

Compositional Proofreading through Critical Self-TuningOmer Karin¹*Department of Mathematics, Imperial College London, London, SW7 2AZ, United Kingdom*

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High-dimensional multicomponent systems, including immune and epigenetic repertoires, must selectively retain rare, beneficial components while purging a large influx of suboptimal variants. I demonstrate that critical tuning of component control parameters through competition naturally implements proofreading in these systems. Competition for shared inputs pins the system to the marginal stability threshold of the most persistent species. This grants that species an extended lifetime and concentrates a macroscopic fraction of the population in that species, while forcing less-stable variants into rapid drift-driven turnover. When the aggregate drive exceeds a critical influx, pinning fails and all components enter a rapid-turnover regime. Applying this framework to biological memory, I identify the hallmarks of this effect in plasma cell accumulation dynamics and propose that altered pinning dynamics may represent failure points across biological domains, including cancer, immunodeficiencies, and the aberrant activation of harmful genomic elements during aging.

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Introduction—A fundamental requirement for biological organization is the ability to amplify and retain high-quality, functional components. At the molecular scale, the fidelity of replication, translation, and signal transduction relies on distinguishing correct substrates from a background of chemically similar, but functionally inferior, competitors. The classical solution to this problem is kinetic proofreading [1–5], where energy dissipation is coupled to irreversible steps to actively reject incorrect intermediates.

An analogous challenge arises at the macroscopic scale, in populations of long-lived components undergoing continuous turnover. Their composition is set by fate decisions in high-dimensional regulatory networks, which must selectively retain rare, beneficial components while purging a far larger influx of suboptimal variants. Examples include cell-based adaptive immunity [6–9], epigenetic memory [10,11], neural development [12–14], and stem cell persistence [15,16]. The exploratory nature of these processes is thought to be crucial for conferring robust and evolvable functionality [17].

An important question is how the underlying regulatory networks may achieve high-fidelity compositional proofreading without centralized control. The dynamics of component removal in these systems point to a possible mechanism. Decisions regarding survival and death are

frequently governed by discontinuous tipping points [16,18–21]. In this dynamical regime, a component may be stable until a control parameter crosses a critical threshold, triggering a rapid, irreversible transition to elimination. Near such tipping points, systems exhibit a steep dependence of transition rates on underlying parameters, as well as critical slowing down [11,16,22,23]. A wide range of biological systems, including immune and epigenetic memory, have components that appear to operate near criticality [9,11,16,24].

Recent work has shown that self-tuning to the vicinity of a critical point naturally emerges from competition over shared factors that couple the control parameters of different components [9,11,16,25]. For example, immune memory cells compete for common survival factors, while epigenetic memory units (such as silenced genomic regions) compete globally over shared enzymatic machinery. The interplay between stochastic production and coupled removal constrains component turnover through a queue-like mechanism. This process, which is termed self-tuning by competition, provides a generic route for components to organize near a critical point and generates characteristic system-level responses to perturbations [11].

Here, I propose that critical self-tuning by competition serves as an efficient compositional proofreading mechanism through a pinning transition. To show this, I extend previous analyses of homogeneous populations to heterogeneous repertoires consisting of species with varying sensitivities to stabilizing signals. In this setting, competition for shared resources pins the common environment to the critical point of the most stable species. This pinning [26,27] creates dynamical segregation in which stable species persist in a critically slowed state, while less stable

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species undergo rapid, deterministic removal and are efficiently depleted from steady-state repertoires. Conversely, increased aggregate production can drive the system into a depinned regime where proofreading capacity is lost, a transition that may contribute to pathological conditions.

Model—Consider a system composed of R interacting species. A Poisson process with rate λ_r introduces components of species r into the system. The removal mechanism of each component is governed by a high-dimensional regulatory network, whose dynamics near a loss-of-stability threshold are represented by the stochastic saddle-node normal form (Supplemental Material, Sec. S1 [28]) as follows:

$$dx_{i,r} = [x_{i,r}^2 - \mu_r + h(t)]dt + \sigma dW_{i,r}, \quad (1)$$

where the variable $x_{i,r}$ represents the reaction coordinate of the i th component of species r , $dW_{i,r}$ denotes a standard Wiener increment, and σ is the noise amplitude. The intrinsic stability parameter $\mu_r > 0$ sets the baseline distance to the bifurcation point. The global field $h(t)$ is determined by the population of active components $N_r(t)$ according to

$$h(t) = \sum_{r=1}^R \gamma_r N_r(t), \quad (2)$$

where the coupling constant $\gamma_r \geq 0$ quantifies the contribution of species r to the global field.

