Hybrid Programmable Bionanomachines

An Architecture for Molecular Workcells and Programmable Manufacturing

Tristan Mentec | Technical whitepaper v3.0 | 11 November 2026

Abstract

Programmable molecular components already provide addressable structures, selective chemistry, motion and material templating. What remains unresolved is how to combine them into physical operations that can be repeated, verified and composed into manufacturing processes. This paper proposes Hybrid Programmable Bionanomachines as one candidate architecture within the broader proposed field of Molecular Workcell Engineering. It combines programmable cores, protein-mediated function, engineered environmental interfaces, optional active elements and explicit metrology inside constrained operating environments.

The architecture pursues molecular manufacturing, atomically precise fabrication and programmable artificial substrates through heterogeneous fabrication routes. Its central hypothesis is that constraints, selective chemistry and verification can convert stochastic molecular encounters into useful operations more effectively than attempting unrestricted robotic positioning. The paper defines physical limits, an operation contract, reliability and cost metrics, and an experimental sequence capable of rejecting the hypothesis. The integrated architecture has not been experimentally validated.

1. The molecular manufacturing problem

DNA origami establishes addressable nanoscale organization [1]; molecular assembly lines and cargo-sorting robots demonstrate bounded programmable tasks [2,3]. Synthetic small-molecule machines can execute sequence-selective chemical synthesis [4]. These results establish valuable capabilities, but their combination does not automatically yield a general manufacturing platform.

The engineering gap lies between a successful component and a reliable process: precursor delivery, docking geometry, reaction selectivity, product identification, error recovery and repeated operation must remain compatible within one operating envelope. A visually correct assembly can carry the wrong chemistry; a correct reaction can produce an object that cannot be released or reused.

> Proposed field: Molecular Workcell Engineering studies environments, molecular machines and verification systems that turn molecular components into repeatable physical operations. Hybrid Programmable Bionanomachines is a testable candidate architecture within that field. Competing architectures remain essential.

This is an architecture and research proposal for open circulation. Numerical examples are calculations or proposed gates, not measured program performance. Specific sequences, unpublished geometries, formulations, collaborator details and integration recipes are excluded. The paper provides the technical argument behind a field-building effort rather than a website narrative or implementation dossier.

2. A hybrid architecture defined by function

A bionanomachine is an engineered molecular or nanoscale system that converts encoded structure and state into bounded physical function. Its structural core can be DNA, RNA, designed protein or a hybrid. Recognition and catalytic interfaces recruit functional components; an environmental interface governs exposure and adsorption. An active chassis is added only when powered mechanical action improves the operation.

