

Neutral Morphological Masking: Constructive Neutral Evolution of Chiral Scaffolds for Information-Maintaining Artificial Cells

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Abstract

A minimal synthetic cell that completes a full replication–growth–division cycle still demonstrates nothing about self-maintenance unless it also carries a state variable that can degrade under a genuine environmental stress and be actively defended. Our earlier proposal (Sandler, 2026b) specified such a module — chiral order $U\chi$ as a programmable memory, D-glucose glycation as a stress channel, and circular dichroism (CD) as a sensor — but treated the robustness that protects $U\chi$ as a static, hand-designed surface property, u_s . That is an adaptationist assumption dressed as an engineering parameter, and it is also why the initial submission read as disconnected from current artificial-life research: a designed robustness knob does not need to cite the literature on how robustness actually arises in living systems. This revision addresses both problems by fusing the chiral-order module with Constructive Neutral Evolution (CNE), the framework in which biological complexity accumulates through selectively neutral steps rather than adaptive design (Stoltzfus, 1999), and specifically with the interlocking-masking mechanism recently formalized for multi-subunit complexes in the Quandary Den artificial-life model (Walsh, 2026). In the synthesized framework, random neutral mutations introduce structural protrusions in one subunit of a multi-subunit chiral scaffold; complementary recesses that neutrally arise in partner subunits mask these protrusions to preserve packing order, and the accumulated interlocking geometry incidentally occludes the scaffold's glycation-vulnerable amine sites. Geometric surface uniformity, u_s , is therefore reframed as an emergent, unselected byproduct of a masking ratchet rather than a design input. We give the resulting multi-subunit dynamical system, retain the original module's mechanistic lattice Monte Carlo and site-diluted XY-model machinery as validation of the underlying stress–state–repair physics, and add a new toy evolutionary simulation demonstrating the internal consequences of the proposed masking rules: a one-directional ratchet in interlocking complexity, an incidental decline in the emergent glycation-rate constant, and accidental cross-protection against a novel stress shock in lineages that accumulated complexity under no direct selection for glycation resistance. We situate the proposal explicitly against current artificial-life and synthetic-biology literature on self-maintaining and homeostatic artificial cells, give an expanded, falsifiable prediction set, and lay out a staged validation roadmap.

1. Introduction

Living systems do not merely carry information; they actively defend it against continual erosion, repairing damage, replacing degraded components, and holding internal state within a viable range. Homeostasis, autopoiesis, fault tolerance, and robustness are different names for the same recurring artificial-life problem: how does a system defend its own organization against an environment constantly working to erode it? A parallel and equally central question, less often asked in the same breath, is where the machinery that performs that defense comes from in the first place — whether it must be designed in, as in most synthetic-cell engineering to date, or whether it can arise on its own.

1.1 Self-maintenance in current artificial-life and synthetic-cell research

Bottom-up synthetic biology has made rapid progress on the first half of the homeostasis problem — building cells, not maintaining them. A modular, multi-plasmid minimal cell chassis now completes a full replication, growth, and division cycle from non-living components (SpudCell; Adamala & Engelhart, 2026), and a fully abiotic polymeric protocell system has demonstrated autonomous growth, reorganization, and self-reproduction without any biochemistry at all (Katla et al., 2025). Neither system was built with an explicit, tunable damage channel: nothing in either chassis is designed to degrade under stress, so neither can be used to study defense against degradation. The clearest artificial-life progress on active maintenance instead comes from a different direction — wet, chemistry-first artificial cells engineered specifically around a homeostatic feedback loop. Krehan et al. (2025) built pH-homeostatic artificial cells that cross-couple pH-modulating enzymes with pH-responsive membranes, and organized them into prototissue spheroids that collectively resist external pH threats, a design in which the maintenance loop itself, not just the compartment, is the object under study. On the computational side, Ishida (2026) shows a chemical oscillator model can exhibit homeostatic self-optimization through active inference even before genetic information is available, and Utimula (2025) extends morphology-capable artificial-life models toward the self-regulating and self-directing capacities a full account of artificial life requires. Stano (2022) surveys this landscape and argues that a mature bottom-up synthetic-cell research program needs a fourth track beyond genome, metabolism, and compartment: a designed capacity for the cell to maintain itself.

Our original proposal (Sandler, 2026b) sat inside this fourth track: an explicit stress–state–repair loop built around chiral order as a programmable, information-bearing internal state variable. What that proposal did not do — and what reviewers correctly flagged — is explain where the robustness parameter defending that state variable comes from, or connect the module to the artificial-life literature on how complexity and robustness arise without being designed. That is the gap this revision closes.

