend on the rotational diffusion of block molecules and the interaction potential of linkage binding. Diffusivity and binding timescales may be estimated based on molecular size and MD simulations respectively. To minimize diffusion path lengths, engineered microfluidic architectures or packed reactor beds filled with functionalized silica or polymer beads may be selected. The measurement of binding efficiency can be determined through careful collection and analysis of the mobile liquid phase after its interaction with the templating surface. A more rapid in situ measurement to determine binding efficiency via spectroscopic signatures may also be possible.

Mitigation approaches for detecting and handling assembly errors are conditional upon the ability to identify and distinguish incorrectly assembled block conformations. For large assembly errors, separation and filtration processes may be successfully implemented to purify errors from desirable macromolecular assemblies. Smaller structural or conformational deviations between final products after removal from the growth surface may require isolation based on subtle differences in functional properties, surface affinity or dielectrophoresis.

[Wintersinger 2023] provides a review of this technology.

Many copies of the same structure can be built in parallel, in contrast to procedures using positional control devices. Thus this architecture is scalable in the sense of being able to make many copies of a specific structure. This could be particularly useful for creating large numbers of identical subcomponents of blocks required for the other proposed assembly architectures at this workshop.

The main challenge for this proposal is achieving de novo design of complex protein building blocks required to create complex assemblies. The block interactions need to be specific and reliable. Modular interaction domains (recognition sites) and the assembled links between blocks need to be resilient to all subsequent steps in the assembly process.

Next steps involve the design and synthesis of a library of protein lego blocks with modular domains for specific, reliable binding interactions necessary to assemble complex structures. Additionally the solid support form factor and functionalized surface chemistry must be selected to begin engineering the initial surface template.

Structures to build with Architecture 3

- lego structures and machines made of multicomponent protein assemblies
- a useful demonstration size would contain about 30 distinct protein parts, similar to the number in a bacteria flagellum. Assembly with that many parts would demonstrate a hierarchical complexity capability on par with nature (with greater control and yield).
- motors actuators and other simple machines
- protein assembly subcomponents for molecular printers and breadboard assemblers, e.g., as used as building blocks for architectures 1 and 2.

ARCHITECTURE 4: ASSEMBLY WITH SCANNING-TUNNELING OR ATOMIC-FORCE MICROSCOPES

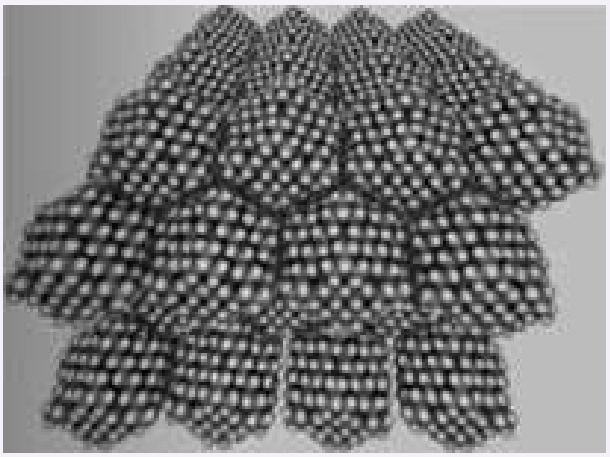
Brenda Rubenstein, Brown University; Eduardo Beltrame, California Institute of Technology; Hein-Pieter van Braam, Ramatak Inc.; Iqbal Utama, Northwestern University; Mark Friedenbach, Machine Phase Systems Inc.; and Philip Moriarty, University of Nottingham

In this proposal, a precise macro-scale actuator picks and places building blocks with an atomic-scale tip. The main features of this architecture are ways to parallelize tips and determining that a block has bound to the structure being constructed.

As discussed in the 2015 DOE Workshop, it is not necessary to massively parallelize the STM tips for STM positional assembly to be effective. Instead, STM positional assembly can synthesize a few productive nanomachines that can manufacture other nanomachines at higher production rates than possible with STM positional assembly.

The technology can be bootstrapped in this way, with productive nanosystems of increasing capability and speed of operation.

This proposal uses the tip to positionally assemble molecular blocks that can self-assemble, namely van der Waals blocks which have flat faces that interact. An example is the construction of atomically precise shell structures [Fisher et al. 2017]. The following image shows an assembly of such blocks, from an Illustration of a block colliding with an assembly of blocks at several speeds: Philip Turner, www.youtube.com/watch?v=OlqFjZAXiYY



A wide variety of shapes could be constructed out of smaller self assembling parts [Damasceno et al. 2012].

Positional control is crucial for this process since van der Waals interactions between blocks is not specific. Thus, attempting to self-assemble the blocks in solution would result in a wide variety of structures, not just the desired one. Using non-specific interactions simplifies the design of the blocks compared to proposals requiring specific interactions between blocks.

Background articles on this approach include:

- Figures demonstrating this approach, the attachment and activation of feedstock molecules to a gold surface, use of these molecules to perform manipulation of the gold-plated AFM tip [Bothra et al. 2023]
- Synthesis and deposition of feedstock molecules to a gold plated surface, and identification from STM imagery [Katano et al. 2013]
- Atomic precision SPM techniques have advanced significantly since this idea was first proposed, e.g., with the development of the qPlus sensor [Giessibl 2019] • Cryogenic temperatures are needed to achieve sufficient resolution for species and structure identification [Yesilpinar et al. 2020]
- Species identification of feedstock molecules would be similar to the method of [Ebeling 2018].

Applications for these structures include molecular machines and quantum computers.

The main challenge for this approach is the design and self-assembly of the molecular building blocks. The blocks could resemble traditional mechanical pieces, e.g. rods with grooves, with flat faces that allow van der Waals bonding to other parts. It is also necessary to have a way to remove synthesized blocks from the construction surface so the probe can pick them up and place them at precise locations. Pulling a block off the surface may break the block, so it no longer has a flat face required to bind with other blocks. One option is to build the blocks on a surface consisting of different atoms which have weaker bonds to the block's atoms than those atoms have to others within the block.

The van der waals mechanical interfaces assembly described here make it feasible to define a path toward large-scale atomically-precise structures and steps needed to achieve a specific complex assembly that could serve as a unifying goal for demonstrating the potential of molecular manufacturing.