Components are defined as active while they reside within the viable region of the state space, $x < x_{\text{esc}}$. The mean residence time $\tau(z)$, defined as the mean first-passage time to x_{esc} for a component with effective barrier $z \equiv \mu_r - h$, interpolates between Kramers escape for $z > 0$ and drift-driven transit for $z < 0$ (Supplemental Material, Sec. S2 [28]).

For clarity, I focus on a finite set of discrete species, ordered by intrinsic stability such that $\mu_1 < \mu_2 < \dots < \mu_R$; exact and near degeneracies, together with continuous stability distributions, are analyzed in Supplemental Material [28]. The mean residence time (or lifespan) of components of species r is given by $T_r = \tau(z_r)$.

Equations (1) and (2) define a closed feedback loop, where component accumulation raises h , reducing the barriers ($z_r = \mu_r - h$) and accelerating removal.

Single-species model—I first analyze the behavior of a single species with stability μ and self-interaction γ . The mean residence time $\tau(z)$ depends on the effective barrier $z = \mu - \gamma N$. The steady-state population N is then determined by the balance between production and removal, $N = \lambda T$.

This governing equation reveals a crossover between two distinct dynamical regimes, separated by a characteristic production scale $\lambda_c = 2\mu^{3/2}/(\pi\gamma)$ (Supplemental Material, Sec. S3 [28]). In the *pinned regime* ($\lambda \ll \lambda_c$), the population

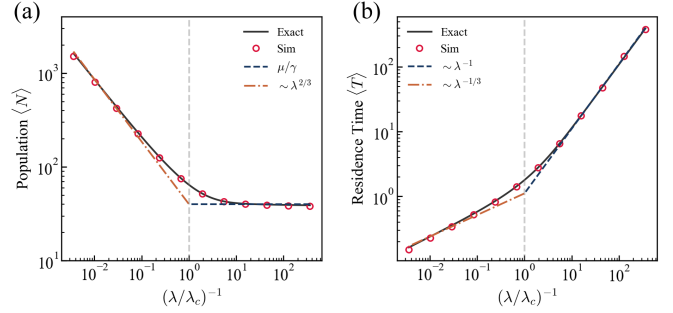


FIG. 1. Single-species competitive self-tuning. Steady-state statistics for $\mu = 2.0$ and $\gamma = 0.05$ versus normalized inverse drive $(\lambda/\lambda_c)^{-1}$. (a) Mean population: $N \approx \mu/\gamma$ when pinned and $N \propto \lambda^{2/3}$ after depinning. (b) Mean residence time, with $T \propto \lambda^{-1/3}$ in the drift-driven regime. Dashed line: $\lambda = \lambda_c$; circles: simulations; solid lines: theory.

increases until the effective barrier vanishes ($z \rightarrow 0$). The occupancy is pinned to the capacity $N \approx \mu\gamma^{-1}$ [Fig. 1(a)], independent of the production rate λ . Consequently, the residence time scales inversely with drive, $T \approx \mu\gamma^{-1}\lambda^{-1}$ [Fig. 1(b)].

Conversely, in the *drift-driven regime* ($\lambda \gg \lambda_c$), the drive is sufficient to collapse the barrier entirely ($z < 0$). The population is then limited only by the transit speed through the saddle-node region. Using the scaling $\tau(z) \approx \pi/(2\sqrt{|z|})$, the population scales as $N \approx \mu\gamma^{-1}(\lambda/\lambda_c)^{2/3}$. The residence time exhibits a crossover to a power-law decay, $T \approx T_c(\lambda/\lambda_c)^{-1/3}$, where $T_c = \pi/(2\mu^{1/2})$ is the characteristic residence-time scale at the onset of the pinned regime. Notice that pinning requires only a sharp threshold dependence of residence time and feedback through a shared field; the exponents derived above are specific to the nondegenerate saddle-node class [45,46].