1.2 Where does robustness come from? The adaptationist default and its alternative

The original module treated geometric surface uniformity, u_s , as a free design parameter: a higher-uniformity scaffold was simply specified to be more robust, with the value chosen by the experimenter. This is standard practice in synthetic-cell engineering, where every component is placed deliberately — but it silently imports an adaptationist assumption that protective complexity exists because someone, evolution or an engineer, selected for exactly that function. Constructive Neutral Evolution (CNE) is the standing alternative to that assumption in evolutionary biology: complex, seemingly well-adapted machinery can accumulate through a sequence of individually neutral steps, each merely tolerated rather than selected for, which subsequently become locked in and irreversible (Stoltzfus, 1999). CNE has been used to explain a wide range of molecular complexity — RNA editing, scrambled ciliate genes, spliceosome evolution, obligate duplicate-gene retention — without invoking adaptive benefit at the point of origin (Stoltzfus, 1999; Muller, 1918).

Walsh (2026) operationalizes CNE as an artificial-life model, the Quandary Den, built specifically to explore how interlocking complexity in protein complexes can increase under neutral drift alone. Two mechanisms emerge from that model: subfunctionalization, in which a function originally performed by one component diffuses across a complex, and masking, in which intracomplex interference introduced by a neutral mutation in one subunit is genetically tolerated only because a complementary structural change in a partner subunit blocks its expression. Masking is the mechanism this paper adopts: it produces exactly the kind of physical, steric consequence — tighter, more interlocking packing — that could plausibly double as protection against an external chemical stressor, without ever having been selected for that purpose.

1.3 Related work and positioning

This paper sits at the intersection of three literatures that have not previously been connected. Bottom-up synthetic-cell engineering (Adamala & Engelhart, 2026; Katla et al., 2025; Stano, 2022) supplies the chassis and the replication/growth capability but no maintenance channel. Engineered homeostatic artificial cells (Krehan et al., 2025; Ishida, 2026) supply working examples of designed feedback-based maintenance, but the feedback machinery itself is, again, placed by the designer rather than emergent. Constructive neutral evolution, both in its original biological formulation (Stoltzfus, 1999; Muller, 1918) and in its recent artificial-life instantiation (Walsh, 2026), supplies a mechanism by which protective complexity can arise without being designed — but had not previously been connected to a measurable, chemically anchored physical state variable, or proposed as a route to robustness inside an artificial cell. The contribution of this paper is that connection: showing how a CNE-masking process, acting on the same multi-subunit chiral scaffold specified in Sandler (2026b), can be the origin of the surface-uniformity robustness knob that the original module simply assumed, and giving falsifiable, quantitative predictions that follow from treating robustness this way rather than as a design input.

From an artificial-life perspective, the proposed framework treats robustness not simply as a biochemical engineering property but as an emergent, historically contingent property of an evolving artificial organism. This places the work within the long-running ALife tradition of asking how life-like organization, complexity, and self-maintaining behavior can arise from local rules rather than being explicitly designed — the question at the center of computational autopoiesis (McMullin, 2004), of formal treatments of emergence in synthetic living systems (Gershenson, 2023), and of minimal evolutionary models in which autopoietic, self-maintaining structure is itself an evolved rather than stipulated outcome (Turney, 2021). It is also continuous with the broader claim that functional diversity and organization in living systems can emerge through the same non-adaptive, opportunistic processes this paper applies to robustness (Moreno & Ruiz-Mirazo, 2009). Read this way, the present proposal is best understood not as a synthetic-biology engineering spec with an ALife veneer, but as an ALife question — can complexity that evolves for one reason accidentally generate robustness against a completely different environmental threat? — for which the chiral-scaffold chemistry supplies a concrete, measurable instance.

1.4 Contribution and structure of this paper

Section 2 gives the synthesized framework, Neutral Morphological Masking, and its comparison to the Walsh and Sandler models. Sections 3–5 rebuild the module's state variable, stress channel, and robustness mechanism under this framework. Section 6 summarizes the retained mechanistic support (lattice Monte Carlo, site-diluted XY model) for the underlying stress–state–repair physics and adds a new toy evolutionary simulation of the masking ratchet. Section 7 restates the module's design principles under the new framework. Sections 8–9 give an expanded prediction set and staged validation roadmap. Sections 10–11 give limitations and conclusions.

2. Neutral Morphological Masking: A Synthesized Framework

Instead of a single, static chiral scaffold whose robustness is a design input, consider an artificial cell containing multiple interacting chiral subunits that must pack together to maintain a global order parameter, $U\chi \approx 1$. Robustness in this framework is not designed; it evolves neutrally, through the following loop.