Next steps:

- Using experiments and simulations, identify size and shape of block faces that give desired binding with other blocks and with tunable strength
- Molecular dynamics simulations of van der Waals interactions with various geometries, to create a toolbox and best practices for making joins and bearing interfaces between molecular parts.
- Create a library of van der Waals blocks

Open questions:

- Are all the blocks the same? At least on the outside where they have a flat surface? So there's no need for an adapter to connect them to the probe (as needed with Architecture 1, Molecular Printer)?
- How to ensure that the blocks attach more strongly to the large flat surface of other blocks than they do to the probe, so the blocks stay on the structure when the probe moves away. Is this simply because blocks have larger flat surface area than the probe?
- How are the mentioned main features of the architecture implemented: "determining that a block has bound" (so the probe can be pulled away to get the next block) and "ways to parallelize tips"?
- The paragraph discussing the 2015 DOE Workshop notes it is not necessary to parallelize the tip and instead can make nanomachines that make other nanomachines? Is this part of the proposal or a note that parallelism isn't necessary? Even though a main feature of this proposal are 'ways to parallelize tips".
- The section "Structures to build with Architecture 4" describes building structures with a dopant atom placed at every 3rd location. Since the proposal involves positioning nanometer-size blocks with van der Waals interactions, not individual atoms, how would it make structures with such precise atomic placement? Is the idea that the chemically synthesized molecular building blocks would have such atomic precision, and the probe would place many of them in a structure, thereby creating a structure with a docent atom at every 3rd location. If so, the precision of atomic placement would be due to the synthesis of the building blocks; the positioning would ensure that precise placement extends over larger distances than possible to create without positional control of the blocks.

Structures to build with Architecture 4

Construct more complex structures with these blocks than possible via self-assembly, such as a large two-atom heterosystem (e.g., containing hundreds of atoms) that cannot be made with chemical synthesis. For example, build a structure out of one type of atom and place a dopant atom at every 3rd location. Such atomically precise structures may have applications to quantum computers.

ARCHITECTURE 5: ASSEMBLY OF HETEROGENEOUS PROTEIN COMPLEXES TEMPLATED BY A CONTROLLABLE DNA BACKBONE

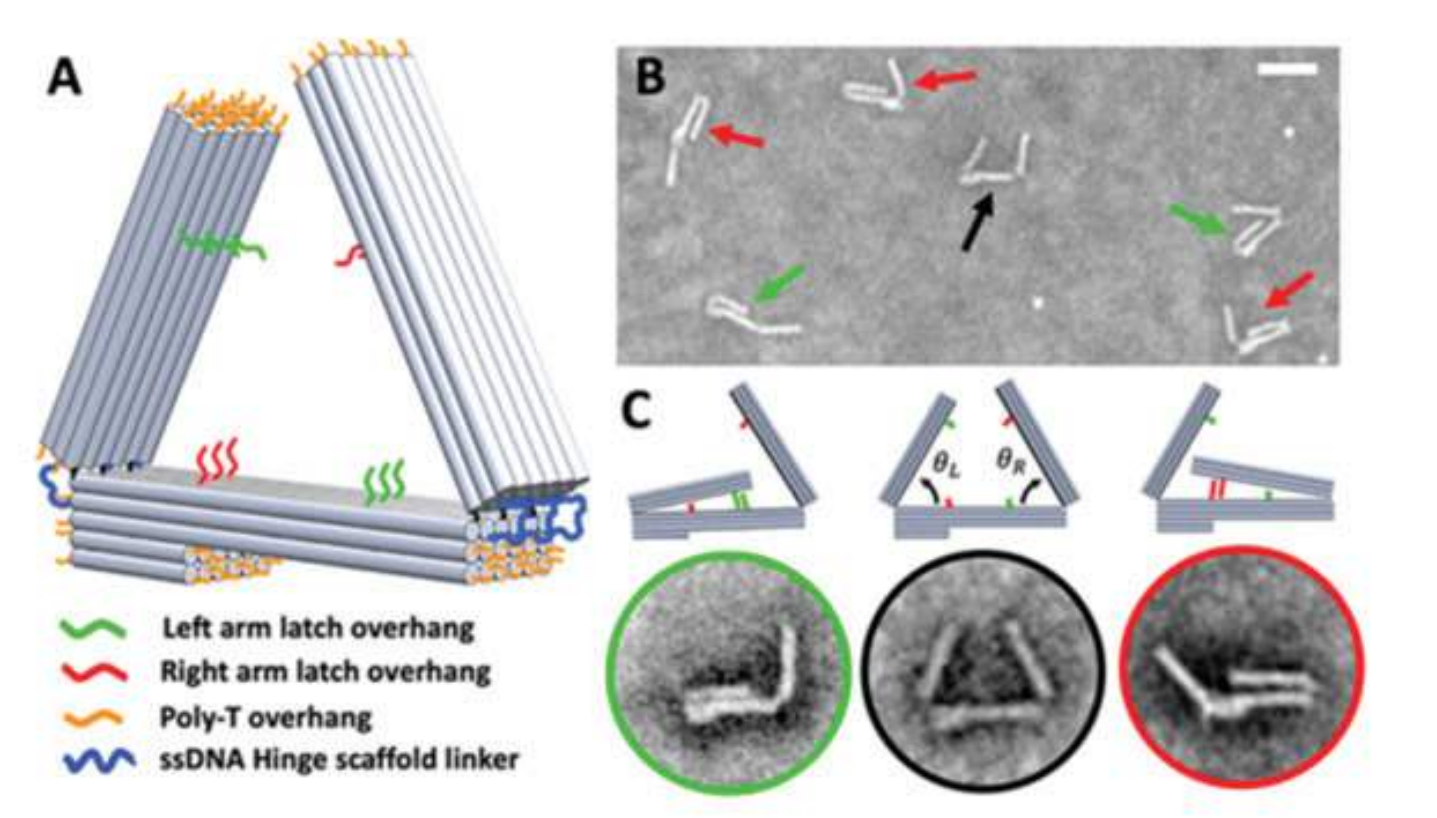
Alexis Courbet, Baker Lab; Carlos Castro, Ohio State University; Erik Benson, University of Oxford; Haichao Wu, Harvard University; Jim Seale, Northwestern University; Julian Englert, Adaptyv Bio; Ted Kaehler, Institute for Molecular Manufacturing; and Petr Šulc, Arizona State University

It is currently extremely difficult to assemble heterogeneous protein complexes. To address this challenge, this architecture achieves precise assembly using backbone chains of rigid segments with programmable joint angles and attachment sites. Molecular blocks (such as proteins) in solution attach to the chain at their corresponding sites. Once these blocks are attached, activating the hinge joints brings the blocks together so they bond. This provides positional control of how the blocks link together.

The molecular blocks and the backbone chain can be freely diffusing and self-assemble in solution. Alternatively, the chain can be attached to a solid support (such as a magnetic bead or mica surface using biotin), and the building blocks can be either added and flushed sequentially, using microfluidics, or all at once.

