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Integrated nanosystems for directed assembly of diverse atomically precise building blocks

═ Molecular Additive Manufacturing ═

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Integrated Nanosystems for Atomically Precise Manufacturing (INFAPM) Workshop
Advanced Manufacturing Office, U.S. DOE
Berkeley, CA, August 5-6, 2015

(revised for workshop report)

Why molecular additive manufacturing?

Positioning mechanisms can serve as platforms
for an expanding range of chemistries and components

Predictable, programmable, positional control
can enable fast experimental cycle times

Applications will follow from innovative
exploitation of fundamentally new capabilities

Topics

Functional requirements

Structures and stepper motors

Pathways and applications

Summary of general approach

- Build nanoscale devices that control tool motion (like 3D printers)
- Implement site-specific workpiece activation by positioning catalytic tools
- Transport reactive molecular building blocks by solution-phase flow
- Build products through interleaved site activation and building-block addition

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Attractive options:

Apply macromolecular self-assembly to build mechanical systems

— Scale of framework and moving parts ~ 50 – 100 nm
— Scale implies ~1e12 functional devices per mg of components

Drive tool motions using optically-actuated stepper motors

— Photoisomerization modulates periodic potentials (~kT amplitude)
— Motor architectures tolerate stochastic actuation, degradation
— Photoactive components are treated as consumables
— Motors can step at >1e3 Hz

Solving problems by avoiding them

To address the system requirements listed in the workshop invitation:

"Transport individual feedstock molecules to the workspace (actively or passively)"

- *No mechanism required:* Employ bulk solvent flow for long-range transport

"Modify the feedstock (if required) to prepare it for the assembly operation"

- *No mechanism required:* Provide fully-prepared building blocks

"Manipulate or transport the feedstock to the attachment point at a specified atomic position"

- *No mechanism required:* Rely on diffusion for local transport
- ***Specify positions by activating selected reaction sites****

"Chemically bind the feedstock to a growing structure or device at that attachment point"

- *No mechanism required:* Employ spontaneous binding and chemical reactions

"Repeat the operation a sufficient number of times to synthesize a product with no defects"

- ***Ensure sufficient machine rigidity to constrain thermal fluctuations***
- ***Ensure fast enough reactions to minimize placement failures***

* Site activation is the Zyvex approach to patterned atomic-layer deposition

Atomically precise assembly:
What components and methods do we have today?

Diverse atomically-precise building blocks that include:

- Products of general organic synthesis
- Engineered polyamide structures (proteins, peptoids, spiroligomers)
- Structural DNA components

Diverse methods of self assembly that include:

- Supramolecular assembly of organic molecules
- Protein & foldamer systems inspired by nature
- Nucleic acid complementarity and junctions

BUT current methods face problematic constraints:

- In chemical synthesis, site-specific reaction strategies don't scale
- In self assembly, structures must be encoded in complex components

Positional control of assembly can circumvent these constraints, enabling a fundamental, qualitative advance in atomically precise fabrication

Directing atomically precise assembly:
Structures, steppers, building-blocks, and site activation

Basic system requirements:

- Diverse, compatible, atomically-precise building blocks
- Mechanical systems that select binding sites for blocks
- Low error rates and reasonable cycle times for adding blocks

Potential system implementations:

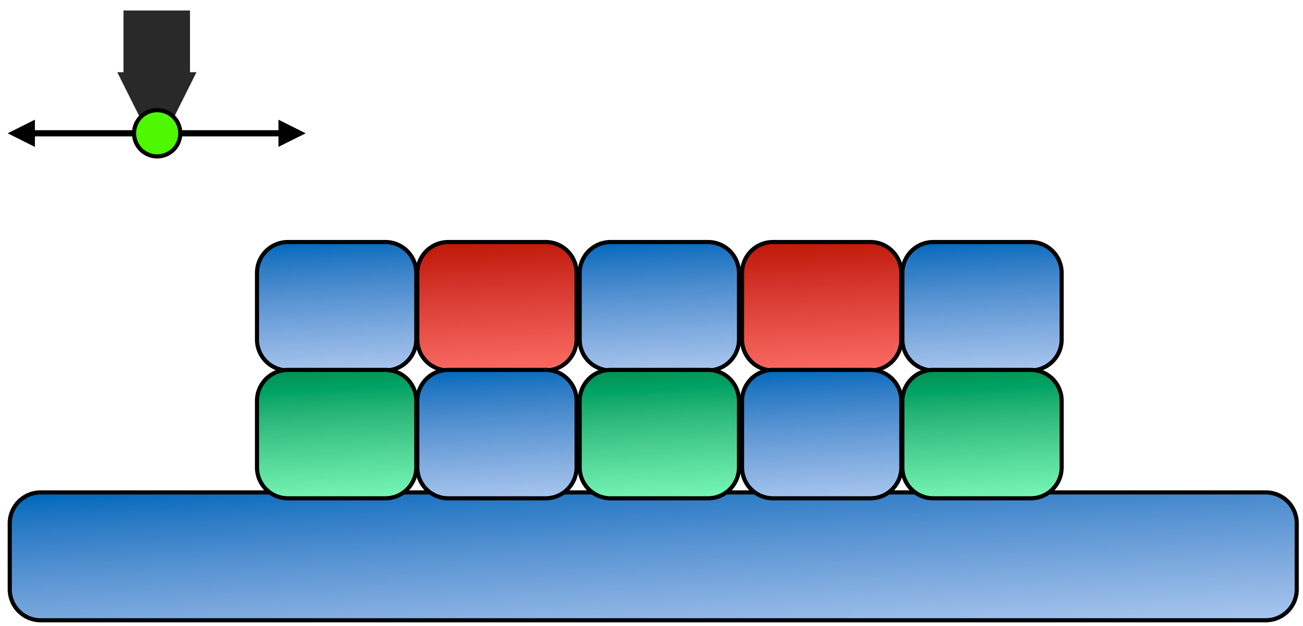
- Self-assembled mechanisms built of macromolecular components
- Solution-phase device operation and building-block transport
- Externally-controlled stepper motors (used in 3D printers)

Potential system characteristics:

- Massive parallelism (100 nm scale ⇒ ~1e15 devices/g)
- High stepper frequencies (>1e3 Hz)
- Moderate interchange frequencies to switch block-types (~0.1 Hz?)
- Macroscale production (grams per gram per day?)

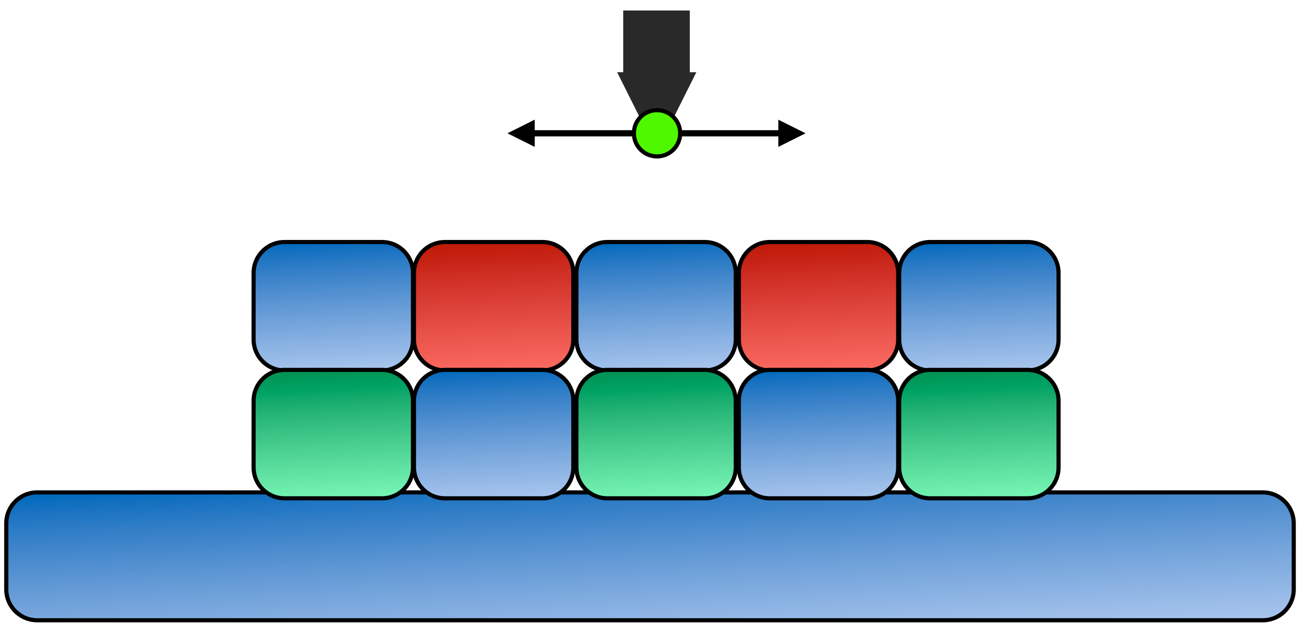
Block-addition cycles with directed activation:

Site-specific operations determine product structure



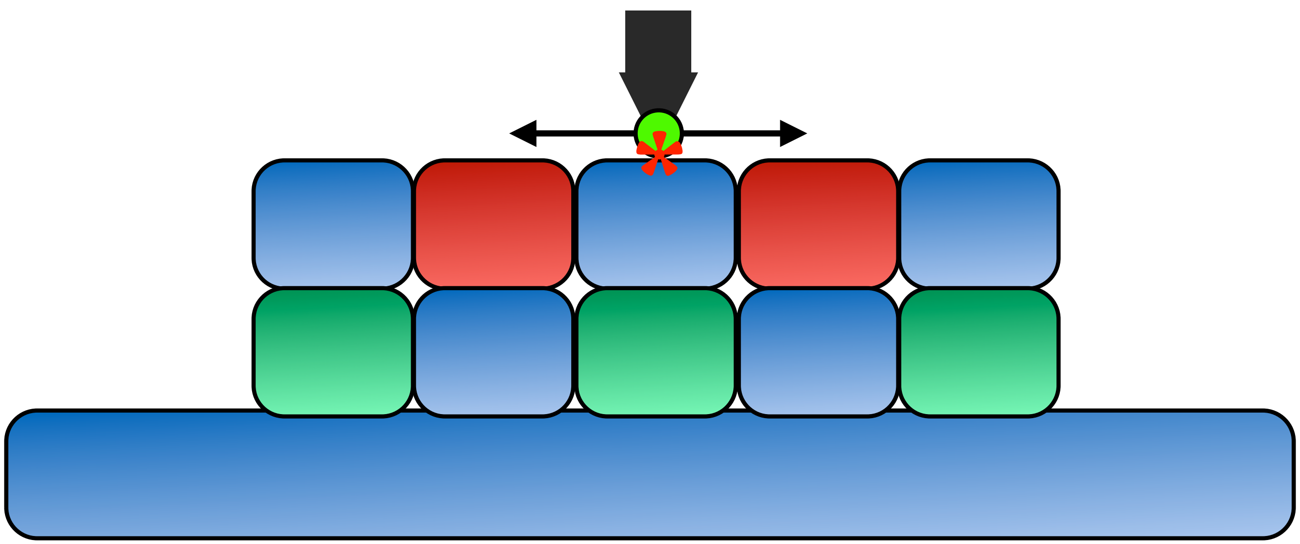
Block-addition cycles with directed activation:
Site-specific operations determine product structure

- ***Position site-activating tool***



Block-addition cycles with directed activation:
Site-specific operations determine product structure

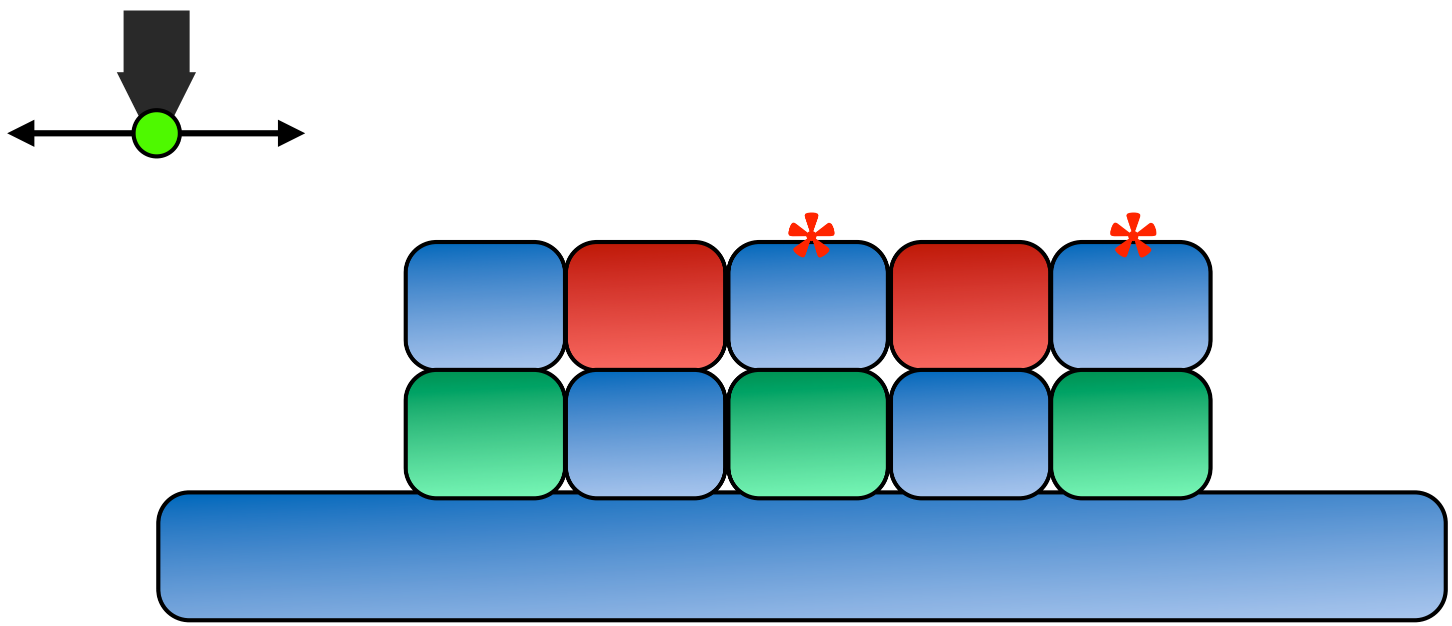
- *Position site-activating tool*
- *Activate site for a type-1 block*



Block-addition cycles with directed activation:

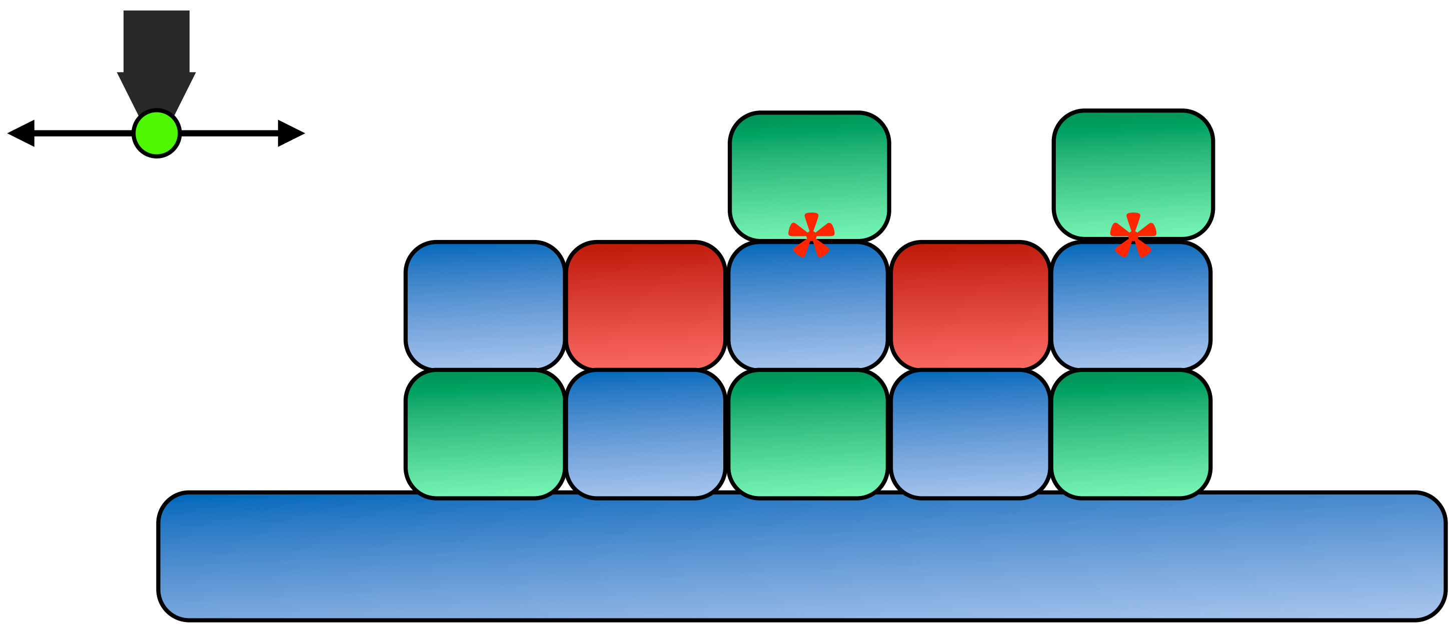
Site-specific operations determine product structure

- *Position site-activating tool*
- *Activate site for a type-1 block*
- *Activate further type-1 sites*



Block-addition cycles with directed activation:
Site-specific operations determine product structure