- Structural drift. Random, selectively neutral mutations in the cell's minimal genome alter the amino-acid sequence of the scaffold's subunits, creating structural protrusions — intracomplex interferences that threaten to disrupt global packing alignment and collapse the cell's stored configurational information, $H\chi$.
- Evolution of interlocking shapes. To be tolerated rather than purged, a protrusion must be masked: other subunits in the complex accumulate complementary, interlocking recesses that encapsulate and neutralize the disruptive protrusion, restoring packing order.
- Architectural payoff. Because masking works by wrapping subunits more tightly around one another, it incidentally increases the steric hindrance of the whole complex. The evolved interlocking geometry becomes a large, emergent robustness knob, u_s , that immunizes the cell against glucose-glycation stress as an accidental byproduct — not because it was selected to.

2.1 The synthesized dynamical system

Expanding the single-shroud picture of Sandler (2026b) into a multi-subunit (i, j) network, the structural configuration of the complex determines the emergent damage rate:

$$I_{\text{global}} = 1 - |\langle e^{i\theta_k} \rangle| \text{ (global information loss)}$$

$$dI_{\text{global}}/dt = [k_0 \cdot (1 - \Phi(C_{ij})) \cdot G \cdot (1 - I_{\text{global}})] - R \cdot I_{\text{global}}$$

C_{ij} , the evolution matrix, represents the spatial, geometric fit between subunit i and subunit j at a given point in a lineage's history. $\Phi(C_{ij})$, the masking function, approaches 1 as neutral subfunctionalization and structural masking accumulate; it plays exactly the functional role u_s played in the original static module (Sandler, 2026b, § 2.4), driving down the emergent glycation rate k_{glyc} purely as a structural byproduct of interlocking complexity, rather than as a chosen parameter.

2.2 Core structural comparison

Table 1

Conceptual mapping across the neutral-evolution artificial-life model (Walsh, 2026), the original static chiral module (Sandler, 2026b), and the framework synthesized here.

Artificial-Life Concept	Walsh Model (Quandary Den, CNE)	Sandler Model (Chiral Scaffold Module)	This Synthesized Framework
Physical substrate	Abstract genotype strings with expressed / masked loci	Homochiral peptide / peptoid lattice	Multi-subunit protein complex with evolvable interfaces
Complexity driver	Neutral fixation + subfunctionalization / masking (Muller, 1918; Stoltzfus, 1999)	Hard-coded engineering parameters	CNE acting on a physical, chemically grounded state variable
Internal state / memory	Phenotypic functional map	Chiral order $U\chi$ via von Mises entropy	Collective configurational order $U\chi$ of an evolving complex
Environmental stress	Task / informational demand (abstract)	D-glucose glycation flux, G	Stereoselective glycation flux on multi-site complexes
Robustness mechanism	Emergent masking of intracomplex interference	Static, designed surface uniformity, u_s	Emergent steric occlusion — u_s as byproduct, not design input

Table 2

Capability comparison against existing minimal synthetic cells, updated so the origin of robustness — not only its presence — is an explicit, testable claim.

Capability	Existing minimal synthetic cells	This work
Genome replication / growth / division	inherited from chassis	inherited from chassis
Programmable information-maintenance module	no	yes (engineered)
Glycation chemistry (stress input)	no	yes (deliberately built in)
Direct internal-state readout	no	yes (CD of $U\chi$)
Origin of robustness	not addressed	proposed as an emergent, evolved byproduct (CNE-masking), not a design input
Enantioselective (stereochemical) control	no	yes (scaffold handedness)

3. Chiral order as a programmable, information-bearing state variable

The definition of the state variable is unchanged from the original module and is repeated here for completeness, since it is the quantity every downstream section (masking, glycation, repair) acts on. Represent the scaffold as a population of chiral units with local packing orientations θ_i on the circle. The internal state variable is the mean resultant length

$$U\chi = |\langle e^{i\theta} \rangle|$$

equal to one for a perfectly ordered, single-handed assembly and zero for a fully disordered one. For a fixed degree of order, the maximum-entropy distribution of orientations is the von Mises distribution with concentration κ (Mardia & Jupp, 2000), for which the order parameter and the differential entropy are both closed-form functions of κ :

$$U\chi(\kappa) = I_1(\kappa)/I_0(\kappa) \quad S(\kappa) = \ln(2\pi \cdot I_0(\kappa)) - \kappa \cdot U\chi(\kappa)$$

Eliminating κ gives a strictly monotonic map between internal order and configurational entropy; defining information content $H\chi = S_{\max} - S \geq 0$ (in nats) makes a fall in $U\chi$ precisely a loss of internal-state information in the Shannon–Boltzmann sense (Jaynes, 1957), not a metaphor for it. Internal state is read non-destructively by circular dichroism (CD): glycation of a homochiral substrate measurably shifts the CD signal (Ahmad et al., 2014), and a baseline-plus-orthogonal-assay calibration (CD paired with ATR-FTIR or mass spectrometry) decouples the $U\chi$ -dependence of the ellipticity from confounding adduct chemistry and secondary-structure change (Berova et al., 2000).