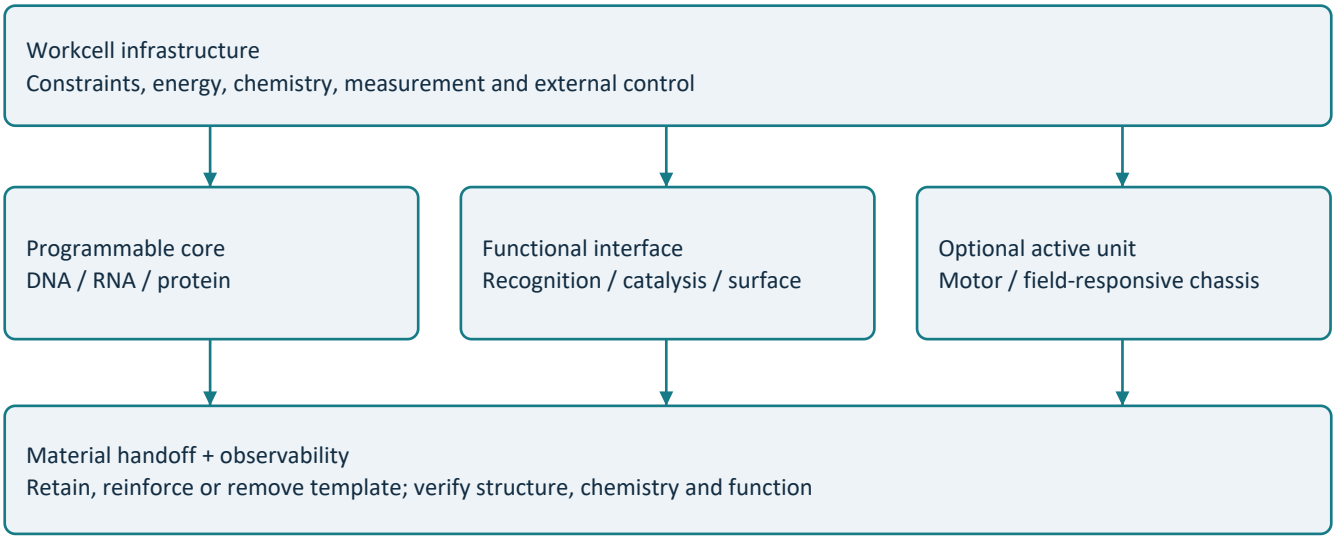


Figure 1. Candidate architecture. Functional roles can be combined or omitted; arrows denote proposed integration, not a demonstrated device. Infrastructure is part of the system boundary.

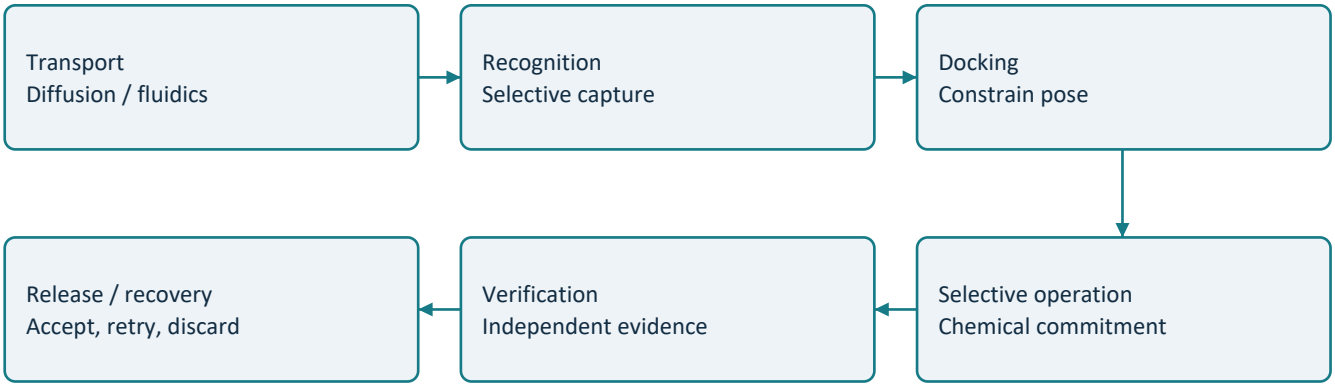
Functional plane	Engineering role
Information	Identity, conditional rules, state and process history; may reside in molecules or external software.
Morphology	Geometry, topology and compliance; core, lattice, hinge or constrained surface.
Function	Recognition, catalysis, transport, optical, magnetic or electrical response.
Interface	Fluid, surface and neighboring-machine interactions; acquired identity and fouling.
Materialization	Transfer molecular organization into reinforced or persistent matter.
Agency	Couple state to chemical flux, shape change or directed physical work.
Observability	Measure relevant geometry, chemistry, state, function and uncertainty.

A plane is a responsibility, not a mandatory layer. A protein may supply both structure and catalysis; a surface may supply morphology and registration. Requiring every plane in every object would increase integration risk without necessarily increasing useful function.

DNA supplies addressable geometry; RNA can supply transient state and structured assemblies [6]; proteins supply recognition, catalysis and designed structure; inorganic materials supply durable physical function. Coupling strategy can alter protein stoichiometry and activity [5]. Passive assembly, input-responsive change, chemical agency and powered work require different evidence. Driven DNA rotation and load coupling have been demonstrated in a specific apparatus [7]; this does not establish a general manipulator. Environmental identity, including acquired coatings or coronas, must be measured under operating conditions.

3. Molecular workcells and physical control

A molecular workcell is an engineered environment that supplies physical constraints, selective chemistry, energy, measurement and, where useful, external control. It can be a registered surface, a pore, a microfluidic compartment, a tethered molecular assembly or an instrument-defined workspace. It need not resemble a miniature factory enclosure.



Failed verification routes to recovery; the next operation requires an accepted state.

Figure 2. Operating cycle. Geometry and chemistry establish a valid docking state; chemical commitment is followed by verification and gated release or recovery. Reuse requires checking the reset state.

Why constrain the environment?