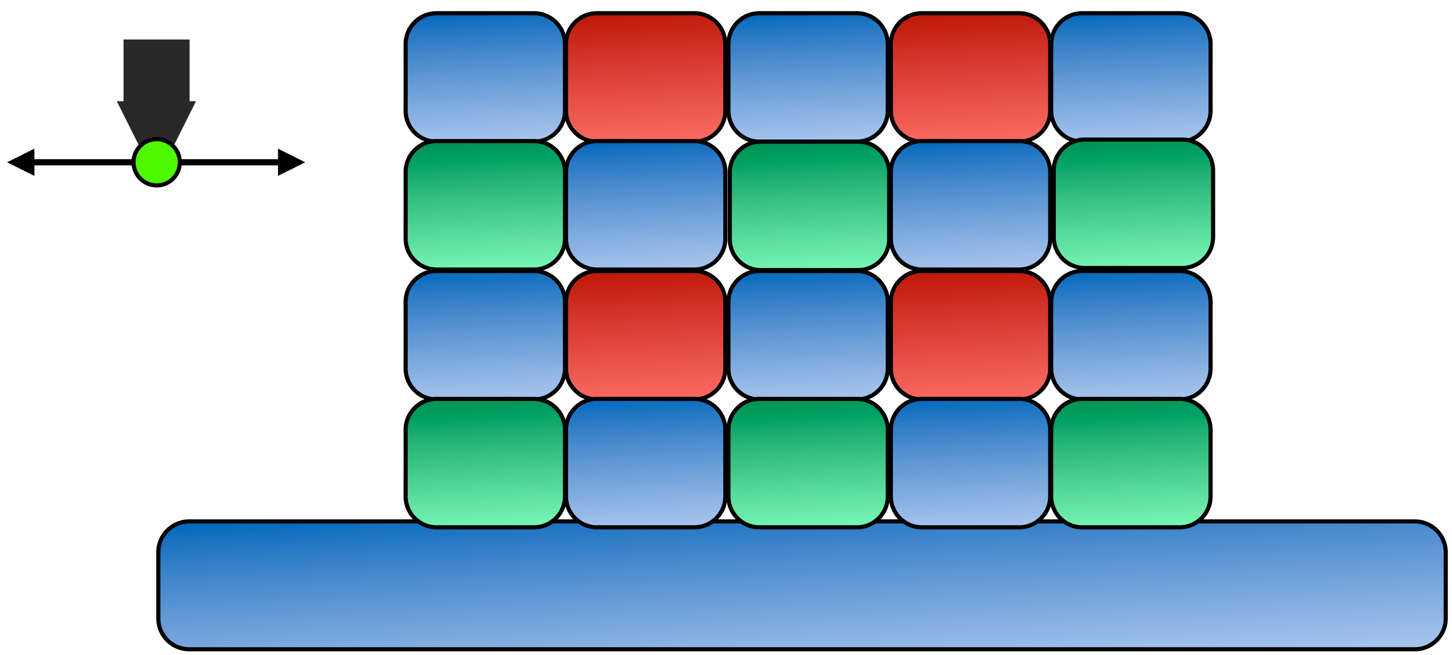
- *Position site-activating tool*
- *Activate site for a type-1 block*
- *Activate further type-1 sites*
- *Introduce, bind type-1 blocks*



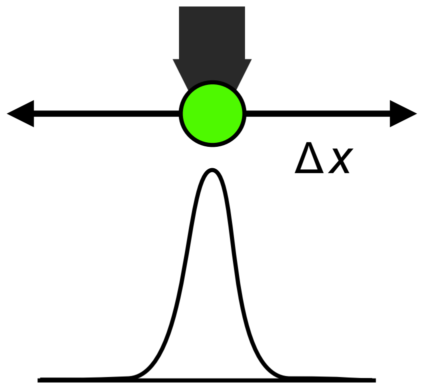
Block-addition cycles with directed activation:
Site-specific operations determine product structure

- *Position site-activating tool*
- *Activate site for a type-1 block*
- *Activate further type-1 sites*
- *Introduce, bind type-1 blocks*

Repeat cycles to add further block types and layers

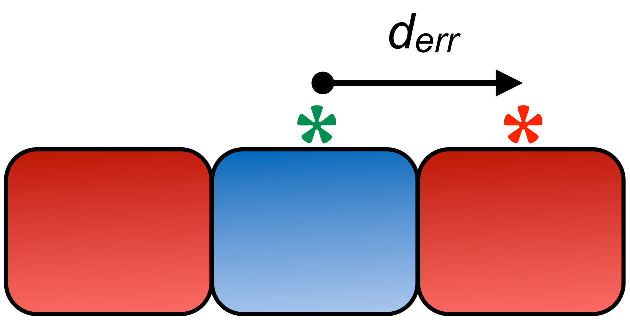


Mechanical stiffness constrains thermal fluctuations



$\sigma_x = \mathrm{sqrt}(kT_B/k_S)$

Linear restoring forces
imply Gaussian distributions of
probability density (effective concentration)



Low error rates require large effective-concentration ratios

For example, may seek:
- On-target failures < 1e-6
- Off-target errors < 1e-6

⇒ concentration ratios > 1e12

$p(X>x) < \frac{1}{2}\exp(-\Delta x^2/2\sigma_x)$
$p(X>8\sigma_x) < 1\text{e-}14$

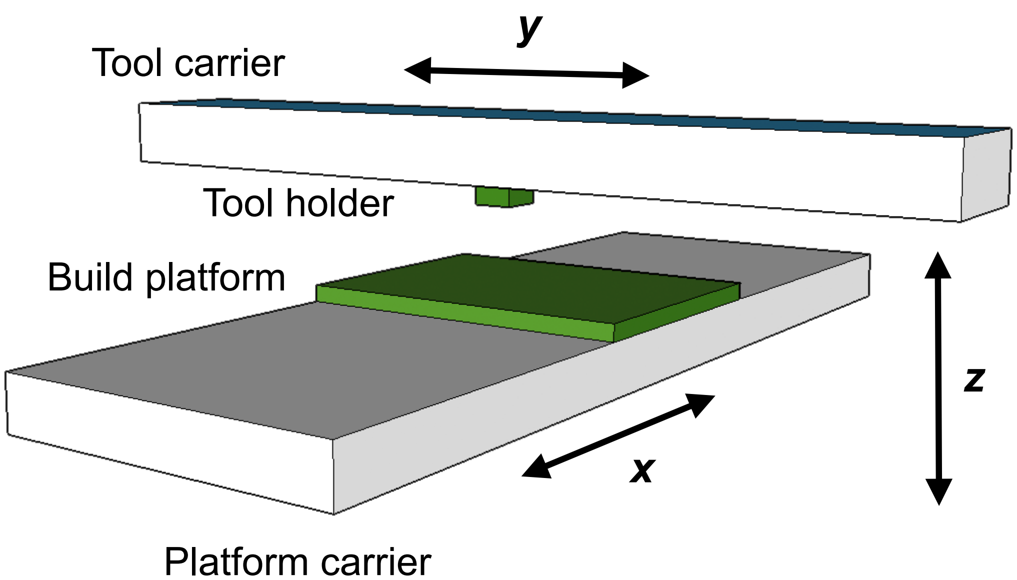
if $d_{err} = 1$ nm $= 8\sigma_x$

require $k_S \approx 0.25$ N/m

Check: $E = \frac{1}{2}\, k_S\, \Delta x^2$
$= 1.25\text{e-}19$ J $> 30\, kT_B$

~ 1 nm site spacing,
~ 0.25 N/m restoring forces,
< 1e-14 placement/failure error rate

Translation along *x, y,* and *z* axes



Nominal scale: ~50–100 nm

Tool carrier (y axis):

- Top surface: *y*-axis motor interface
- Bottom surface: tool-holder interface

Platform carrier (x axis):

- Top surface: build-platform interface
- Bottom surface: *x*-axis motor interface

Outer-frame (z axis) mechanism:

- Two moving components (not shown)
- Complementary *x, y* motor interfaces
- Full *z*-axis motor mechanism

Geometry and scale enable large motor interfaces:

⟹ Numerous actuators (hundreds of photoactive molecules)

⟹ Corrugated potentials, additive energy barriers and restoring forces

⟹ Architecture tolerates stochastic actuator failures and activation cross-talk

Topics

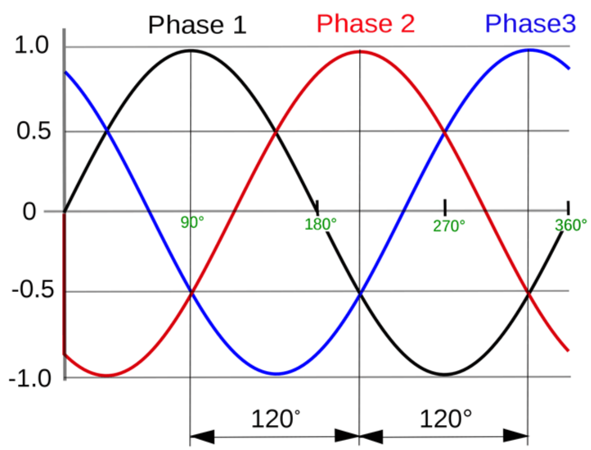
Functional requirements

Structures and stepper motors

Pathways and applications

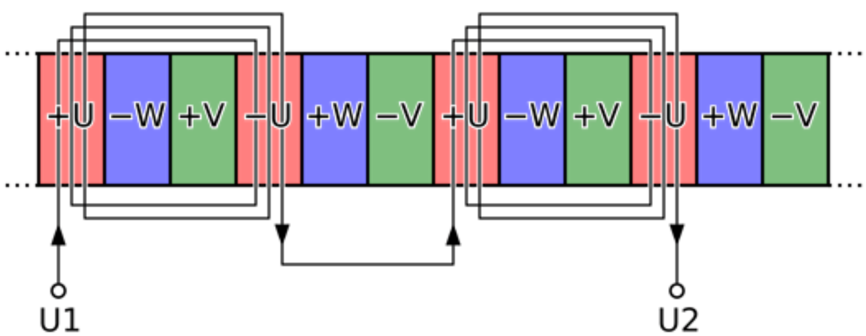
Stepper motors:
A candidate photoactuated approach