4. The stress channel: stereoselective glycation

Non-enzymatic glycation is the spontaneous reaction of reducing sugars with free amine groups, proceeding through a Schiff base and Amadori rearrangement to a heterogeneous set of crosslinked adducts (Maillard, 1912; Monnier & Cerami, 1981). On a homochiral scaffold bearing amine sites, each adduct perturbs local packing and each crosslink pins the assembly into a strained, disordered configuration, driving a fall in $U\chi$. Because D-glucose is itself single-handed, the stress channel is genuinely stereochemical: an all-D and an all-L scaffold exposed to the same D-glucose stress are predicted to lose internal order at different rates, tracking a Boltzmann-scaled activation-barrier difference, $\exp(\pm\Delta\Delta G^\ddagger/k_BT)$, denoted ε . This mechanism, and the parameters anchoring it to measured chemistry (glycation kinetics of model peptides; degradation kinetics of synthetic peptide hydrogels), are unchanged from Sandler (2026b, § 2.3, 3.1) and are not repeated in full here.

5. Robustness as an evolved, not designed, property

Where the original module wrote $k_{\text{glyc}} = k_0 \cdot (1 - s \cdot u_s)$ with u_s a free, hand-set parameter, the synthesized framework treats u_s as the output of the masking loop of § 2:

$$u_s(t) = \Phi(C_{ij}(t))$$

with $C_{ij}(t)$ built up one masking event at a time by the structural-drift-and-mask loop, and never decreasing once fixed — a ratchet, in the same sense CNE lock-in is a ratchet (Stoltzfus, 1999): losing a masking interface would re-expose the protrusion it hides, which is itself destabilizing, so masked states are asymmetrically retained relative to unmasked ones. The steady-state balance of Sandler (2026b, § 2.5–2.6) is otherwise unchanged in form:

$$I^* = (k_{\text{glyc}} \cdot G) / (k_{\text{glyc}} \cdot G + R) \quad \rho = R / (k_{\text{glyc}} \cdot G) \quad I(\rho) = 1 / (1 + \rho)$$

but ρ is now a quantity with a history: two lineages with identical instantaneous G and R can occupy different points on the sustainability curve because they carry different amounts of accumulated, neutrally fixed masking complexity. This is the qualitative content of Prediction 1 in § 8.

6. Results

6.1 Retained mechanistic support for the stress–state–repair physics

The lattice kinetic Monte Carlo and site-diluted XY-model formulations of Sandler (2026b, § 3.5–3.6) are retained unchanged as validation that the phenomenological Box-1 dynamics of § 5 follow from local, microscopic rules rather than being imposed: stress-driven decay of U_X is well fit by the governing ODE across a fivefold range of stress magnitude, the measured stress-response rate falls roughly 2.3-fold as an imposed surface-uniformity parameter rises from 0 to 1, and a single stereochemical barrier ϵ produces a persistent, racemic-control-bounded handedness split. Those results establish that if a lineage arrives at high u_s by whatever route — designed or evolved — the physics of § 5 behaves as claimed. They do not, on their own, establish that a lineage can arrive at high u_s without a designer, which is the question § 6.2 addresses.

6.2 New: a toy simulation of the masking ratchet

To give the CNE-masking mechanism of § 2 a first, illustrative quantitative test, we built a minimal toy simulation, deliberately simpler than the structural lattice model of § 6.1: a population of lineages, each carrying a scalar masked-interlocking-complexity count $C(t)$. At each generation, a neutral protrusion mutation arises with small probability. If it arises, it must be masked to be tolerated — an unmasked protrusion is treated as structurally disruptive and is purged, so there is a real filtering step in the model, but that filtering acts on structural viability, not on glycation resistance. Surviving, masked protrusions increment C and are retained irreversibly, modeling the CNE claim that masking is what converts a structurally disruptive neutral mutation into a tolerated one. The emergent glycation-rate constant is read out as $k_{\text{glyc}}(t) = k_0 \cdot \exp(-\alpha \cdot C(t))$, consistent with the steric-occlusion picture of § 5, but no term in the simulation rewards or selects for a low value of k_{glyc} itself. Figure 2 shows the result across 300 independent lineages run for 400 generations with no direct selection for glycation resistance, so that

any decline in k_{glyc} reflects a side effect of structural filtering, not selection on the robustness phenotype.