Diffusion can deliver reactants and explore orientations without continuous tracking. Tethers, binding pockets, multivalent docking or surface registration can reduce the accessible configuration space before a selective operation. Feedback can then schedule chemistry, classify state or reject defects. This division reduces the demand for continuous free-space position control while retaining energy and measurement costs.

A useful dock must constrain the degrees of freedom relevant to the reaction. Recognition alone may leave azimuthal ambiguity or a flexible linker that allows unwanted contact. Capture radius, rotational compliance, linker length, steric clearance, reversible binding and dwell time must be compatible with both intended and competing reaction rates. Stronger binding can improve retention while worsening kinetic trapping and product release. Reversible association and annealing before irreversible locking can reduce defects only if trapped states escape on useful timescales; compare the full yield gain with the extra time and reagent burden.

What makes this manufacturing?

The distinguishing proposal is a composable operation contract: defined inputs, a registered state, a selective transformation, a measurable accepted output and an error route. Ordinary synthesis and self-assembly can implement parts or all of this contract. Workcells merit a distinct engineering effort only if organizing these elements improves selectivity, sequence control, recovery or verified output at useful cost relative to those existing approaches.

Primitive contract: input identities + environmental envelope + geometric tolerances + energy / reagent budget + state transition + independent success criterion + failure / recovery rule. Two primitives compose only when the first output meets the second input contract.

3.1 Control limits: calculate the operating envelope

There is no universal diameter below which control fails. Geometry, temperature, viscosity, confinement, magnetic or electric coupling, sensing latency and reaction times determine the envelope. Translational diffusion, rotational diffusion and bond-constrained motion require separate models. For a no-slip sphere of radius a in a Newtonian fluid far from boundaries:

$D_t = k_B T / (6 \pi \eta a)$; $D_r = k_B T / (8 \pi \eta a^3)$
RMS displacement in 3D = $\sqrt{6 D_t t}$
First-rank orientational correlation time = $1 / (2 D_r)$

Worked example: a 300 nm diameter sphere

Assume a = 150 nm, T = 298 K and η = 1.0 mPa s. Then $k_B T$ = 4.11 pN nm, D_t = 1.46 micrometres^2/s and D_r = 48.5 s^{-1}. Over 10 ms, translational RMS displacement is about 296 nm. The orientational correlation time is 10.3 ms. The alternative timescale $1/D_r$ is 20.6 ms; quoting a rotational timescale without its definition is ambiguous. These are idealized estimates, not values for every 300 nm machine.

Near one angular minimum, let $U = \kappa \theta^2/2$. Equipartition gives angular variance $k_B T/\kappa$. A 10 degree RMS tolerance in one angular coordinate requires κ about 32.8 $k_B T/rad^2$, or 135 pN nm/rad^2. For a permanent dipole in a uniform field, local angular stiffness is mB. At B = 10 mT, this tolerance would require m about 1.35 x 10^{-17} A m^2. Whether a particular particle supplies that moment must be measured; induced or anisotropic magnetic systems require their own energy model.

Authority, bandwidth and confinement

Compare force over a target displacement with $k_B T$, torque-derived energy with $k_B T$, relaxation time with controller latency, and docking lifetime with reaction time. A harmonic translational coordinate with 1 nm RMS displacement would require stiffness $k = k_B T/(1\ nm)^2$ = 4.11 pN/nm. Flexible scaffold and linker fluctuations add to the error budget even if the core is immobilized.

More sophisticated feedback can use available force and information more efficiently, but cannot supply missing actuator authority. Higher viscosity slows diffusion and deterministic motion together; it does not change the equilibrium variance of the same conservative trap. Confinement changes the energy landscape and boundary conditions. Crowding and adsorption may invalidate the simple Newtonian model entirely.

Use stochastic transport and binding when specificity and dwell time suffice. Introduce active control for timed switching, disturbance rejection, load-bearing motion or site selection that passive chemistry cannot provide. A chemically constrained reaction coordinate cannot be assigned the free-particle diffusion constant without a model of its constraints.

4. Selective operations, sensing and verification

The minimum useful operation is a site-selective transfer or attachment of a defined payload, with retained function and independently established outcome. It must distinguish capture, docking, chemical attachment and release. Colocalization or a FRET change can report proximity or conformation; neither alone proves the intended bond formed.