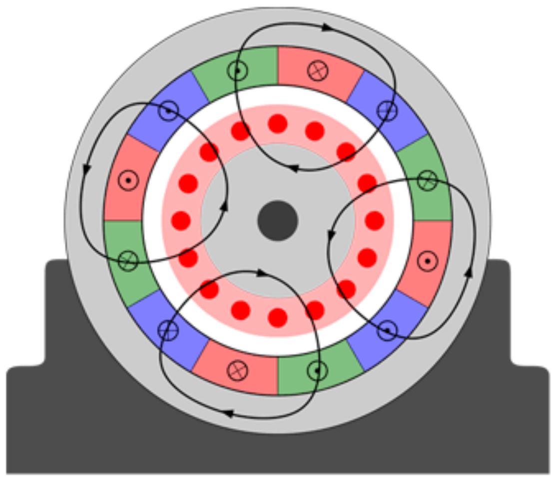
Borrowing from macroscale engineering:
3-phase, bidirectional stepping mechanisms



Principle of operation:

- Modulate 3 potentials (optionally, one weak & constant)
- These sum to form a movable potential well
- Motion can be discrete and bi-directional





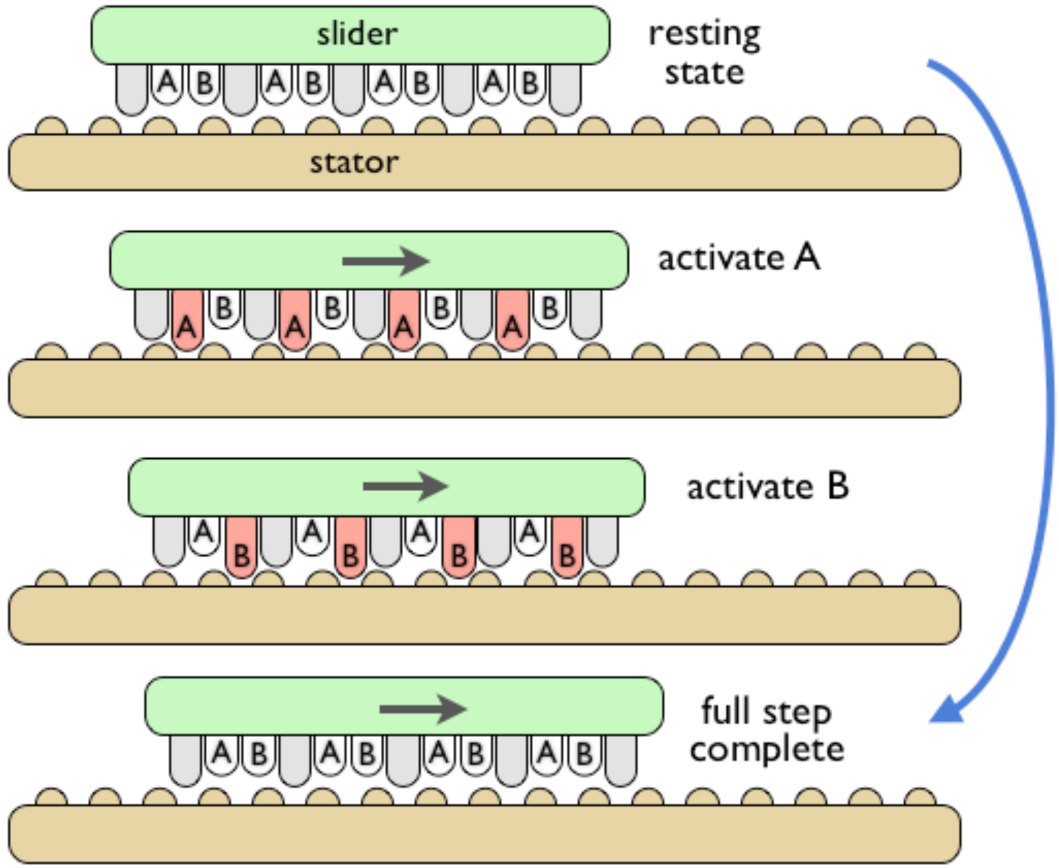
Molecular actuator-arrays can implement linear stepper motors

Schematic diagram of a 3-phase linear motor:

The A, B, and grey protrusions represent structures that induce particular on-axis free-energy profiles between the slider and stator. Here, these are diagrammed as if they involved mechanical interactions with stator bumps; the interactions shift the slider-bumps into alignment with stator-notches.

Grey slider–stator interactions are time-invariant and can be implemented by any suitable axially-periodic interactions between the slider and stator.

The ‘A’ and ‘B’ interactions are switched on and off by light pulses. Their implementations need not involve alignment of any sort (neither along nor transverse to the axis); the only requirements are the depth, shape, and relative phases of the modulations that their state-changes induce in the axial potential-energy profile between the slider and stator.



Candidate photoactuated stepper architecture

Operating principles:

- Harvest light at 3 distinct wavelengths using arrays of dye molecules
- FRET transfers excitation energy to azobenzene actuators
- Azobenzene isomerization modulates interaction potentials (each ~ kT)
- 3 wavelengths can implement *three* independent sets of reversible motors

Several problems and solutions:

- Problem: actuators are weak (*e.g.,* ~1 kT binding energies)
  - — Can sum potentials over many actuators (large interfacial arrays)
- Problems: stochastic activation, crossover activation, and photodegradation
  - — Summed potentials accommodate stochastic components
  - — Can replace degraded components by solution exchange

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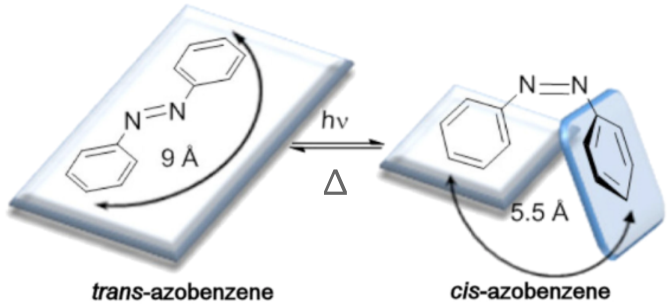
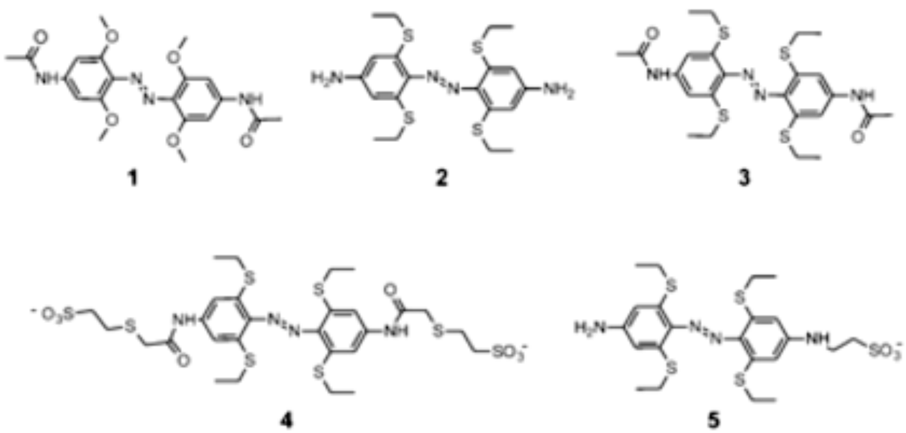
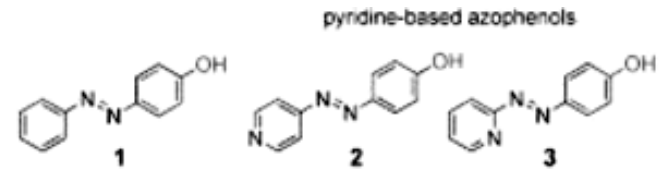
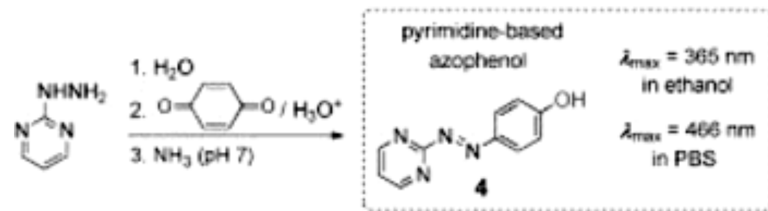
Azobenzenes for fast photoactuation
(recent advances: violet → red, minutes → nanoseconds)







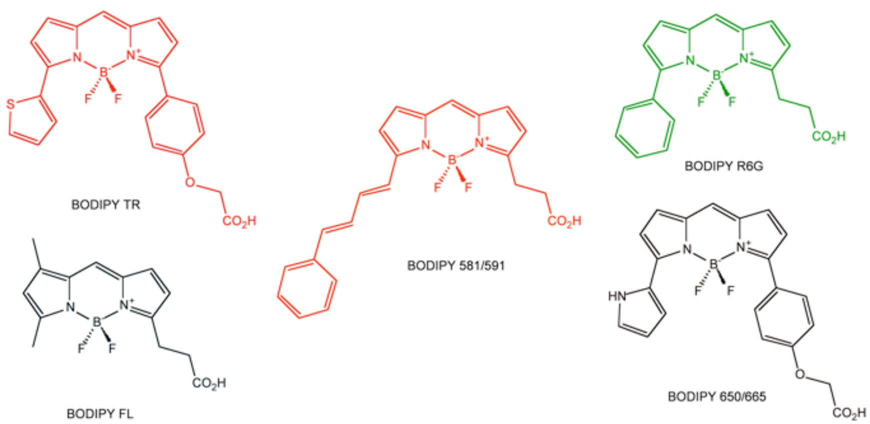


Samanta, Subhas, et al. "**Robust visible light photoswitching with ortho-thiol substituted azobenzenes.**" *Chemical Communications* 49.87 (2013): 10314-10316.
(enables trans→cis switching with red light)