This toy model is intentionally minimal — a single scalar $C(t)$ stands in for what § 2.1 specifies as a full evolution matrix C_{ij} — and is offered as a demonstration of the internal consequences of the proposed masking rules, not as a mechanistic replacement for the lattice/XY machinery of § 6.1 or as independent evidence that those rules govern a real evolving complex. Because k_{glyc} is defined as a monotonic function of C , and C is constructed to accumulate irreversibly, the simulation shows that the three qualitative consequences of the proposed rules (ratchet accumulation, accidental byproduct robustness, and cross-protection against a novel stressor) can be reproduced in the simplest possible formalization of Walsh's (2026) masking rule; it does not, on its own, show that those rules are what a real multi-subunit complex would follow. A structural, multi-subunit version of this simulation, using an explicit C_{ij} interface-compatibility matrix rather than a scalar count, is proposed as Stage 0 of the validation roadmap (§ 9) and is the natural next computational step for turning this internal-consistency check into a genuine test of the framework.

6.3 Scope of the evidence

The present results provide three distinct levels of support, which should not be read as interchangeable. First, the lattice Monte Carlo and site-diluted XY calculations of § 6.1 support the local stress–state–repair dynamics of § 5, conditional on a specified robustness parameter — they say nothing about where that parameter comes from. Second, the scalar evolutionary simulation of § 6.2 demonstrates the qualitative, internal consequences of the proposed masking rules, but does not establish that those rules arise in a structurally realistic evolving complex; it is a consistency check on the framework's logic, not a validation of its biology. Third, the connection between CNE-derived interlocking geometry and physical occlusion of glycation-vulnerable amine sites (§ 2, § 5) remains a testable structural hypothesis with no computational or experimental support yet. Accordingly, the present work should be interpreted as a theoretical artificial-life framework with preliminary, internally consistent computational support, rather than as experimental or simulated evidence that evolved glycation resistance actually occurs in a physical system. Sections 8–9 give the falsifiable predictions and staged roadmap intended to close that gap.

7. Design principles for information-maintaining artificial cells, revisited

7.1 Modularity

The stress channel (glycation), the state variable (U_X), and the repair channel (turnover) remain functionally and physically separable, as in Sandler (2026b, § 4.1). What changes is that the robustness channel, u_s , is no longer a fourth independent knob alongside them — it is now a slowly varying, historically contingent output of the masking loop, coupled to the others only through evolutionary time.

7.2 Robustness and fault tolerance, reframed

Geometric uniformity is still a passive robustness parameter in the sense that it lowers the effective damage rate with no immediate compensating cost – but under the synthesized framework it is not free in the sense of being unearned: it is paid for over evolutionary time by the accumulation of interlocking complexity, and it comes with the CNE signature of irreversibility (§ 5) that a designed parameter would not have.

7.3 Self-maintenance, recoverability, and complexity as a first-class object

Turnover R remains an active maintenance process in the sense of Sandler (2026b, § 4.3–4.4). The synthesized framework adds a second, slower maintenance-relevant process operating on masking complexity itself: because masked states are retained and unmasked states are purged, the population-level distribution of C is itself a form of accumulated, inherited information about historical stress exposure – the mechanism behind Prediction 3 (§ 8).

7.4 Sensing and closed-loop potential

Unchanged from Sandler (2026b, § 4.5): CD gives non-destructive, real-time access to U_X , which is what would be required to close an active feedback loop between measured state and repair rate R. The present proposal still does not implement such active feedback.

8. Testable predictions

Predictions 1–2 and 4–5 restate the original module's falsifiable claims (Sandler, 2026b, § 5), unchanged because the underlying stress–state–repair physics of § 6.1 is unchanged. Predictions 3, 6, and 7 are new, and follow specifically from treating robustness as evolved rather than designed.