Measurement	What it can establish	Key limitation
Optical / fluorescence	Location, stoichiometry, kinetics, conformational reporters	Bleaching, blinking, label loss and proximity-to-chemistry ambiguity.
AFM / electron imaging	Geometry, occupancy and selected defect classes	Preparation effects; often endpoint or destructive; limited chemical identity.
Electrical	Conductance, blockade or local switching in instrumented sites	Contact variability and multiple hidden states can give similar signals.
Magnetic	Ensemble state, torque coupling or magnetic payload response	Limited single-site specificity without suitable spatial encoding.
Spin-sensitive	Local spin chemistry and potentially structural-state contrast	Chemical calibration, photon budget and environmental sensitivity.
Chemical / functional	Product identity, attachment persistence, retained activity	Bulk assays can average away rare or site-specific failures.

Spin reporters as a separate research avenue

Meng and colleagues demonstrated RF manipulation and optical readout of radical-pair spin chemistry in flavoproteins [8]. Their DNA study reports flavin-functionalized oligonucleotides with programmable ODMR response, duplex-dependent contrast and spin-enhanced molecular beacons [9, preprint]. This suggests a route to DNA-localized state reporters. It has not established verification of a manufacturing bond, universal positional readout or closed-loop atom placement.

A reporter project should first compare known docked, undocked, reacted and deliberately defective states under the intended workcell conditions. Only reproducible discrimination from an independent chemical assay would justify adding it to the operation contract. RF and optical excitation, photochemistry, background and reporter-induced perturbation belong in the error and energy budgets.

Acceptance, rejection and recovery

Report true correct-operation probability, incorrect attachment, wrong-site reaction, unreacted payload, damaged scaffold, throughput and batch variation. Calibrate reporter false-positive and false-negative rates with blinded controls. Distinguish specificity for negative controls from the probability that an accepted item is correct, which also depends on defect prevalence. A second readout must address a different failure mechanism rather than repeat the same proxy.

Use reversible rejection before irreversible attachment where possible. After commitment, repair is justified only if the repaired product can be reverified; otherwise discard or isolate it. Recovery must include reagent carryover, site fouling and reset failure. An inability to recover can still permit a disposable workcell, but changes its economics.

5. Reliability, scaling and manufacturing economics

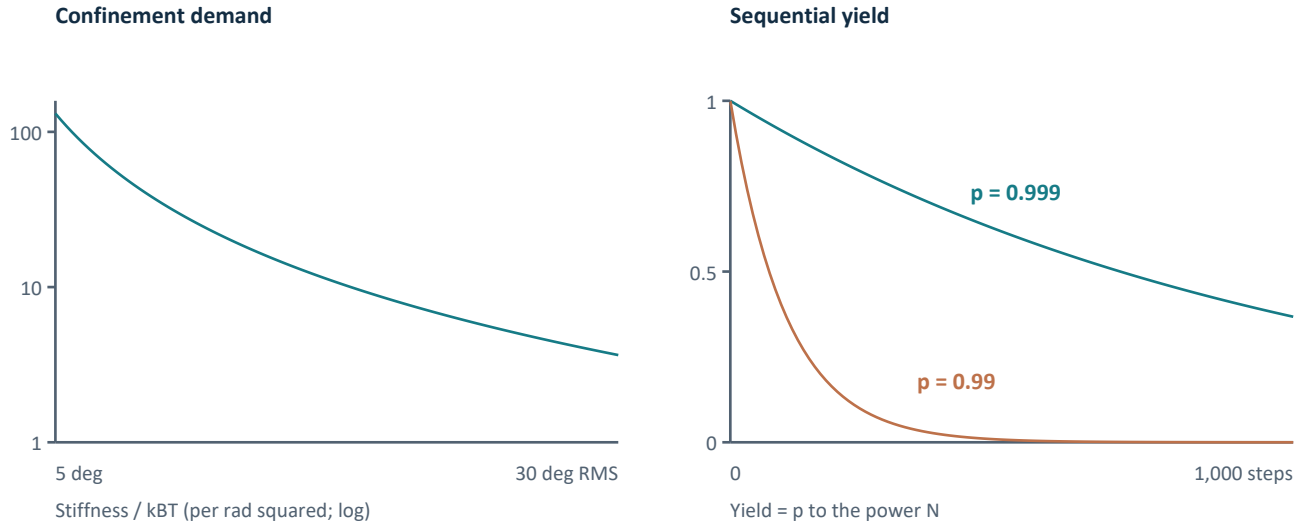


Figure 3. Calculated examples, not experimental results. Left: one-coordinate harmonic stiffness demand scales as 1/theta^2 under the local harmonic approximation. Right: independent per-operation probabilities produce sharply different yields.