Garcia−Amorós, Jaume, et al. "**Fastest thermal isomerization of an azobenzene for nanosecond photoswitching applications under physiological conditions.**" *Angewandte Chemie International Edition* 51.51 (2012): 12820-12823.
(enables fast cis→trans relaxation)

Dyes for multi-band light harvesting

(BODIPY dyes have suitable action spectra, photostability)



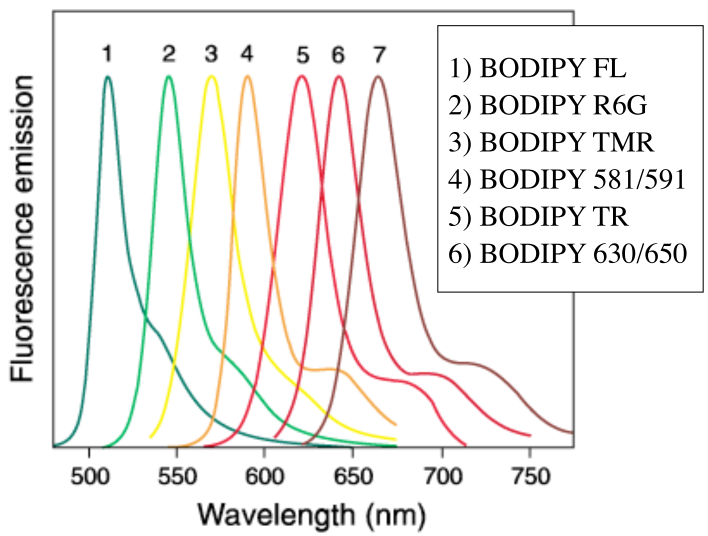
Actuation at **3** wavelengths (R, G, B) enables **3** sets of reversible motors:

x stepper: •RG•RG• ... •GR•GR•

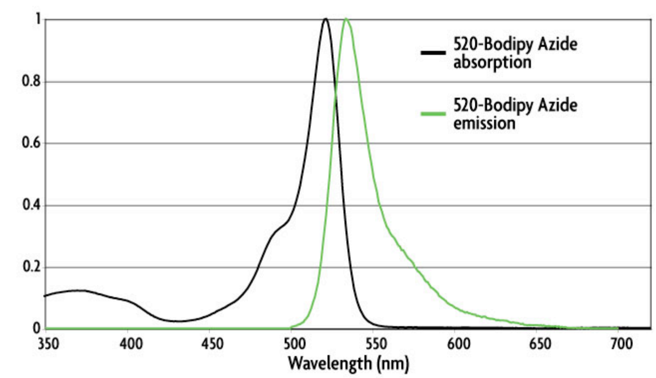
y stepper: •GB•GB• ... •BG•BG•

z stepper: •BR•BR• ... •RB•RB•

Can select sets of dyes with sufficiently low band overlap:



Absorption and emission bands have similar widths:

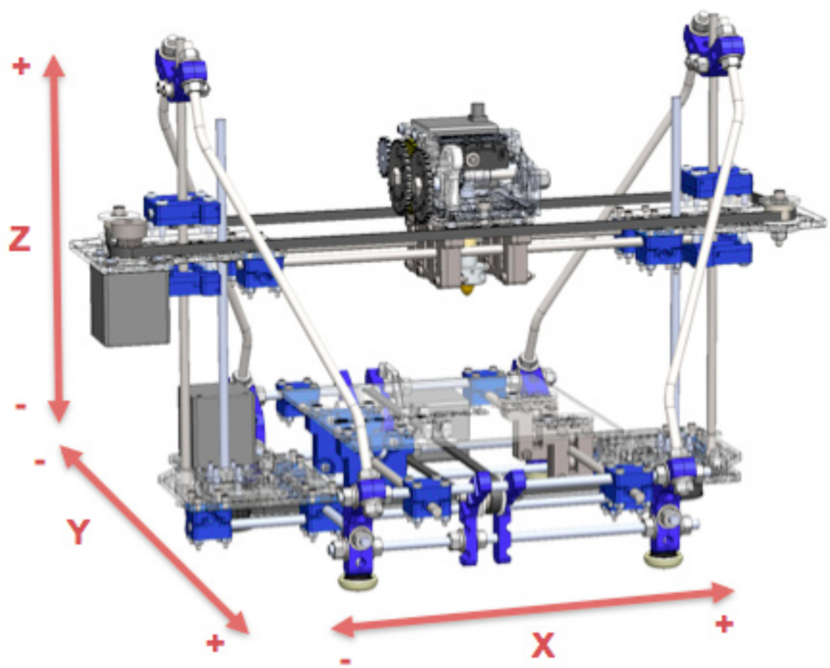


Structures and mechanisms:

A candidate configuration

Typical 3D-printer configurations aren't suitable for molecular additive manufacturing

— Scaled structures would fail to satisfy stiffness constraints —



Printer structures don't maximize stiffness

Why?

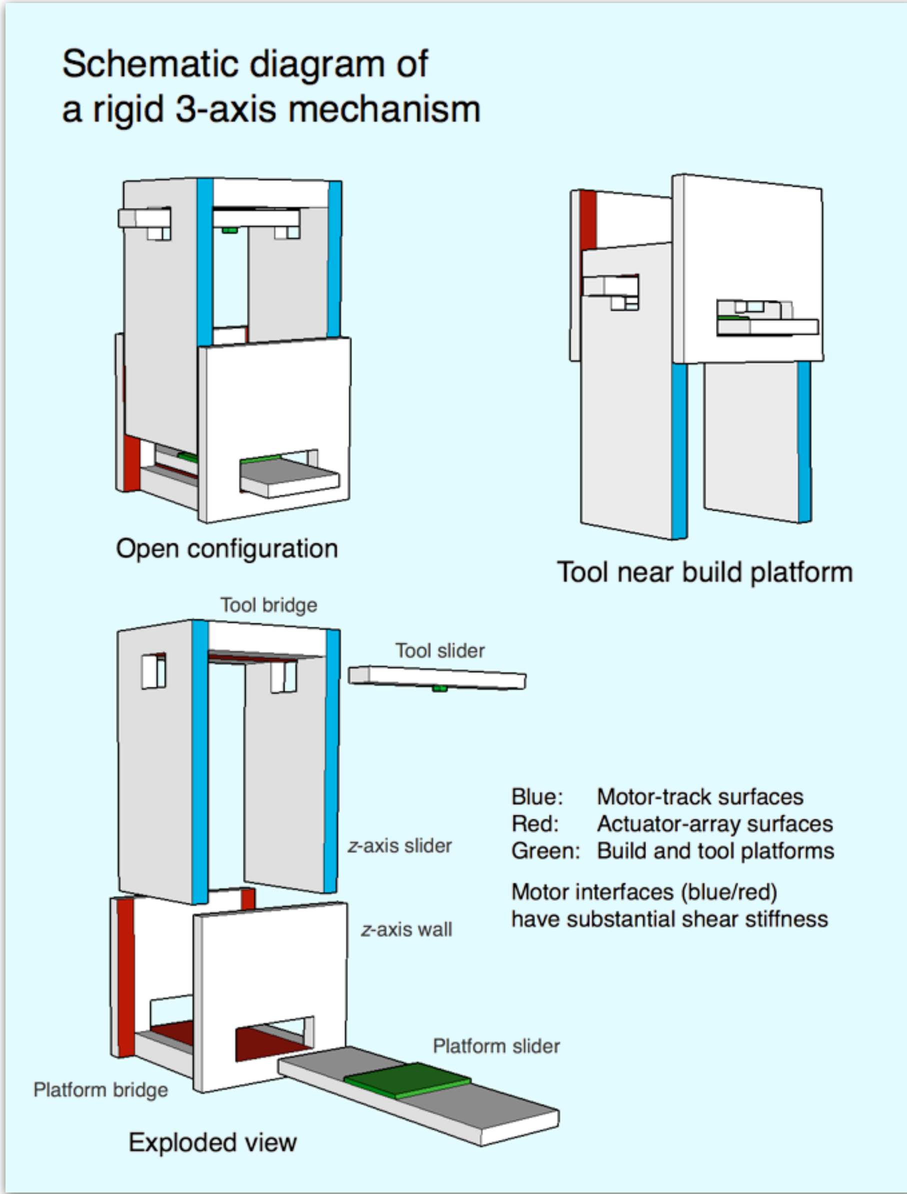
- Thermal fluctuations aren't relevant
- Saving materials reduces costs

Printer motors are small, indirectly coupled

Why?