This approach leverages the well-established technology of reconfigurable DNA origami [Wang Y et al., 2023] to use DNA to assemble structures [Aldaye et al., 2008]. This technology can construct chains of segments that can bend in one or more directions with large ranges of motion, up to about 180 degrees. Bends can be out-of-plane allowing the segments to fold into a 3D structure. There are known ways to actuate these chains. The most robust and addressable approach is DNA binding and strand displacement. This allows specific actuation of individual joints and actuation strands could be added in sequence to control the order of assembly.

This figure from [Wang Y et. al. 2023] shows hinge joints between three segments of 18-helix bundles (3x6) of DNA origami.

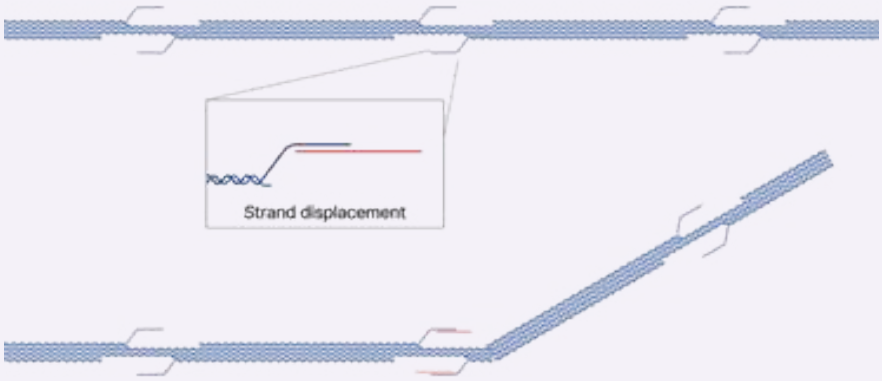


It is simpler to design a single large protein instead of a complex of proteins. At about 1500 amino acids, yield begins to drop, and complexes are the way to make larger structures [Wicky et. al. 2022]. This approach intends to overcome the 1500 reside limit and allow the assembly of large protein structures.

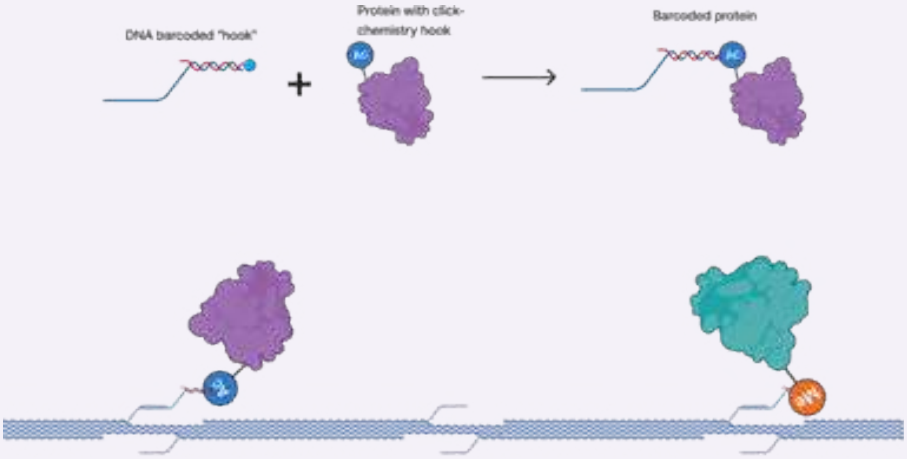
Protein conjugation methods to attach proteins to DNA origami are well-established. One example is click chemistry to attach a DNA to a protein (e.g. [Xu et al., 2019]). The protein can then be attached to specific sites on an DNA origami chain through sequence-specific base pairing.

The following figures illustrate the steps of this manufacturing process.

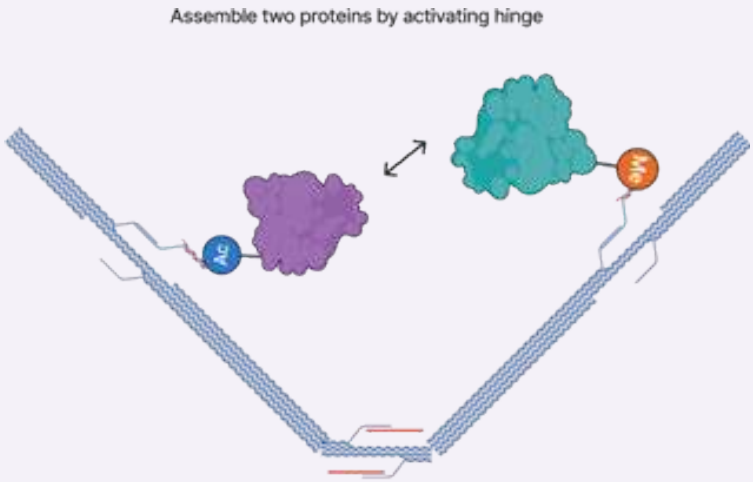
First, build programmable joints between rigid DNA bars with addressable control of the angle of each joint:



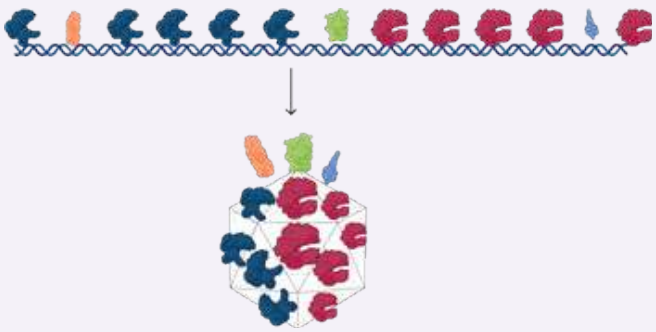
Attach proteins (or other molecular building blocks) to an unfolded DNA backbone chain:

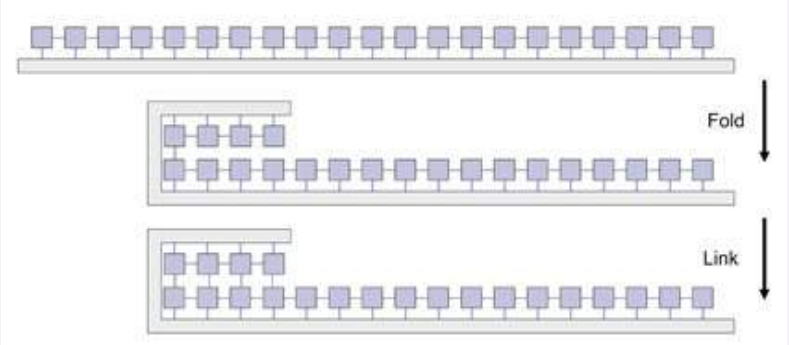


Activate a hinge in the backbone to bring the attached proteins together where they link:



Using a larger number of attached blocks and activating several hinges in the backbone results in more complex structures as shown in the following diagrams:





This approach avoids spurious interactions among the molecular blocks in solution by arranging for them to only become active once bound to the backbone. One way to do this is to use detergents that disrupt protein interface interactions but do not disrupt protein folding or

DNA origami. Then switch buffer conditions once proteins are docked onto the backbone. The designed folding of the backbone ensures that each block only approaches its intended linking partner.