Component yield is not operation yield. A scaffold, interface and reporter can each work alone while their combination fails because of orientation, environmental incompatibility or process order. If N independent indispensable operations have correct probabilities p_i, final defect-free yield is the product of p_i. At p = 0.99, 100 operations give 36.6% yield; at p = 0.999, 1,000 operations give 36.8%. At p = 0.9999, 1,000 operations give 90.5%.

Shared reagent failures, drift and fouling violate independence. Estimate yield conditional on batch and process history; report lot failures separately. Inspection can improve the fraction of accepted outputs that are correct while reducing accepted volume. Functional redundancy or defect tolerance can relax the requirement that every site be perfect, but must be tested at the system level.

Central economic metric:
Cost per verified successful operation = total allocated process cost / number of truly correct, verified successful operations.
Count reagents, purification, recovery, metrology, energy, labor, equipment use, maintenance and discarded runs. Report accepted calls separately from estimated true successes.

Illustrative capacity: 10^6 independent sites, a 10 s cycle and 50% combined availability-and-success produce 50,000 verified successes/s before any shared readout bottleneck. If a verifier handles only 1,000 sites/s, that is the ceiling unless inspection is multiplexed or replaced by validated process sampling. At an assumed fully allocated cost of $100/hour, these two rates imply about $0.56 and $27.8 per million operations. These are arithmetic scenarios, not cost forecasts; molecular products may require many operations each.

Chemically encoded transitions and bulk reagent delivery can be massively parallel. Individually addressed imaging, scanned-probe work and serial product handling remain instrument-limited. Parallel sites also compete for reagents and optical channels. Workcells lose when equivalent function is obtained more cheaply by solution synthesis, self-assembly, enzyme cascades or lithography, or when added measurement and recovery exceed the value of sequence or spatial control.

6. Beyond biology: toward atomically precise matter

The long-term objective is programmable manufacturing of increasingly complex matter, including nonliving artificial substrates. Biomolecular machines are a possible construction and control substrate, not the final limit on material composition. The development paths below are distinct fabrication regimes; movement between them requires a verified handoff rather than an assumed technology ladder.

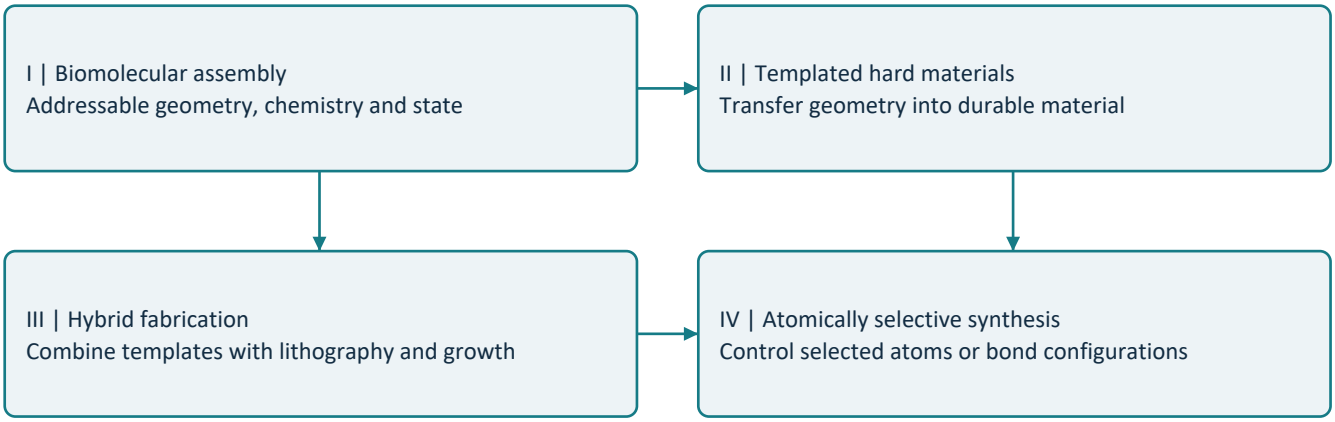


Figure 4. Proposed fabrication relationships. Arrows indicate research opportunities, not an obligatory progression or proven interoperability. Independent atomically precise routes can contribute without a biomolecular precursor.