- 1. Basic stress-response law. CD ellipticity declines with cumulative D-glucose exposure following $I(t) = 1 - (1 - I_0) \cdot \exp(-k_{\text{glyc}} \cdot G \cdot t)$ in the low-repair limit.
- 2. Designed-uniformity robustness. Scaffolds templated on higher geometric-uniformity chiral surfaces exhibit lower k_{glyc} and higher steady-state U_X at matched stress.
- 3. The ratchet effect (new). Multi-subunit complexes evolving under low or zero selective stress will progressively increase their interlocking-boundary complexity, C_{ij} , over generations due to neutral drift alone, and this increase will be effectively irreversible – an evolutionary ratchet, not a random walk (Figure 2A).
- 4. Sustainability boundary. Repair above the threshold $\rho = R/(k_{\text{glyc}} \cdot G) > (1 - I_c)/I_c$ holds U_X above a chosen collapse floor indefinitely; below it, internal order collapses.
- 5. Chiral-signature stress response. Under single-handed D-glucose, all-D and all-L scaffolds lose internal order at significantly different rates, with a racemic control intermediate; no such split appears under a non-chiral control stressor.

- 6. Accidental cross-protection (new). Lineages that accumulate high interlocking complexity under conditions imposing no direct selection for glycation resistance will show significantly lower decay constants, k_{glyc} , when suddenly exposed to a high D-glucose shock, compared to ancestral, un-interlocked lineages, despite glucose resistance never having been a target of selection (Figure 2C; illustrated in the toy model of § 6.2, to be tested structurally at Stage 0 of § 9).
- 7. Chiral divergence in co-evolution (new). If a population of complexes is split and evolved under D-glucose versus L-glucose stress, their interlocking topologies (C_{ij}) will diverge into distinct, enantiomer-specific geometric patterns, showing that CNE-driven masking preserves a selective, stereochemical memory of historical environmental stressors even though no single masking event was itself under stereochemical selection.

9. Design and validation roadmap

The roadmap of Sandler (2026b, § 6) is retained as Stages 2–5 below, each gating the next; a new Stage 0–1 is inserted ahead of it to test the CNE-masking claim computationally before committing to wet-lab work.

- Stage 0 – Structural evolutionary simulation. Replace the scalar toy model of § 6.2 with an explicit multi-subunit lattice in which each subunit pair carries its own C_{ij} compatibility score, mutation introduces protrusions at specific interfaces, and masking is a local, geometrically explicit compensatory mutation. Confirm that Predictions 3, 6, and 7 hold in this richer setting.
- Stage 1 – Baseline module. Synthesize a homochiral scaffold and characterize internal order by CD, establishing the $U_{\chi} \approx 1$ baseline and sensor calibration (unchanged from the original roadmap).
- Stage 2 – Stress-response characterization. Expose the purified scaffold to graded D-glucose in vitro; fit decay to Box 1 (Prediction 1).
- Stage 3 – Designed robustness. Vary geometric surface uniformity across templating conditions and measure k_{glyc} versus uniformity (Prediction 2), as a control condition against which evolved robustness (Stage 4) can be compared.
- Stage 4 – Directed neutral evolution of robustness (new). Propagate scaffold-encoding lineages under a low- or zero-glucose regime for many generations, permitting neutral drift, and test whether interlocking complexity and glucose resistance both increase without direct selection on either (Predictions 3, 6).
- Stage 5 – Stereochemical signature and in cellulo integration. Prepare all-D, all-L, and racemic scaffolds, measure the CD split under D-glucose versus a non-chiral control stressor (Prediction 5), test co-evolutionary chiral divergence under D- versus L-glucose (Prediction 7), and introduce the scaffold plus repair mechanism into a minimal synthetic-cell chassis to test the sustainability threshold ρ^* directly (Prediction 4).

10. Limitations

This remains a theoretical and computational proposal, not a report of a built system, and every limitation noted in Sandler (2026b, § 7) still applies to the physical module itself. Three further limitations are specific to this revision. First, the toy simulation of § 6.2 uses a single scalar complexity variable, $C(t)$, in place of the full evolution matrix, C_{ij} , specified in § 2.1; it demonstrates that the three qualitative predictions of the synthesized framework are internally consistent, not that they hold in a structurally realistic multi-subunit model — that is the explicit purpose of Stage 0 in the roadmap. Second, the CNE-masking mechanism is adapted from an artificial-life model of neutral evolution in abstract genotype space (Walsh, 2026); mapping its “protrusion” and “recess” language onto real, three-dimensional steric occlusion of amine sites is a structural-biology hypothesis, not yet a demonstrated correspondence. Third, Stage 4 of the roadmap (directed neutral evolution of a real scaffold-encoding lineage over many generations) is a substantially longer and more demanding experimental program than the single-generation characterization in Stages 1–3, and its feasibility with a minimal synthetic-cell chassis that does not yet manufacture its own repair machinery is an open engineering question, not a solved one.