The product formed by the assembled blocks can be released from the backbone by strand displacement, which will remove their attachments from the chain. Alternatively, enzymatic digestion of DNA strands can remove the product. The separation from the remaining building blocks in the solution can be by gel electrophoresis (separation by size). Alternatively the DNA backbone chains can be attached to a surface (e.g. through biotin) and the unattached remaining building blocks can be washed away.

One application of this approach is creating multi-valent therapeutics (e.g. bi- or tri- specific antibodies) due to the ability to precisely control spatial arrangement of the molecular blocks. The spatial arrangement is important for immune activation, in particular breaking symmetry of blocks for antigen presentation. Thus, this architecture could manufacture asymmetric vaccines, which cannot be done with current protein design methods.

The precise positioning allows functionalizing the structure. For example, templating lipids on the outside of the structure to make synthetic organelles or adding molecular motors to provide a transport mechanism. The building blocks are not limited to proteins, and could include, for example, nanoparticles or quantum dots.

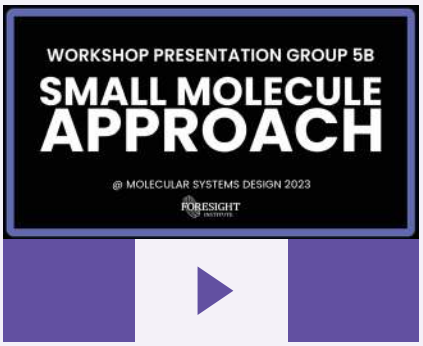
Structures to build with Architecture 5

One way to demonstrate feasibility of this architecture is to make a 5-protein ring complex with a 5-segment DNA origami architecture. This could start with existing proteins and try to put two dissimilar units in specific relative positions. Demonstration of a 3D structure could follow by making some of the joints bend out-of-plane. In the first stage of the project, we would use oxView/oxDNA modeling to test in-silico different DNA origami segment designs and their joint movements via strand displacement. Once we obtain a design that successfully performs in simulation, we will proceed to experiments. After the proof of principle verifications on smaller complexes, we will proceed to larger complexes, such as heterogeneous icosahedral cage, (see image above), with promising application as e.g. vaccine adjuvant or multivalent binder.

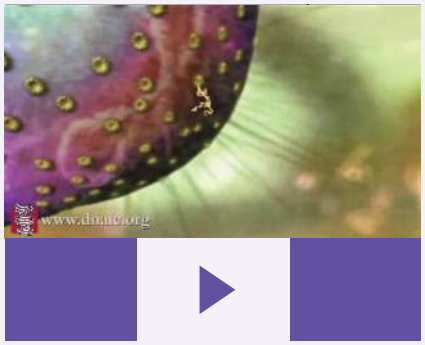
Status

The parts of this technique are all experimentally proven methods. A convincing demonstration of this technique could begin very soon, if funding were available.

ARCHITECTURE 6: AN ARTIFICIAL RIBOSOME



Irene Regeni, Leiden University; Marco Ovalle, Groningen University; Max Ledent, University of Liege; Stefan Borsley, Durham University; and Zoe Ashbridge, University of Amsterdam



As with many aspects of nanotechnology, visions of using molecular-scale machinery for synthesis date back to Feynman's lectures on the topic [Feynman 1960]. Drexler greatly expanded on the premise [Drexler 1990], imagining "nano-factories and assembly lines" and conjuring images of a nano-industrial revolution where molecular robots can assemble molecules one atom at a time regardless of chemical reactivity and thermodynamic preference. There has been a tendency to attempt to realize these ideas by shrinking macroscopic concepts [Ornes 1990].

Proposals for molecular manufacturing [Feynman 1960, Drexler 1990] may hold merit, but they overlook the fully-operational biological example of this technology, namely the inner workings of cells [Nicholson 2019]. In contrast to macroscopic machinery, biomolecular machines use ratchet mechanisms to control stochastic processes, taking advantage of thermal fluctuations rather than attempting to fight against them [Kay et al. 2007].

This serves as the basis of our approach. Rather than attempt to beat fundamental physical forces into submission, we propose instead harnessing them, taking inspiration from biology's most exquisite synthesizing machine: the ribosome [Spirin and Finkelstein 2012]. The ribosome 'reads' information from an input polymer—ribonucleic acid (RNA)—and transcribes it to create peptide sequence polymers with high fidelity. These peptides then fold (often with the assistance of other machines) to give the 3D structures of proteins, which perform myriad cellular functions.

A small molecule approach

When considering the challenge of atomically-precise synthesis, it is important to consider what specifically is envisioned. Feynman's seminal discussions [Feynman 1960] which inspired Drexler [1990] talked about placing individual atoms at will. Self-assembly strategies are remarkably powerful, with DNA origami [Hong et al. 2017] particularly notable for its ability to program complex

structures. However, Feynman's vision was explicitly different from this thermodynamically-driven self-assembly approach. Moreover, given the nanometer scale of the DNA strands, it is hard to argue that such approaches really constitute atomic (Ångstrom) precision.

One could argue (as Feynman himself did [Feynman 1960]) that for the past century, chemistry has provided an approach to such Ångstrom precision, with small molecules routinely designed and reacted in a specific manner. However, this approach is fundamentally limited, and its complexity vastly increases with the size of molecules.

Instead, building complex sequence-determined polymers in one-dimension significantly simplified the problem, with folding allowing access to complex 3D structures. This is the approach taken by biology, and serves the basis of our proposed approach. We consider how an artificial machine capable of sequence-specific synthesis in a manner reminiscent of the ribosome might be developed. We limit ourselves to non-biological building blocks to create something truly artificial, and we will try to enable the synthesis on as small a scale as possible (i.e. minimizing the number of atoms in our building blocks). This will enable the artificial atomically-precise synthesis of programmable polymers. While the task, as a whole, exceeds the current limits of artificial nanotechnology, by considering the individual tasks, we hope to offer some useful guidelines for how this might be achieved.

Fundamental requirements and design criteria

There are several key features which must be considered for the design of an artificial machine capable of performing synthesis in a phenomenologically similar manner to the ribosome:

1. Information is supplied through an information polymer [Rutten et al. 2018]. This instruction strand codes the resultant synthetic product. Crucially, the ribosome is promiscuous, and can 'read' different instruction threads.

   Task 1: Design an information bearing polymer.