Regime	Demonstrated anchor	Unresolved transition
Biomolecular assembly	DNA geometry, cargo routing and sequence-directed chemistry [1-4]	Repeatable linking, functional interfaces, recovery and cost.
Templated inorganic fabrication	Functional silicification and DNA-templated metal deposition [10,11]	Shape distortion, nucleation statistics, material purity and extraction.
Hybrid fabrication	DNA-derived patterns can mediate hard-mask processing [11]	Registration to device contacts and yield across multiple processes.
Atomically selective fabrication	Single-atom silicon device and editable hydrogen lithography [12,13]	Chemical breadth, throughput, tool-state stability and product integration.

Atomically precise fabrication means controlled atomic identity, bonding or placement within a specified structure and uncertainty. A sequence-defined molecule has precise covalent identity while its thermal conformation fluctuates. Nanometre placement of a nanoparticle is a different achievement from deterministic atomic construction. Atomic-layer deposition describes a growth method; its name does not establish arbitrary atom-by-atom spatial placement.

6.1 Material handoffs and persistent programs

From molecular organization to durable function

A scaffold can position seeds, constrain local precursor supply, direct deposition or define a temporary mask. Functional silicification demonstrates that coatings can add designed chemical and optical behavior [10]. DNA-templated selective deposition demonstrates another way to transfer organization into inorganic structures [11]. Neither result establishes lossless transfer of every molecular coordinate or general manufacturing across material classes.

Measure the handoff as a transformation with explicit tolerances: feature displacement, shrinkage, connectivity, composition, defect density and functional performance before and after processing. Compare against unpatterned, randomly organized and conventional templates at equal material loading. A geometrically faithful coating may still bury catalytic sites, short an electrical feature or prevent later reconfiguration.

Where atomic precision creates functional value

Selected dopants, molecular junctions, catalytic active sites or defect-based devices can benefit from exact local configurations. Scanning-probe hydrogen lithography and a single-atom transistor establish specialized examples [12,13]. They do not establish arbitrary covalent mechanosynthesis. The research question is whether a workcell can extend the set of verified reactions and usable products while preserving registration and economic relevance.

A positionally directed chemical tool requires controlled tooltip identity, stable reactivity, load and alignment tolerance, site selectivity, contamination control and repeated access. Tool wear or tip changes can corrupt both fabrication and the images used to judge it. Independent metrology and reference structures are therefore as important as the actuation mechanism. Extraction and packaging can erase the benefit if the final atom-defined state is lost.

Separate operating environments, explicit transfer modules

Warm aqueous assembly and many clean-surface atomic fabrication methods require incompatible solvents, temperatures, vacuum conditions and contamination budgets. A biological scaffold cannot simply enter a high-temperature, ultra-clean process unchanged. Viable routes may use sacrificial templates, staged solvent exchange, protective intermediates, separately fabricated inserts or external lithographic registration. Each transfer adds a yield and contamination penalty. Some routes will prove physically or economically incompatible.

Programmable artificial substrates: the ambitious endpoint

A persistent nonliving lattice could, in principle, retain a construction specification, sense local state and recruit externally supplied matter for repair or reconfiguration. This would require durable information, selective transport, energy transduction, waste removal, error detection and interfaces spanning length scales. A lattice that merely grows around seeds does not yet carry an executable construction program.

The decisive future experiment is conditional construction at a predefined location, followed by verified restoration or modification after a controlled defect. Progress would be measured by preserved function, repair specificity, cycle life, energy and material budgets. General programmable matter, broad mechanosynthesis and self-maintaining artificial physical substrates remain speculative endpoints. The architecture retains them as research targets while exposing the missing dependencies.

7. Experimental roadmap and advancement gates

The first proof of concept should test constrained, selective operation rather than integrate every proposed subsystem. Use an immobilized, addressable molecular scaffold with one defined protein-mediated payload interface, one intended site and decoy sites. Deliver a defined payload, observe docking, apply a selective attachment step, independently establish attachment and retained function, then clear or release the product. A separate reporter identifies whether its state agrees with chemistry. No motor, RNA layer, spin sensor or inorganic conversion is required initially.