11. Conclusion

A synthetic cell that maintains internal order by design tells us that maintenance is possible; it does not tell us where the machinery that performs it comes from. This revision reframes the robustness knob in our original chiral-order module (Sandler, 2026b) from a static, hand-designed surface property into an emergent output of neutral morphological masking, the interlocking-complexity mechanism recently formalized for artificial life by Walsh (2026) and grounded in Constructive Neutral Evolution (Stoltzfus, 1999). The resulting synthesized framework keeps every piece of mechanistic support from the original submission — the information-theoretic definition of U_X , the stereoselective glycation stress channel, the lattice Monte Carlo and site-diluted XY-model validation — while adding a concrete answer to where robustness comes from, a new toy simulation demonstrating the ratchet, byproduct, and cross-protection signatures that answer predicts, and an expanded, more falsifiable prediction set. We situate the proposal explicitly against current bottom-up synthetic-cell research (Adamala & Engelhart, 2026; Katla et al., 2025; Stano, 2022) and current engineered-homeostasis artificial cells (Krehan et al., 2025; Ishida, 2026; Utimula, 2025), and give a staged roadmap, beginning with a purely computational test (Stage 0), for taking the synthesized claim from a plausible narrative to a measured result.

Declarations

Author Contribution

L.S. conceptualized the theoretical framework, developed the mathematical and computational models, performed the simulations, analyzed the data, and wrote the manuscript.

Data Availability

The simulation code generating all theoretical figures and models is open-source and available on GitHub at <https://github.com/sandlerleon/neutral-morphological-masking> and archived on Zenodo (DOI: 10.5281/zenodo.22150668). The manuscript preprint is archived on Zenodo (DOI: 10.5281/zenodo.22150664). All parameter values are specified in the codebase.

Data and Code Availability

The simulation code (`stress_repair_lattice.py` -- lattice kinetic Monte Carlo / site-diluted XY-model validation of the retained stress–state–repair physics, Sections 5–6.1 -- and `masking_ratchet_toy_model.py` -- the new CNE masking-ratchet toy simulation behind Figure 2, Section 6.2) used to generate every figure and quantitative result reported in this revision is provided as open-source Python (NumPy, SciPy, Matplotlib) at <https://github.com/sandlerleon/neutral-morphological-masking> (MIT license) and archived with a permanent DOI on Zenodo: <https://doi.org/10.5281/zenodo.22150668>. The manuscript itself is additionally archived as a preprint on Zenodo: <https://doi.org/10.5281/zenodo.22150664>. All parameter values are specified as named constants in the code for reproducibility.