2. The information on the polymer must be encoded through an "alphabet" of information bearing units [Lutz 2015]. Biology used the four nucleobases, with triplet codons corresponding to specific amino acids [Smith 2000]. Pulling back the complexity would require a more-simple 'alphabet' where one information unit codes for one monomer of the target polymer. The chemistry/interactions must be highly specific and orthogonal to the other chemistries employed in the machine. For simplicity, a binary code might be selected.

   Task 2: Design an "alphabet" to carry instructions for the synthesis.

3. 'Reading' information from a polymer is a huge challenge in its own right. Biology employs a ratchet mechanism to move RNA information thread directionally through the ribosome [Spirin and Finkelstein 2012.]. Artificial systems have employed nanopore sequencing to read DNA sequences [Wang et al. 2021], and recently a small molecule tape-reading ratchet was reported that could read chiral information encoded in an information tape [Ren et al. 2022].

The key consideration of all these systems is the need for directional motion.

Task 3: Design a way to move directionally along a thread.

4. Having 'read' the instruction polymer, transcription to synthesize useful structures requires a way to 'write' the information [Lutz 2015]. Polymer chain extension in a programmable manner is another significant challenge.

   Task 4: Design a way to transcribe information to create atomically-precise sequence-specific polymers.

There are (at least) two further tasks that we have identified that are crucial for atomically precise synthesis of complex 3D structures: error correction and folding. Sequences must be checked and mistakes corrected [Hopfield 1974]. Likewise, proteins often require chaperones to aid folding to give the specific desired structure and function [Saibil 2013]. Even for biology, these tasks are beyond the scope of a single machine. Instead, several other enzymes are involved in these processes. While these two issues are beyond the scope of our discussion here, they are paramount to the success of any atomically precise synthesis.

The design

Task 1: Recently, significant work has been undertaken in the field of creating information polymers. The Hunter group [Núñez-Villanueva and Hunter 2022] have employed hydrogen bonding as well as covalent interactions to create information polymers which can be replicated in a complementary manner through a stepwise process. Backbones for these polymers have been varied and are generally selected due to ease of synthesis. We note that our backbone will also need binding sites to allow the machine to bind to it. The design of the information polymer will thus contain a simple spacer, binding sites, and blocks where the information may be placed.

Task 2: Creating an 'alphabet' for storing information is closely related to **Task 1**. As noted above, the Hunter group has employed hydrogen bonding as well as covalent interactions in this capacity [Núñez-Villanueva and Hunter 2022]. It has also been widely noted that binary information storage significantly simplifies the problem [Cafferty et al. 2019]. Dynamic covalent chemistry provides a potentially very attractive 'alphabet' for information storage. Formation of covalent bonds under reversible thermodynamic control provides a best-of-both-worlds approach [Rowan et al. 2002], allowing the high specificity of covalent interactions (crucial for high-fidelity of information transfer) with the lability of non-covalent interactions (crucial for processing the information efficiently). Moreover, dynamic covalent interactions have been shown to be highly orthogonal [Lascano et al. 2016], allowing the chemistry to be addressed independently (Figure 1.).

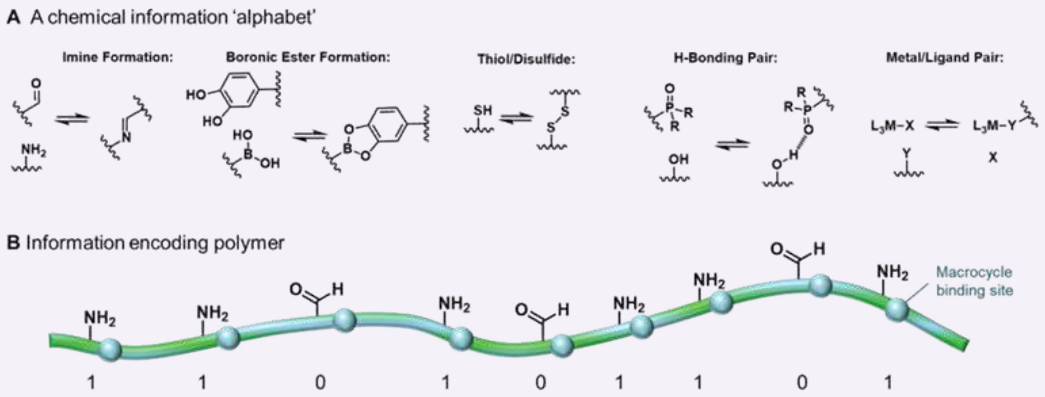


Figure 1. (**A**) A proposed compilation of several highly specific dynamic covalent interactions to be utilized in the 'alphabet' for information storage (Task 2). (**B**) use of two 'letters' from the 'alphabet' enables binary coding of information along an information-bearing polymer.

Task 3: Achieving directional motion is a long-standing challenge in chemistry. However, significant progress has been made in recent years, particularly in the realm of interlocked molecules. Stoddart [Cheng et al. 2015], Leigh [Erbas-Cakmak et al. 2017] and Credi [Baroncini et al. 2012] have all created pumps based on interlocked molecules where macrocycles are threaded directionally onto a thread. Directional movement of these macrocycles can then allow information to be read in a progressive manner [Kay and Leigh 2015]. The interlocked architecture is crucial for ensuring processivity, and indeed it should be noted that the ribosome functionally forms an interlocked structure to read RNA polymers. A number of mechanisms to control directional movement of macrocycles have been developed, harnessing oscillations in electrochemical potential or pH to affect the movement in a stepwise manner through an energy ratchet mechanism, or perhaps more attractively harnessing energy from catalysis to drive autonomous motion through an information ratchet mechanism [Armano et al. 2012]. Any of these approaches might be amenable to information reading in this present system. Notably, the 'writing' in **Task 4** will require an element of catalysis, so it would be elegant to use the same catalysis to 'write' the information and provide the energy to drive directional motion.

Task 4: 'Writing' information through programmable polymer chain extension is perhaps the most difficult element. While some progress has been made, e.g., native chemical ligation to transfer a sequence from a thread to an information polymer [Lewandowski et al. 2013], such an approach is unlikely to be directly translated to the more advanced machine discussed here. Instead, examining robust living polymerisation reactions is attractive. We have particularly identified ring opening metathesis polymerisation as a potentially suitable target [Gutekunst and Hawker 2015]. This is highly orthogonal to the other chemistries discussed, and can be controlled through a ruthenium catalyst.