- Rotary steppers are common, inexpensive
- Long, linear steppers would be costly
- Indirect coupling is acceptable

A rigid mechanical configuration



Structural configuration:

- Box-like structure, good rigidity
- Bending compliance primarily on the *z* axis
- Low *z* axis stiffness is acceptable
- **Result**: tolerates low-modulus materials

Stepper motor configuration:

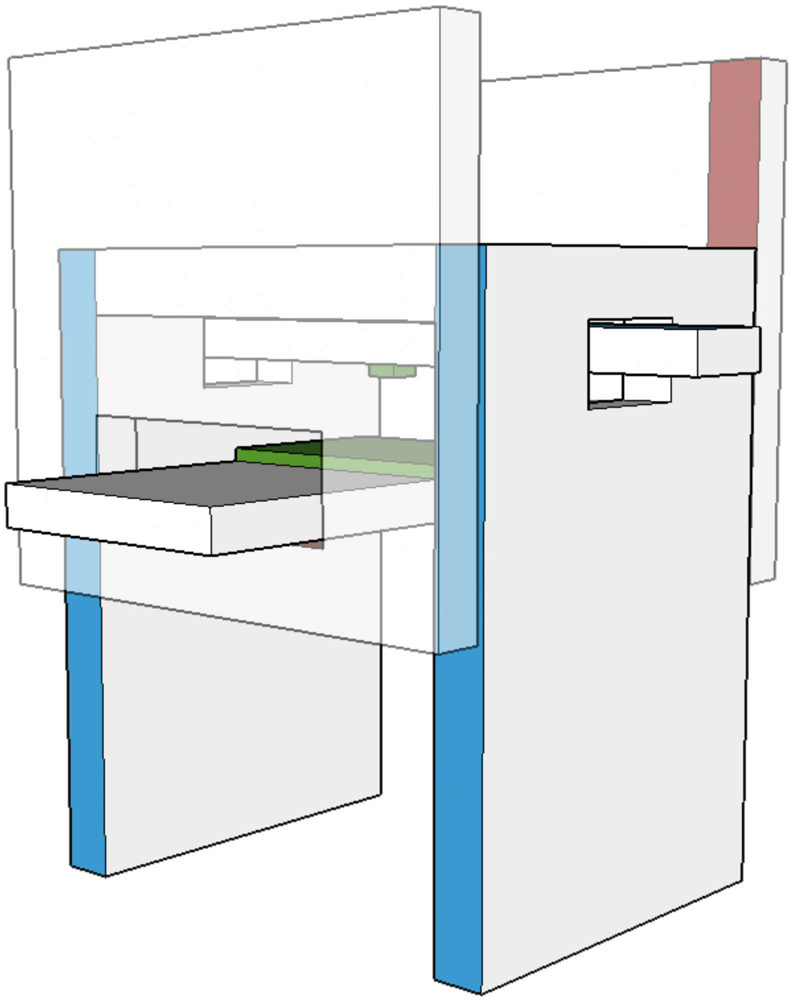
- Configuration allows large actuator arrays
- Large arrays enable stiff motor interfaces
- Large arrays tolerate stochastic actuators

Motion and clearances:

- Workspace comparable to device width
- Open *z*-axis position allows product exit

Nominal scale: ~50–100 nm

A rigid mechanical configuration



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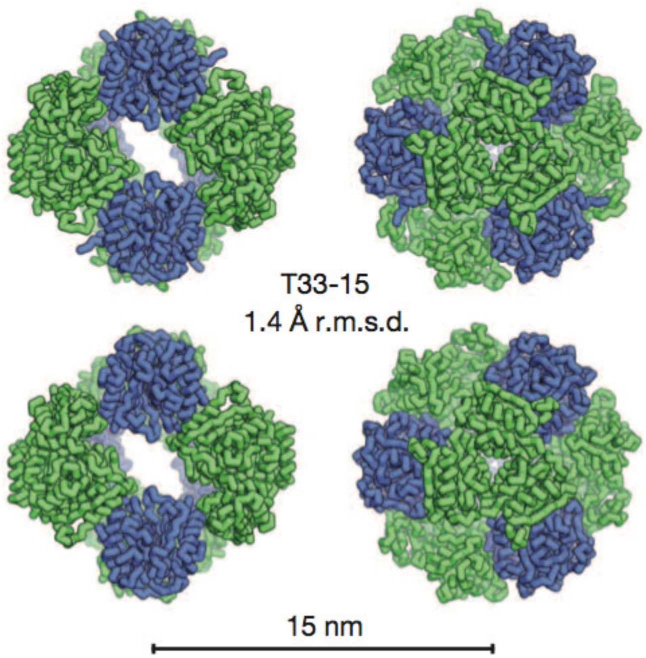
Structural materials: Folded peptide polymers
(protein-nanostructure engineering)

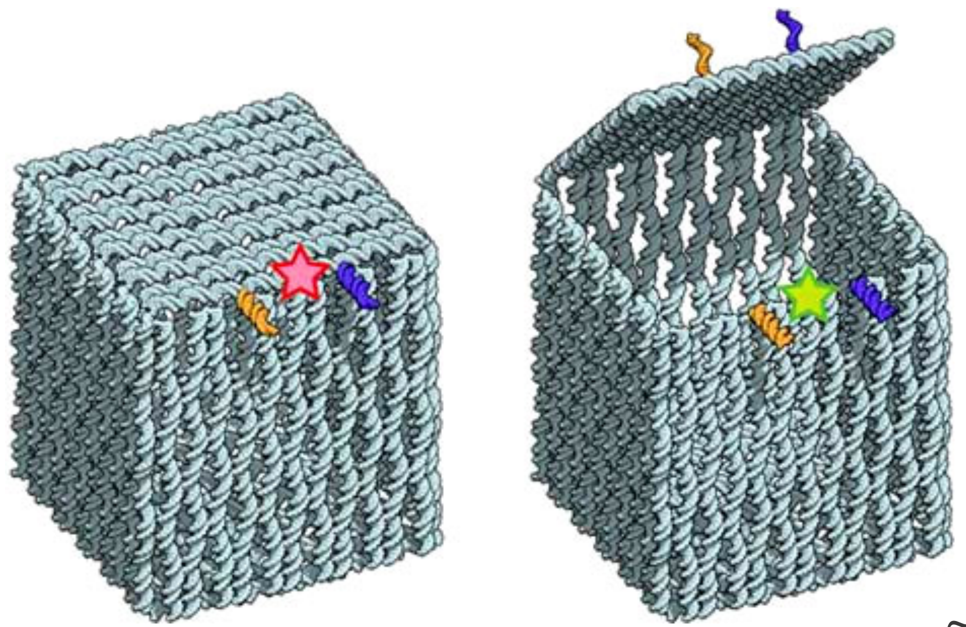


“The capability to **design highly homogeneous protein nanostructures with atomic-level accuracy** and controllable assembly should open up new opportunities in targeted drug delivery, vaccine design, plasmonics and other applications that can benefit from the **precise patterning of matter on the subnanometre to 100-nanometre scale**. Extending beyond static structure design, methods for incorporating the kinds of dynamic and functional behaviors observed in natural protein assemblies should make possible the design of **novel protein-based molecular machines with programmable structures, dynamics and functions**.”

King, Neil P., et al. "Accurate design of co-assembling multi-component protein nanomaterials." *Nature* 510.7503 (2014): 103-108.

Structural materials: dsDNA + crossover junctions

(structural DNA nanotechnology)



Andersen, Ebbe S., Mingdong Dong, Morten M. Nielsen, Kasper Jahn, Ramesh Subramani, Wael Mamdouh, Monika M. Golas et al. "Self-assembly of a nanoscale DNA box with a controllable lid." *Nature* 459, no. 7243 (2009): 73-76.

DNA scaffolds + protein assemblies?

Topics

Functional requirements

Structures and stepper motors

Pathways and applications

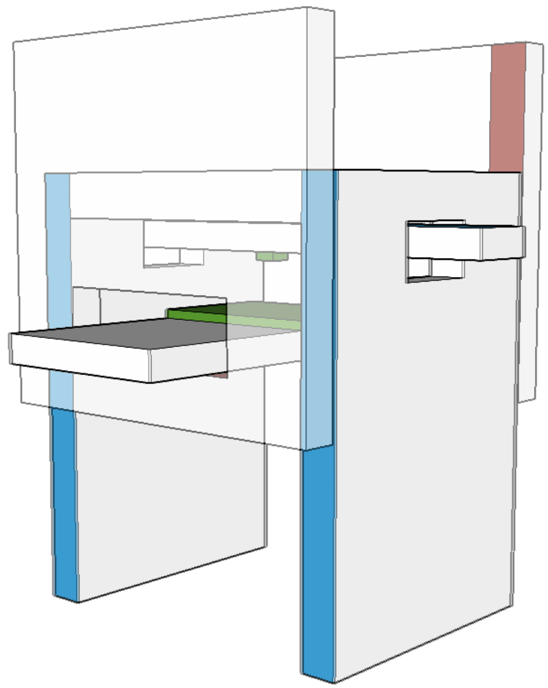
System design options:

Outlined one potentially attractive architecture...

Box-like structural configurations

Photoactuated steppers

Engineered protein structures



X, Y, Z positioning

Alternatives?