The proposed gates below are decision criteria for a benchmark, not reported performance or universal manufacturing specifications. Use at least three independently prepared batches; randomize conditions and blind endpoint classification. Report per-batch estimates, uncertainty and all exclusions, rather than treating thousands of observations from one batch as independent replication.

Gate	Required evidence	Advance / stop decision
G0 | Measurement	Positive, negative and defective-state controls; chemical endpoint independent of proximity reporter.	Demonstrate identifiable states and an error model before claiming an operation.
G1 | One operation	Correct payload at intended site; attachment and retained function established.	Target lower 95% confidence bound on correct operation >90%; upper bound on wrong-site attachment <1%.
G2 | Recovery	Reset or product release followed by repeated operation.	Target at least 10 cycles; quantify fouling, carryover and loss relative to the first cycle.
G3 | Composition	Two distinct linked operations on the same object with intermediate checks.	Output identity and joint yield agree with a prespecified model within uncertainty; investigate deviations.
G4 | Transfer	A second laboratory repeats the benchmark using public operation contracts.	Reproduce the main effect and acceptance criteria; characterize failures rather than average them away.
G5 | Expansion	Material handoff or small parallel array, selected by the leading uncertainty.	Show functional benefit and net verified yield / cost improvement over a simpler route.

At G1, compare the full workcell against a static scaffold, unconstrained solution reaction and simpler nonhybrid surface attachment at matched exposure and readout. Measure speed, correct yield, misconnection, reagent use and verification burden. Proceed only if the added architecture creates a practical advantage or exposes a transferable design rule.

7.1 Falsification and research priorities

Assumption capable of invalidating the architecture	Discriminating result and response
Confinement improves useful selectivity	If constrained docking adds trapping or misreaction without improving verified output, simplify the geometry or use solution chemistry.
Hybrid interfaces preserve component function	If orientation and stoichiometry losses dominate despite attachment optimization, remove the interface or choose a single-substrate machine.
The desired chemical state is independently observable	If reporters cannot distinguish docking from reaction at the required error rate, narrow the operation or make verification the research priority.
Operations compose and can be reset	If fouling, carryover or incompatible environments destroy linked yield, use disposable modules or separate process stages.
Reusable rules improve design and economics	If each task remains bespoke or measurement cost overwhelms product value, narrow the platform to a specific application.

An operation library should contain measured distributions, environmental bounds, interface compatibility, calibration, provenance, failure modes and cost. A compiler initially means a constraint-aware design record and decision aid. Predictive compilation is earned only when it selects new combinations or predicts failures better than a task-specific baseline. A catalog of compatible-looking components is insufficient.

Sequencing, infrastructure and opportunity cost

Begin with established molecular synthesis, protein reagents and shared microscopy. Partner for specialized chemical verification and materials processing. Add microfluidic automation after the operation is identifiable, repeatable and worth accelerating. Access cleanroom and scanning-probe facilities for a narrow precision question before considering dedicated facilities. Owning every fabrication regime would impose capital and coordination costs before the common architecture has demonstrated value.

8. Scientific outlook and open questions

The architecture is credible as a research hypothesis if it produces reusable, independently verified operations. The hardest questions concern coupling: whether docking constrains reactive groups sufficiently, whether measurements distinguish hidden failure states, whether output contracts survive sequential processing, and whether metrology can scale with fabrication. These are empirical questions with strong alternatives, not gaps that systems terminology can resolve.

Molecular Workcell Engineering should support DNA-based, protein-based, enzyme-driven, surface-based and fully synthetic approaches. This candidate contributes a common way to allocate function, constrain motion, manage material handoffs and account for verified yield. Its long-range ambition is to make digital descriptions increasingly executable in matter, progressing toward molecular manufacturing, atomically selective fabrication and programmable artificial substrates through demonstrated advances in each necessary operation.

References

Numbered citations support bounded component capabilities. None establishes validation of the integrated architecture. DOI links resolve to the cited record; reference [9] is explicitly unreviewed. Bibliographic records were checked for this edition.

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https://doi.org/10.1038/nature04586
Evidence scope: Addressable DNA scaffolds; no claim of rigid atomic positioning.

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Evidence scope: A bounded assembly-line demonstration, not general manufacturing.

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Evidence scope: Synthetic machine-mediated sequence-selective chemistry.