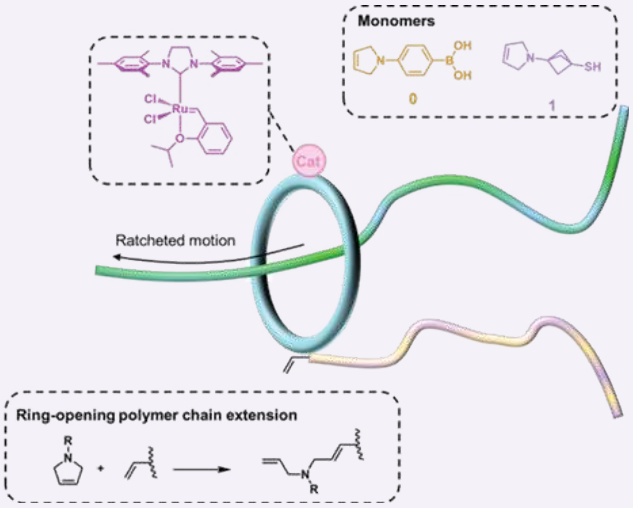


Figure 2. Task 3 and 4 might be performed by the same catalyst. Ring opening polymer chain extension via alkene metathesis is catalyzed by a Hoveyda–Grubbs Gen II catalyst. This extends the growing polymer and the energy release from this reaction can be harnessed to drive directional ratcheted motion of the information polymer.

Considering the design aspects discussed, we envisage a machine to operate roughly as described below (Figure 3.). An information polymer will contain macrocycle binding sites (such as ammoniums), spacers and the information. The binary 'alphabet' will leverage orthogonal boronic ester and hydrazone formation, with the information polymer bearing aldehyde and boronic acid 'letters' to code for the sequence information. The machine will be based on a macrocycle (e.g., crown ether, which will bind to the ammoniums on the information polymer). The macrocycle will contain catechol and hydrazide binding sites, to bind to the information polymer to 'read' the information. The building blocks for the resultant sequence specific polymer will selectively bind next to either of these reading units. Upon 'reading' the polymer thread (forming a hydrazone or boronic ester) stereoelectronic changes will activate the monomers to alkene metathesis reaction which will be catalyzed by a ruthenium catalyst bound to the macrocycle. This ring opening alkene metathesis reaction will extend the growing sequence-defined polymer and also provide the energy release to ratchet the machine along the polymer to read the next information site.

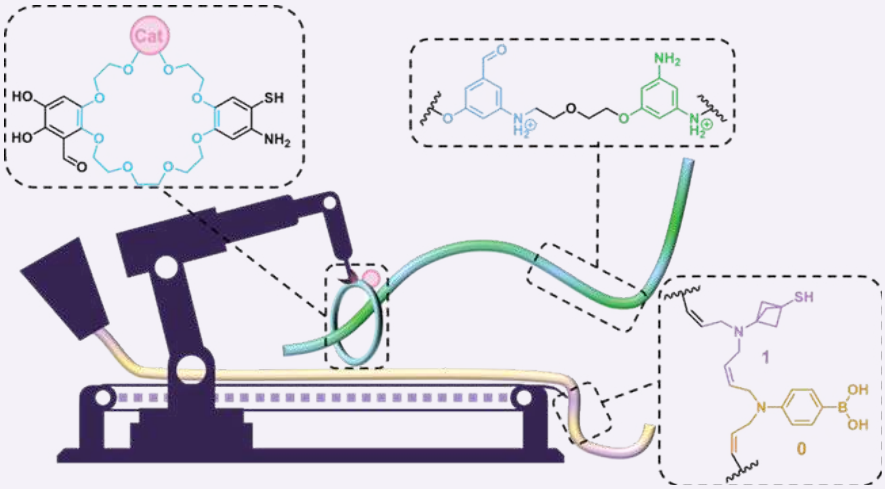


Figure 3. A proposed small molecule information polymer. A crown ether macrocycle (pale blue) is appended with a ruthenium catalyst (pink) and 'reading' sites. The information polymer (blue and green) contains the 'letters' to be read by the macrocycle. The sequence polymer (pink and gold) will grow as more information is 'written'.

Status and outlook

The full design proposed here is highly speculative, to the extent that the design cannot possibly work. However, the purpose of this design and discussion is to highlight the individual challenges and provide broad brush potential ways in which they might be tackled. At the current stage, each individual task still presents a substantial challenge in its own right. Nonetheless, there are a number of exciting rapid advances feeding into these individual tasks. Information polymers have now been designed, replicated and read [Núñez-Villanueva and Hunter 2022]. The kinetics of polymerisation reactions can increasingly be controlled [Gutekunst and Hawker 2015], and processive action of a catalyst on a polymer substrate has been demonstrated [Thordarson et al. 2003]. The understanding of how to control directional motion through ratchet mechanisms is rapidly developing [Kay et al. 2007], and ratchets have even been employed for information reading [Ren et al. 2022]. Determining how multiple elements of these different systems can perform all together remains a significant challenge, though as evidenced through rapid advances in the field of systems chemistry interfacing multiple components and competing reactivities presents a wealth of opportunities [Otto 2022]. Ultimately, it seems likely that within the next 30 years the development of a system that mimics some of the basic function of a ribosome will be within the grasp of artificial nanotechnology. Feynman noted of biology, "*they [biological machines] manufacture various substances; they walk around; they wiggle; and they do all kinds of marvelous things*" [Feynman 1960]. An artificial system truly capable of mimicking a ribosome would achieve all of this

Molecular Machine Design Software

The manufacturing architectures described at the workshop require designing the molecular building blocks, paths for their synthesis, and the steps for positional assembly of those blocks into final structures. Such designs could allow applying these architectures to manufacture new atomically-precise structures beyond currently demonstrated structures made by self assembly in solution.

The workshop included discussions of several molecular design tools. These tools could simplify the design process, particularly for users who are not experts in synthetic chemistry or molecular dynamics. The integration of large language models, such as ChatGPT, could further simplify the use of such software by allowing users to request operations in natural language rather than having to learn the underlying programming language.

These software tools are:

- CANDO [Shafmeister 2016] designs spiroligomers with specific bindings, which could be used as the building blocks for molecular printing (architecture 1).
- SAMSON [https://www.samson-connect.net/] provides visualization, animation, simulation, and construction of complex molecules. It includes a voice interface to a large language model which allows users to request operations on the molecules.
- OXDNA [https://oxdna.org /] and oxView [https://oxview.org]]designs DNA-based structures, such as used for the molecular breadboard (architecture 2) and foldable chains for meta protein assembly (architecture 5A). This software has a community of designers who provide examples [https://nanobase.org].
- MSEP, a molecular design tool intended to encourage broad participation by citizen engineers to explore, design and simulate complex molecular designs. This could allow a large community to contribute to a library of validated components for molecular machines, so other users can build on these components without each user having to separately run time-consuming simulations to evaluate component behavior.