...But there are *many* potential alternatives

>> A large design space! <<

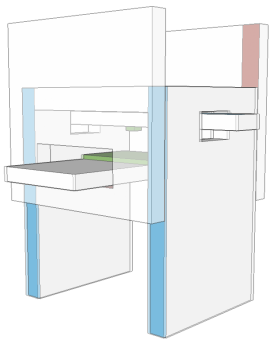
Box-like structural configurations
Rigid-strut configurations
Plate-mounted arrays
3D lattice frameworks
Surface-lattice walkers

Photoactuated steppers
Electric field actuation
Acoustic actuation
Mechanical shear
Ion, pH, ligand interchange

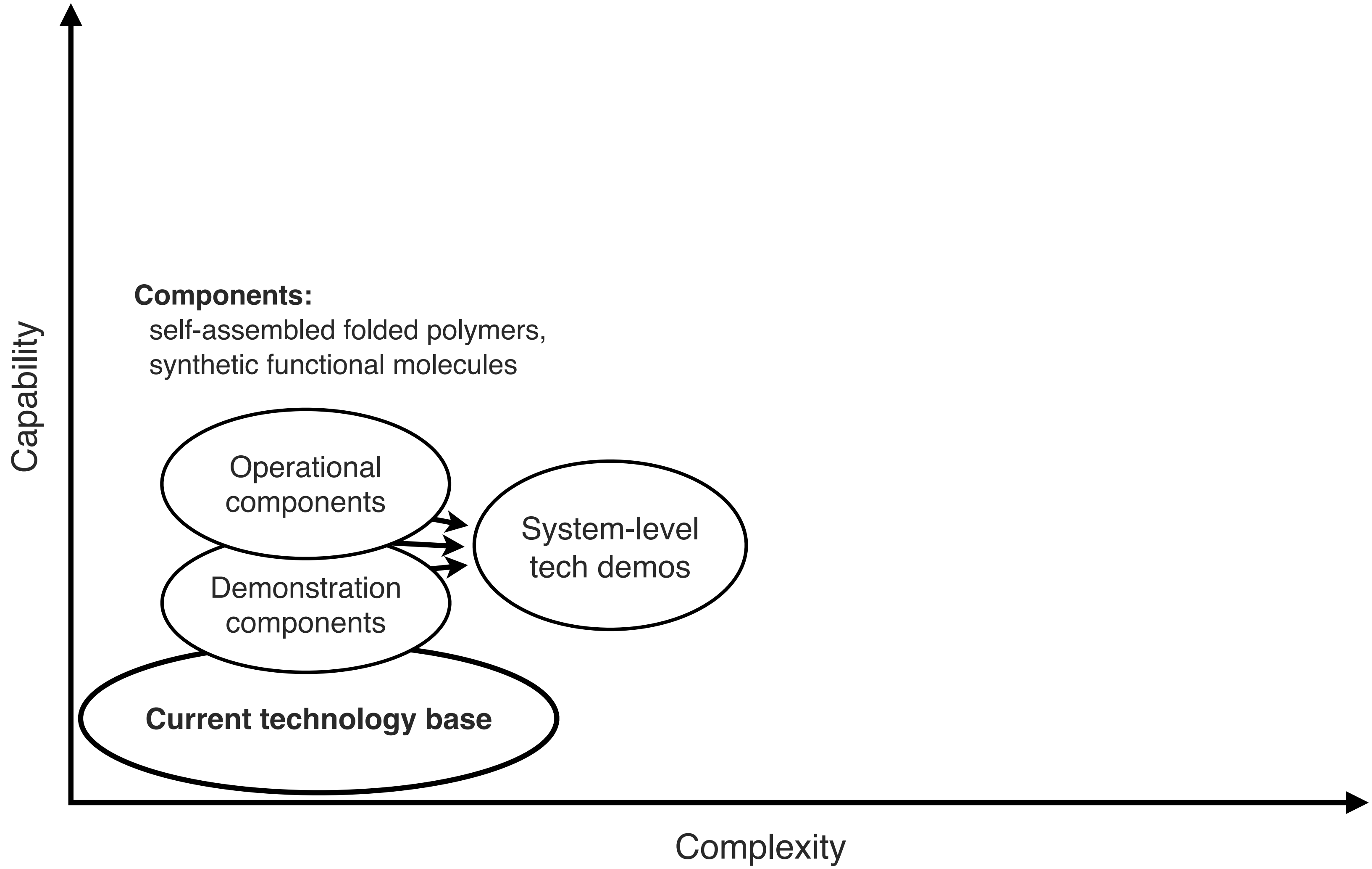
Engineered protein structures
Structural DNA frameworks
Spiroligomers, peptoids
Carbon nanotubes
— Composites —

X, Y, Z positioning
(X, Y, ±) positioning (=2½ dof)
Transverse rotational axis
Six-axis mechanisms
Coordinated systems, templating

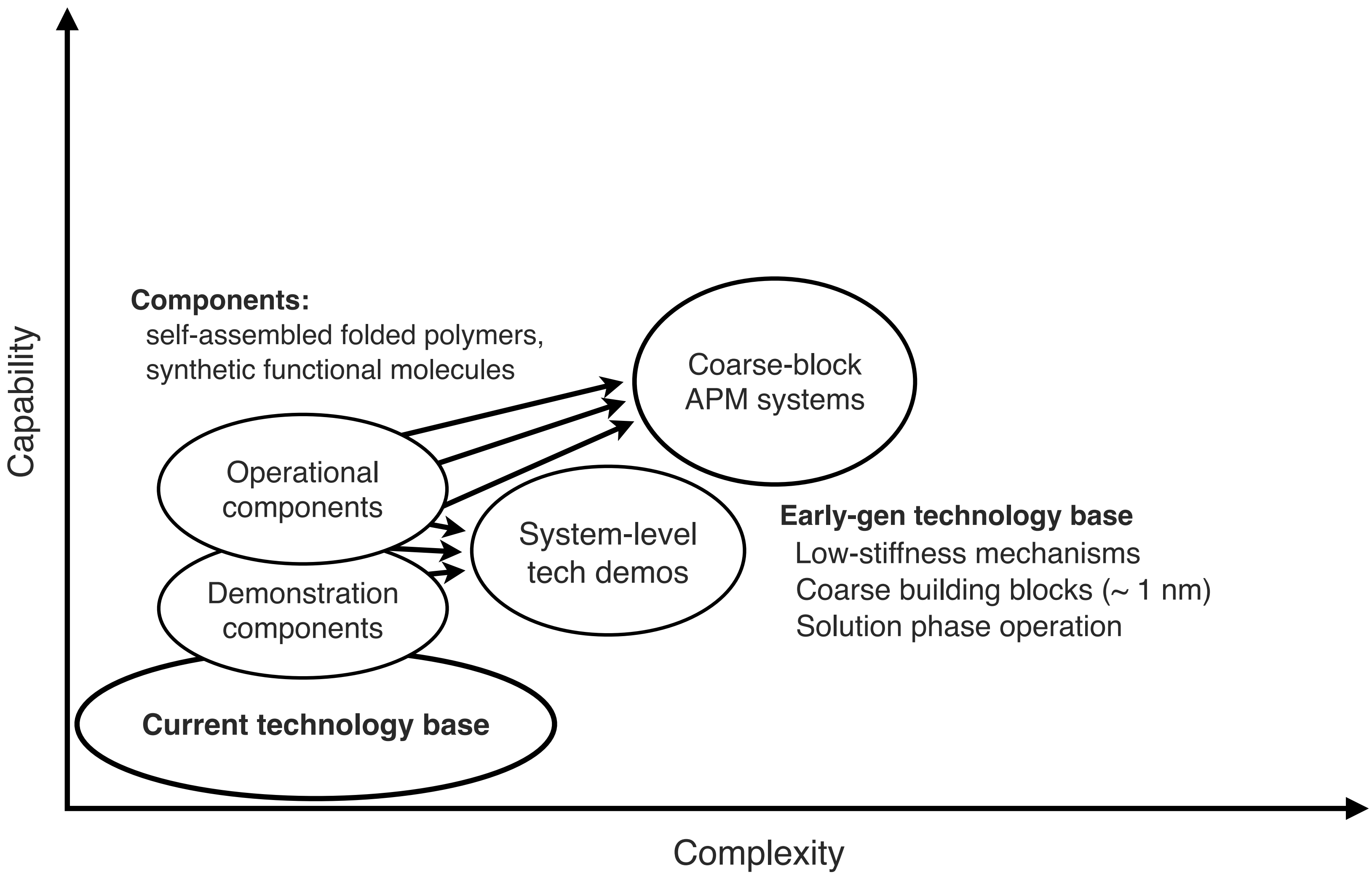
Alternative compatible families of building blocks
Alternative deprotection/activation schemes
Direct placement methods
Asynchronous programmed mechanisms