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https://doi.org/10.1021/acsnano.1c05411
Evidence scope: Experimental effects of coupling strategy on stoichiometry and function.

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https://doi.org/10.1126/science.aao2648
Evidence scope: Designed nucleic-acid structures; substrate interchangeability is not implied.

[7] Pumm, A.-K. et al. (2022). A DNA origami rotary ratchet motor. Nature 607, 492-498.
https://doi.org/10.1038/s41586-022-04910-y
Evidence scope: Driven rotation and load coupling in a specific apparatus.

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https://doi.org/10.1038/s41587-026-03158-5
Evidence scope: RF manipulation and optical readout of protein radical-pair spin chemistry.

[9] Meng, K., Einholz, C., Krueger, L., Rosenow, M. & Bucher, D. B. (2026). Optically addressable and programmable spins in DNA. bioRxiv, September 2026. Preprint; not peer reviewed.
https://doi.org/10.64898/2026.09.14.751464
Evidence scope: Programmable DNA-localized spin systems and molecular-beacon applications; no manufacturing verification claim.

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Evidence scope: Functional silica coatings; not a demonstration of arbitrary atom placement.

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Evidence scope: Template-mediated deposition and hard-mask fabrication.

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Evidence scope: A specialized atom-defined silicon device architecture.

[13] Achal, R. et al. (2018). Lithography for robust and editable atomic-scale silicon devices and memories. Nature Communications 9, 2778.
https://doi.org/10.1038/s41467-018-05171-y
Evidence scope: Hydrogen lithography and error correction on a specific silicon surface.

Evidence boundary

Demonstrated capabilities belong to their published systems and operating conditions. Constrained hybrid workcells, a transferable operation library, predictive substrate allocation and reliable cross-regime handoffs are proposed integrations. Broad mechanosynthesis, persistent programmable construction lattices and general self-maintaining artificial matter are long-horizon hypotheses. No simulation, schematic or calculation in this paper changes those evidence categories.

Appendix A. Calculation and measurement notes

A1. Reproducible physical assumptions

The sphere calculation uses k_B = 1.380649 x 10^{-23} J/K, T = 298 K, eta = 10^{-3} Pa s and a = 150 x 10^{-9} m. Translational drag is 2.83 x 10^{-9} N s/m; rotational drag is 8.48 x 10^{-23} N m s. These give D_t = 1.455 x 10^{-12} m^2/s and D_r = 48.50 s^{-1}. Increasing viscosity tenfold decreases both diffusion constants tenfold and increases free-particle relaxation times tenfold. Boundary corrections, nonsphericity and viscoelasticity require different drag models.

For small-angle harmonic confinement, kappa = k_BT/$sigma_{theta}^2$. At $sigma_{theta}$ = pi/18 rad, kappa = 1.35 x 10^{-19} J/rad^2. The dipole estimate assumes a permanent moment locked to the particle and a locally uniform static field. It addresses one small angular coordinate; rotation about the dipole axis remains unconstrained. This estimate therefore does not specify a complete six-degree-of-freedom docking system.

A2. Reporter calibration and rare errors

Let p be the true success fraction, s the probability of acceptance given success, and f the probability of acceptance given failure. The accepted fraction is A = ps + (1-p)f; the correct fraction among accepted items is ps/A. This simple model excludes correlated reporter errors. For multiple reporters, do not multiply error rates unless independence is justified experimentally.

With zero observed errors in n independent Bernoulli trials, the one-sided 95% upper bound is 1 - $0.05^{1/n}$, approximately 3/n. About 299 trials with zero errors are needed to place that bound below 1%. A claim below 10^{-6} requires roughly three million independent error opportunities with zero observed errors, adequate detection sensitivity and representative conditions. Large numbers of correlated sites on one defective scaffold do not supply that many independent opportunities.

A3. Measurement definitions for the operation record

Quantity	Required denominator or qualifier
Correct-operation yield	True intended outputs / all attempted operations, including failed capture.
Misconnection and off-target chemistry	Define wrong payload, wrong site and unwanted bond separately; include all exposed opportunities.
Throughput	Verified correct outputs / elapsed process time, including reset and shared instrument constraints.
Repeatability	Within-batch and between-batch variation; drift, cycle count and independent laboratory results.
System yield	Functionally acceptable final objects / starting objects; report defect tolerance and rejection.
Cost	Allocated total process cost / true verified successes; report currency, utilization and uncertainty.