Simulation is an important tool to check that designs have desired properties. The behavior of molecular machines typically involves longer time scales than directly accessible with molecular dynamics, leading to approaches to extend to longer times [Singharoy and Chipot 2017]

Introductory Keynotes

Introduction to the Workshop

ALLISON DUETTMANN, FORESIGHT INSTITUTE

Duettmann presents the annual Molecular Systems Design Workshop organized by Foresight Institute. Founded in 1986, Foresight Institute champions groundbreaking science and technology with transformative potential. Duettmann covers the upcoming workshop, discussing the main topics– which range from Molecular Machines to AI. She notes that the 2023 event is structured via keynote presentations on advanced technologies, followed by collaborative project discussions.

Introduction to the Workshop Presentations

BENJAMIN REINHARDT & ADAM MARBLESTONE

This talk explains the workshop's focus on architectures for systems capable of specifying molecular bonds. This includes presentations on current advancements, and their alignment with these architectures. Day one of the workshop covers potential architecture components, exploring their constraints and viability. The following day offers an in-depth look at specific architectures, mapping out their realization. A prominent theme is designing tools for large-scale, precise molecular bonding, especially the artificial ribosome concept and its potential for 2D or 3D assemblies.

Molecular 3D Printing Architectures

ADAM MARBLESTONE, CONVERGENT RESEARCH

Marblestone delves into molecular 3D printing, aiming to craft printers proficient at binding individual molecules. He stresses the need for clarity on chemistry challenges and potential designs. An intriguing highlight is the idea of an artificial ribosome for molecular bonding. He also shares his vision of programmable molecular machines that can form precise covalent bonds, and considers expanding this to 2D or 3D assemblies. Several potential architectures, such as breadboards, solid phase synthesis, and the use of DNA origami for positioning, are presented. Throughout, Marblestone encourages collaborative discussions to navigate challenges and foster innovation.

Computational Design of Self-Assembling Protein Nanomachines

ALEXIS COURBET, BAKER LAB

Courbet examines the power of computing in manipulating protein folding, shifting from sequences to intricate structures. He accentuates the impact of computational methods in identifying sequences for desired shapes, noting that machine-learning advancements have enhanced this process. With the evolution of AI, he sees potential in tailoring specific backbone structures and harnessing reinforcement learning for optimal solutions. This technological advancement, paired with diffusion models, may enable atomic-scale design. Courbet imagines a future where advanced protein machines are expertly designed, starting simply but evolving into complex entities with features such as light or chemical activation. To ensure their efficacy, he recommends computational studies of molecular physics and acknowledges current biophysical measurement constraints in evaluating nanoscale machine performance.

Programing Mechanical Function of DNA Origami

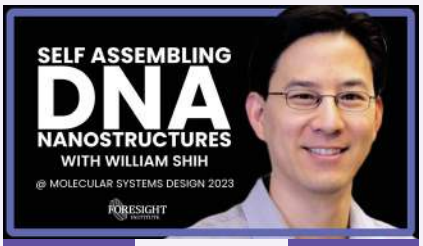
CARLOS E. CASTRO, OHIO STATE UNIVERSITY

Castro delves into the mechanics of DNA origami programing, showcasing its potential in nanorobotics, biomedical devices, and unique biological tools. He presents a technique using DNA origami to interact with biomolecules, merging rigid and flexible domains to guide structure movement. He notes how recent studies have enabled the adjustment of DNA origami's mechanical properties, resulting in tools exerting distinct forces on molecules. This innovation provides insights into chromatin decompaction. Castro envisions coordinated systems from dynamic devices, bolstered by efforts to create assemblies with precise mechanical properties

CANDO & Programmable Spiroligomers

CHRIS SCHAFMEISTER, TEMPLE UNIVERSITY

Schafmeister sheds light on spiroligomers– unnatural building blocks forming rigid segments about two nanometers long. Their primary use is for protein binding and diagnostic device development. Supported by the US Department of Defense, a vast collection of spiroligomer molecules have been synthesized, showing potential in catalysis and molecular separation. Software predicting spiroligomers' 3D configurations aids design. Current work aims at automated assembly for larger, more intricately structured molecules. Schafmeister stresses that continued research depends on acquiring further funding and resources.



Self-Assembling DNA Nanostructures

WILLIAM SHIH, HARVARD UNIVERSITY

Shih delves into self-assembling DNA nanostructures, aiming to craft structures beyond DNA origami scaffolds. He touches on applications such as flexible robots and ultra-sensitive, enzyme-free diagnostic tools. The crisscross polymerization technique stands out, requiring building blocks primed for assembly, and a seed to initiate. Building blocks use DNA origami slats with specialized adhesives, and seed-directed assembly ensures structure formation. Electron micrographs confirm structures nearing a micrometer. Additionally, Shih notes how the technique has shown potential in diagnostic signal amplification and implosion. Using single-stranded building blocks with a seed and a strand displacement strategy suggests exponential growth, heralding potential breakthroughs in enzyme-free, ultra-sensitive detection, especially beneficial for under-resourced regions.

Making a Protein Printer That Turns Bits Into Molecules

JULIAN ENGLERT

Englert presents insights from Adaptive Bio, a company dedicated to streamlining protein engineering. The firm aspires to establish a comprehensive protein engineering foundry, seamlessly merging synthetic biology, DNA design, protein synthesis, and continuous evaluation. A salient challenge Englert highlights is the prohibitive cost of DNA synthesis. To counteract this, the idea of a protein printer is introduced. This printer is conceived to directly encode amino acids' functionality, eliminating the dependence on DNA. By utilizing encoding agents and a codon-selection rotary dial, this concept aims to revolutionize the efficiency and affordability of protein engineering. The pursuit of refining and realizing this notion remains an ongoing effort for the company.

MEMS STM Platform

REZA MOHEIMANI, UT DALLAS

Moheimani emphasizes the potential of MEMS technology to enhance scanning-tunneling microscope (STM) devices. STM, characterized by its metallic probe that images surfaces through tunneling electrons, offers insights into the electronic properties of surfaces. A notable application of STM, as discussed, is lithography on hydrogen-passivated silicon surfaces, pivotal for crafting silicon quantum devices. By integrating MEMS technology, the objective is to increase STM's efficiency– resulting in compact, swift, and more precise instruments. Moheimani showcases various designs of MEMS-integrated STM devices, distinguishing between platinum and silicon-tipped variants. Importantly, these advanced STMs retain the functionality of their traditional counterparts, evident in their imaging and lithography capabilities. Addressing the challenge of post-processing the tips, Moheimani suggests an innovative design solution. Collaborative efforts aiming to achieve a two-degree-of-freedom movement for these devices are also highlighted. Moheimani concludes by highlighting the potential of MEMS-based STM devices in atomic force microscopy under ultra-high vacuum conditions.