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Figures

Architecture of an Information-Maintaining Artificial Cell

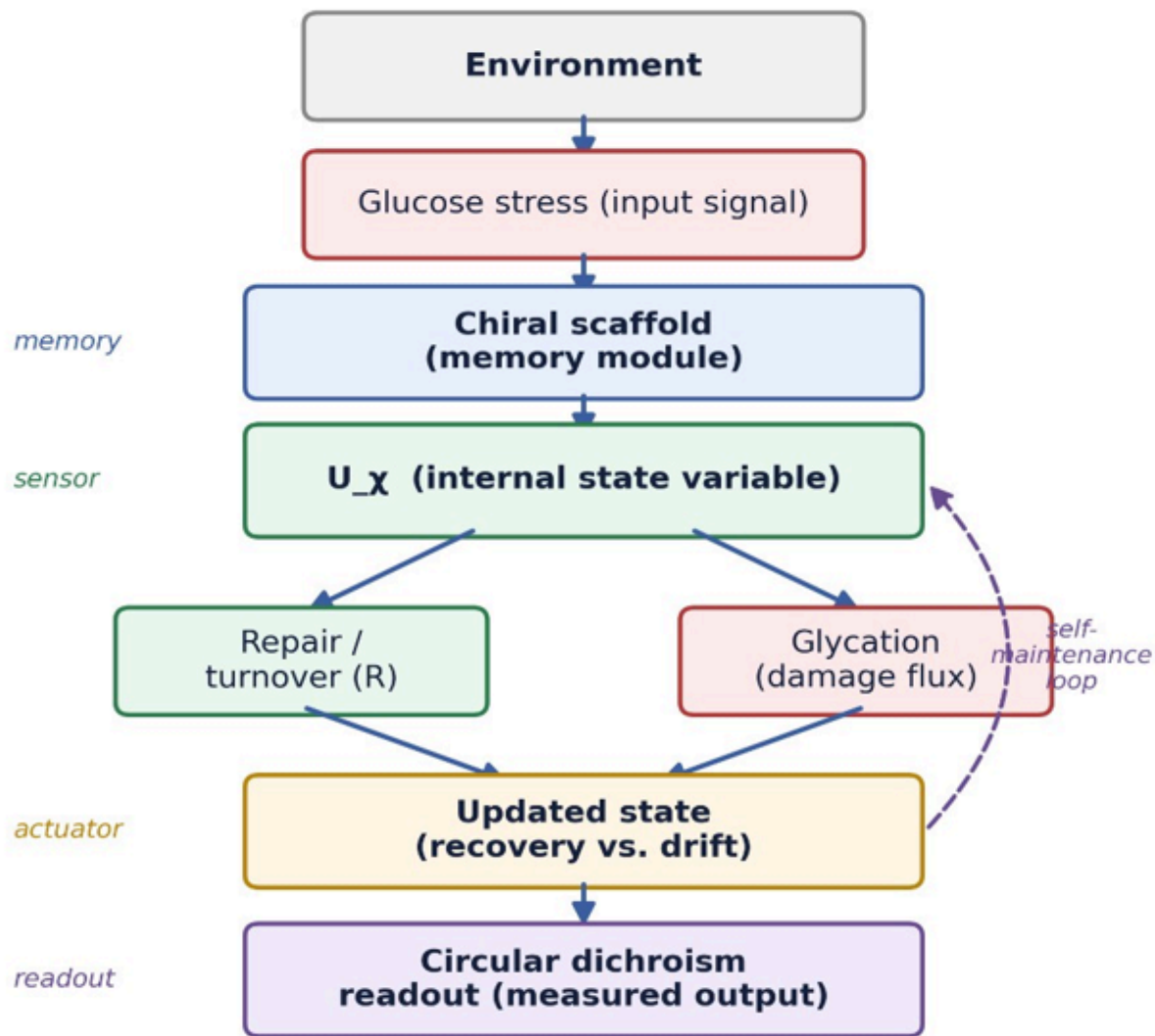


Figure 1

Architecture of an information-maintaining artificial cell, retained from the original submission (Sandler, 2026b). In the synthesized framework, the “Repair / turnover (R)” and internal-state boxes are additionally shaped over evolutionary time by the masking loop of § 2: what this diagram shows as an engineered steady state, § 6.2 shows can instead be an evolved one.

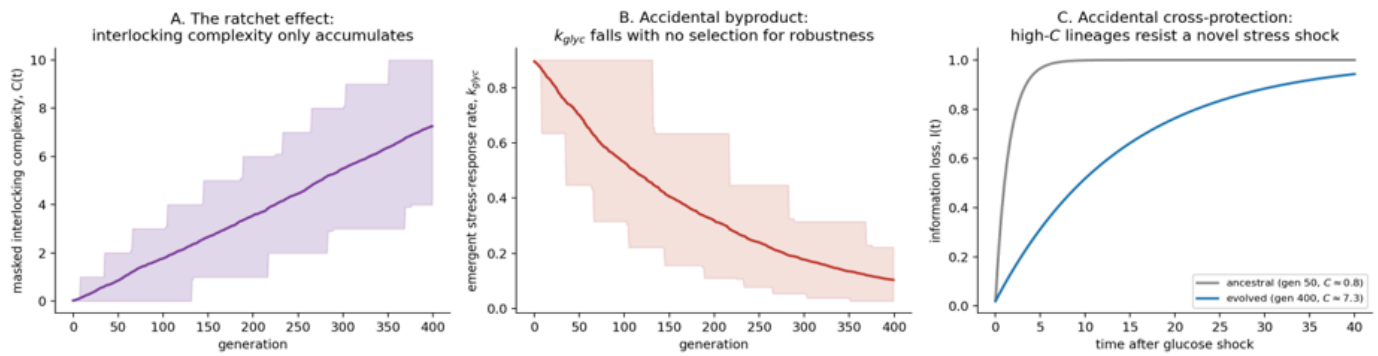


Figure 2

Toy simulation demonstrating the internal consequences of the proposed masking rules (300 lineages, 400 generations, no direct selection for glycation resistance). (A) Interlocking complexity $C(t)$ accumulates monotonically — a ratchet, not a random walk, because masking events are retained rather than reversed. (B) The emergent glycation-rate constant k_{glyc} falls as an incidental byproduct of that accumulation, with no term in the simulation rewarding low k_{glyc} . (C) Lineages frozen at generation 50 (low accumulated C) and generation 400 (high accumulated C) are both exposed to an identical, novel glucose shock at $t = 0$; the high- C lineage shows markedly slower information loss — an accidental cross-protection this framework predicts, illustrated here rather than independently confirmed.