A sketch of a development landscape



A sketch of a development landscape



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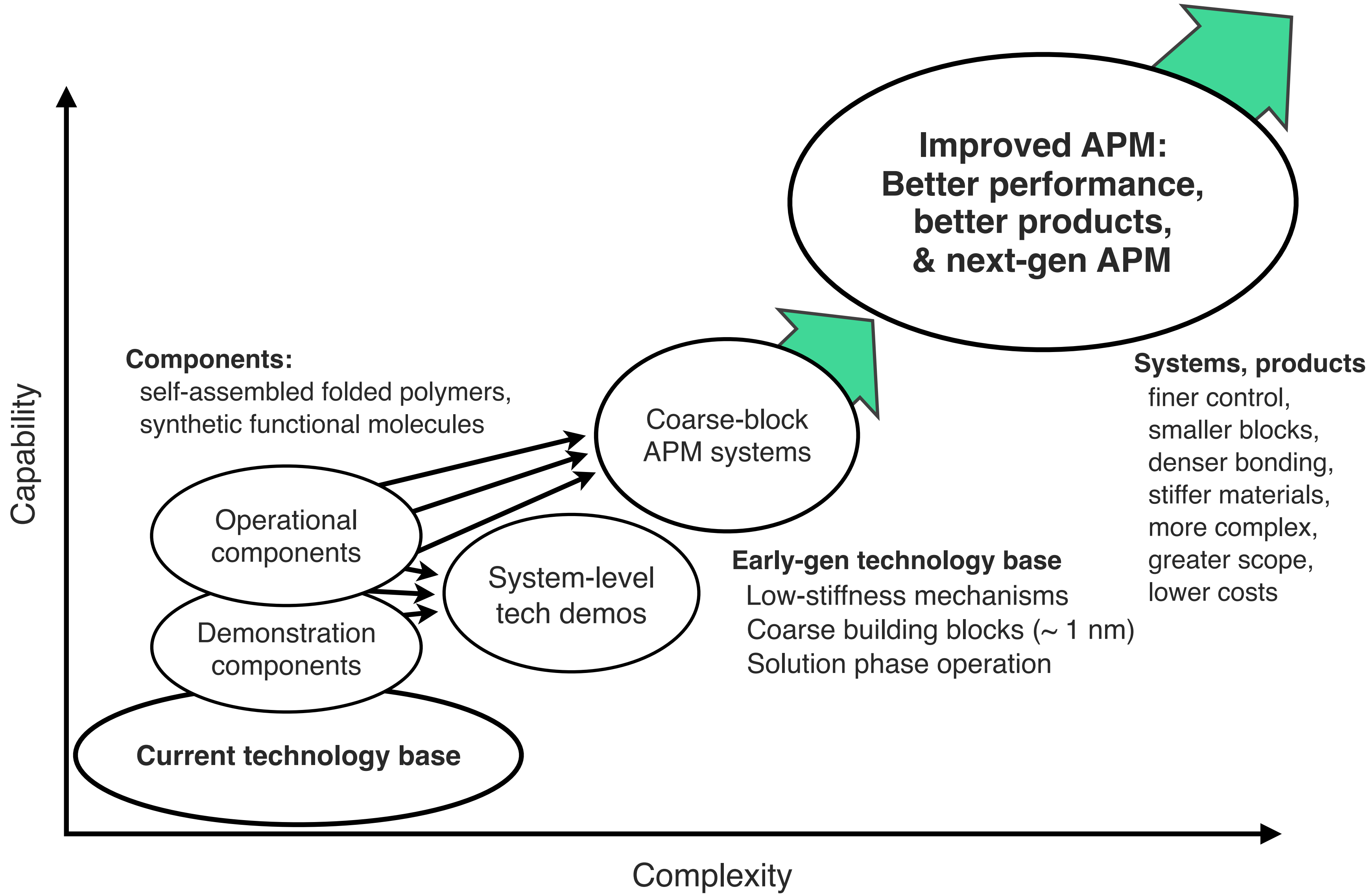

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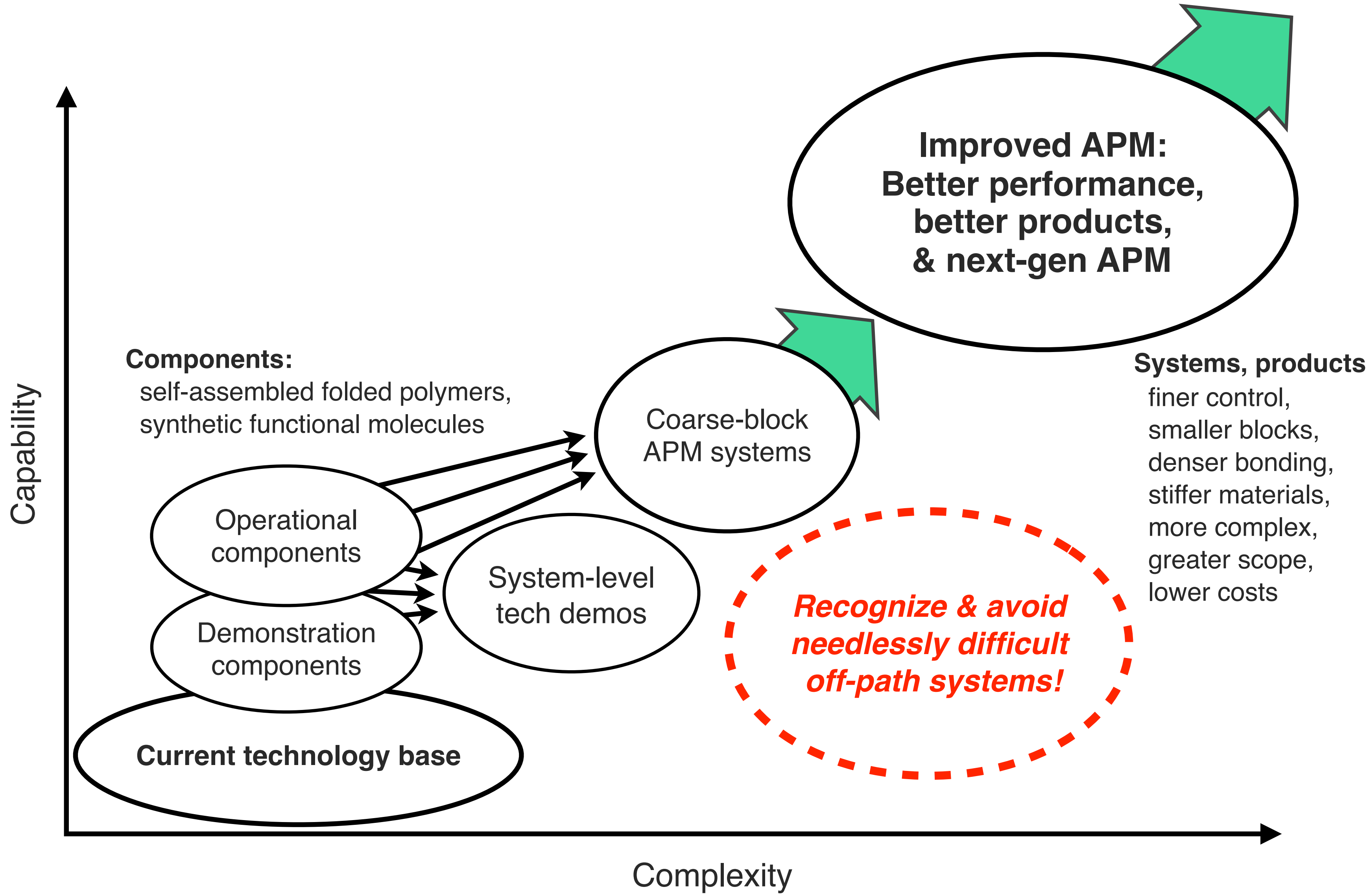

APM pathway technologies

Demonstrations & prototypes

- Stepper motors *(for photoactuation approach)*
  - Detailed photophysical / photochemical design and analysis
  - Corresponding photoactuators and light-harvesting systems
  - Mobile interfaces, actuator arrays, single-axis stepper motors
- Structures and interfaces *(for self-assembly approach)*
  - Comprehensive functional description of requisite structures and interfaces
  - Prototype structures (scaffolded macromolecular self-assembly)
  - Build platform and tool-binding interfaces
- Building-block and tool chemistries *(for solution-phase approach)*
  - Families of building blocks with protection & cross-link functionalities
  - Complementary catalytic tools for target-site deprotection / activation

Early-generation systems

- Integrated system prototypes and demonstration products
- Operational systems, products (& upgraded, next-generation components)
- Upgraded APM systems:
  - better structures & motors, improved speed, reliability, positional resolution
  - Additional building blocks, greater functionality, expanded product scope

Potential applications
of early-generation molecular additive manufacturing

- Robust, non-aqueous, enzyme-like catalysts and catalytic templates
- Templates for synthesizing precise inorganics and carbon nanotubes
- Templates for high-throughput assembly of nanoscale covalent structures
- Precisely-structured pores for selective filtration membranes
- Precisely-structured electrocatalytic membranes for fuel cells
- Self-assembled 3D device arrays on silicon chips (*e.g.,* petabit-scale memory)
- Atomically precise probes, sensors, transducers, DNA readers...
- Novel diagnostic and therapeutic products for nanomedicine
  - — Diagnostic sensors with molecular pattern-recognition capabilities
  - — Highly-selective, pattern-sensitive targeting of cancer cells
  - — Transcriptome modulators for targeted exosome delivery
  - — Antibiotic agents with novel kill mechanisms
- Surprising applications in unexpected domains
  - — Like 3D printing: A *broadly enabling* fabrication technology
  - — Like 3D printing: The *platform* is the most exciting product

Takeaways

- Solution-phase operation can simplify system requirements
- Mechanical functions can be reduced to tool positioning
- Accessible structures and steppers can implement positioning
- The accessible design space includes attractive architectures
- Broad applications make the *platform* the most exciting product

Thank you!