Adding a Dimension to Atom-by-Atom Assembly

PHILIP MORIARTY, UNIVERSITY OF NOTTINGHAM

Moriarty delves into the intricacies of atom-by-atom assembly, leveraging tools such as scanning probe microscopy (SPM) and atomic force microscopy (AFM). A significant impediment to achieving precise, single-atom resolution, stems from the microscope's tip, particularly in regulating electronic orbital density. Despite this, Moriarty notes that strides have been made in crafting diverse structures– notable examples being graphene-like lattices and artificial atoms. The overarching aspiration is to facilitate computer-directed chemistry on this granular atomic level, however, constructing 3D structures remains elusive. Techniques like SPM and QPlus AFM, employed under ultra-high vacuum and frigid conditions, allow meticulous examination of atomic and submolecular entities. Given the microscope tip's important role in both imaging and atom manipulation, even minute alterations in its configuration can produce profound effects. Moriarty concludes with the visionary aim of conceptualizing a self-rejuvenating tip to increase the precision and efficacy of atom-by-atom assemblies.

The Surface Chemistry Bottleneck

ADAM BRAUNSCHWEIG, CUNY ADVANCED SCIENCE RESEARCH CENTER

Braunschweig discusses the complexities of precisely constructing organic systems on surfaces. He introduces the innovative hypersurface printer, a machine engineered to address the current limitations of the field. This printer employs a microfluidic system, directing various reaction mixtures into a designated fluid chamber. Uniquely, the reactions are instigated only upon illumination of specific areas, ensuring precise bond formation. The precision in light delivery is managed by a digital micromirror device, mandating that the selected chemistry is inherently photodriven. Demonstrating the machine's potential, Braunschweig showcases a six-dimensional hypersurface embedded with two concealed images, achieved via grafted surface polymerization. This intricate procedure entails the growth of polymers from surfaces, synchronized with specific ink delivery and light exposure. He notes that a pattern of such complexity is created within approximately 15 minutes. The hypersurface printer boasts a remarkable pixel resolution, reaching two microns in both X and Y dimensions, with certain iterations attaining feature sizes as minute as 50 nanometers. Braunschweig underscores that the surface reactions explored aim to erect structures from surfaces, distinctly differentiating them from catalytic reactions.

Placing Molecular Pumps on Polymeric Micelles

JAMES SEALE, NORTHWESTERN UNIVERSITY

Seale outlines the concept of molecular machines, underscoring their hallmark feature of unidirectional motion. Specifically, molecular pumps exemplify this motion, facilitating the movement of a ring along a thread molecule. Whilst enzymes and molecular switches possess dynamic qualities, they may not squarely fit within the molecular machine classification. Seale notes that the molecular pump's functionality is the creation of a steadfast molecule accompanied by a threaded ring. Such pumps hold promise in fabricating polymer threads adorned with multiple rings. By harnessing reprogrammable tools, stable intertwinements between the rings and threads could be achieved. An electrochemical framework is viable for executing redox cycles, thereby pumping rings onto polymer chains. Notably, Seale indicates the potential to affix molecular pumps to micelles, drawing parallels with transmembrane ion pumps.

User-friendly Molecular System Design

HEIN-PIETER VAN BRAAMM, RAMATAK INC

Van Braamm introduces the MAP1 project, which aims to develop state-of-the-art open-source tools for the nanotechnology community. The ambition of MAP1 is to provide a user-friendly platform which facilitates the exchange of code and collaborative work, therefore advancing the field of molecular system design. MAP1 seeks to address the issue of accessibility of scientific tools, and broadly aims to empower a wider range of users, or "citizen engineers" by making scientific instruments universally accessible. This project also plans to incorporate scientific tools into a game content, using them as part of the scoring system. Going forward, MAP1 aims to establish a new standard for precision at the atomic scale in engineering, and to create a repository of designs that can be utilized by the community. Van Braaam highlights that feedback from professionals familiar with existing tools is sought to refine MAP1. The launch of MAP1 on GitHub is awaited and will occur once the plugin interface is fully developed. This talk ends via a discussion of the unique aspect of MAP1, which is its ability to demonstrate the differences between molecular and macroscopic machines through detailed simulations and characterizations, enhancing the user's understanding of these complex systems.

Multiscale Modeling for Nanostructure Design

PETR ŠULC, ARIZONA STATE UNIVERSITY

Šulc highlights the importance of computer modeling in designing advanced DNA, RNA, and protein-DNA hybrid nanostructures. Through simulations, his team both discerns and creates complex nano-devices. Addressing simulation challenges, they introduce the "oxdna" model, notable for its representation of the strand displacement process. Šulc discusses that accompanying this model is an ecosystem facilitating experiment; including tools for design, and a server for sharing and characterizing nano-designs in the broader community.

SAMSON Computational Nanoscience

STEPHANE REDON, NANO-D

Redon provides insights into the SAMSON Computational Nanoscience platform, a comprehensive tool designed for global nanotechnology research. Developed in 2015 and later transitioning into a company in 2018, SAMSON offers functionalities such as interactive physics, assembling, measuring, and communication. Users can enhance its capabilities with extensions available on SAMSON Connect. Redon emphasizes recent updates, which include an integrated Blender renderer, an embedded Python interpreter, and the introduction of SAMSON AI for document processing and user inquiries. He notes that the vision for SAMSON is ongoing enhancement via collaboration with its user community.

Quantum Accuracy at Human Speed

BORIS FAIN, STANFORD UNIVERSITY

Fain focuses on the advancements in quantum accuracy in molecular simulations, emphasizing the transformative potential in fields such as drug discovery and materials science. His core aspiration is to seamlessly integrate molecular simulation into broader scientific methodology. Recognizing the prevailing limitations in molecular simulation predictions, Fain underscores the importance of accurate force fields and the prediction of protein binding and solvation energies. Addressing these challenges, the aim is to pioneer models anchored in quantum mechanics, developing a polarizable force field that precisely captures polarization. This innovation would enable the prediction of compound behaviors in diverse solvents without empirical interventions. Further harnessing machine learning techniques with traditional formulas, Fain's team has secured precise predictions in various contexts, including salt dissolution, water pH, and protein binding.

Protein Binding Simulations with Pathways and Kinetics

LILIAN CHONG, UNIVERSITY OF PITTSBURGH

Chong highlights the significance of advanced protein binding simulations in explaining functional transitions in biological systems. Traditional methods often fall short in capturing rapid processes, such as protein folding. However, Weighted Ensemble Molecular Dynamics emerges as a solution. By segmenting progress and running concurrent simulations, Ching notes that it delivers unbiased pathways with enhanced efficiency and compatibility across different scales. This approach has proven successful in refining kinetics and protein-protein binding simulations, adeptly identifying pivotal residues and rate-determining stages. In conclusion, Chong emphasizes the game-changing potential of these refined simulation techniques in understanding biological complexities.

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