Proofreading in multispecies competition—I now generalize to R interacting species coupled via the global field h . The steady state is determined by the self-consistency conditions on individual species, $N_r = \lambda_r \tau(z_r)$, from which the self-consistency condition on the global field derives

$$h = \sum_{r=1}^R \gamma_r \lambda_r \tau(\mu_r - h). \quad (3)$$

The system's macroscopic state is controlled by the aggregate interaction flux, $\Lambda \equiv \sum_r \gamma_r \lambda_r$. Competition between this aggregate drive and the maximum barrier in the repertoire, $\mu_{\text{max}} \equiv \max_r(\mu_r)$, gives rise to a transition and defines the characteristic influx scale (Fig. 2; Supplemental Material, Sec. S3 [28]) as follows:

$$\Lambda_c = 2\mu_{\text{max}}^{3/2}/\pi. \quad (4)$$

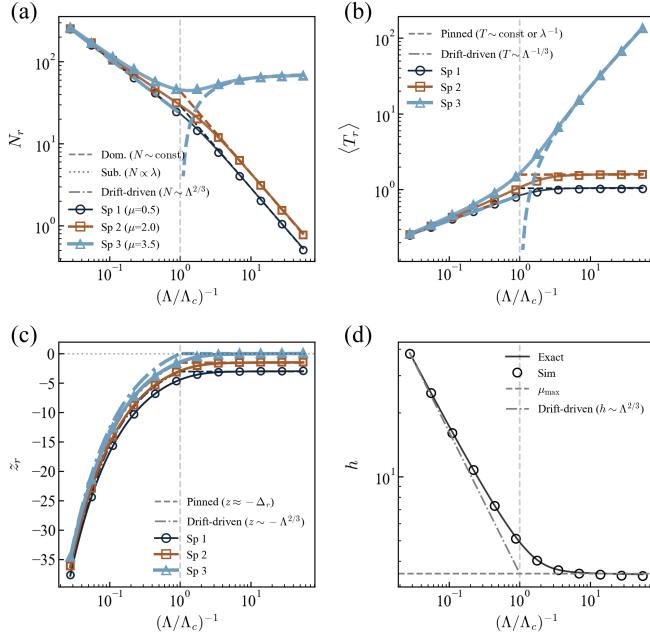


FIG. 2. Multispecies competitive self-tuning. Steady states for three species with $\mu \in \{0.5, 2.0, 3.5\}$ versus normalized inverse aggregate flux. (a) Populations, (b) residence times, (c) effective barriers, and (d) global field. The field pins near $\mu_{\max}$ below Λ_c and grows as $\Lambda^{2/3}$ above it. Dashed line: Λ_c ; symbols: simulations; lines: theory.

This scale organizes the crossover between the pinned asymptotic regime, $\Lambda \ll \Lambda_c$, and the drift-driven asymptotic regime, $\Lambda \gg \Lambda_c$. The precise loss-of-pinning threshold, Λ_{cond} , additionally depends on the species composition and is given in Supplemental Material, Sec. S3 [28].

For low drive, the self-consistency condition [Eq. (3)] demands that the global field be pinned near the largest barrier: $h \approx \mu_{\max}$. The maximally stable species is assumed to be unique r^* , with $\mu_{r^*} = \mu_{\max}$. Exact or near degeneracies replace this single dominant species by a copinned set of near-maximally stable species, without changing the pinning mechanism itself. This pinning creates a sharp timescale separation between the dominant species (r^* , where $\mu_{r^*} = \mu_{\max}$) and all subdominant species ($r \neq r^*$). The subdominant species have a finite effective stability gap $\Delta_r = \mu_{\max} - \mu_r > 0$. For gaps outside the noise-rounded critical region, $\Delta_r \gtrsim \sigma^{4/3}$, their populations are linear in their production rates as follows:

$$N_r \approx \lambda_r \tau (-\Delta_r) \quad (r \neq r^*). \quad (5)$$

In contrast, the dominant species fills the remaining capacity. Its population is determined not by its production rate, but by the space left by the subdominant species as follows:

$$N_{r^*} \approx \frac{1}{\gamma_{r^*}} \left(\mu_{\max} - \sum_{r \neq r^*} \gamma_r N_r \right). \quad (6)$$

This mechanism grants the dominant species an effective lifetime $T_{r^*} \propto \lambda_{r^*}^{-1}$ that can be orders of magnitude larger than the intrinsic timescales of the subdominant components. Because the dominant population is set by the residual capacity rather than by its own influx, even a rare stable variant comes to occupy an $\mathcal{O}(1)$ fraction of the population, approximately independent of λ_{r^*} . No tuning of the shared field is required, as competition itself places it near the marginal stability of the most stable species present. This condensation [47,48] of the population into the dominant species, triggered by the pinning of the global field h , is the fundamental mechanism driving compositional proofreading.

When the aggregate flux exceeds Λ_c , the pinning mechanism fails. The global field grows as $h \approx \mu_{\max} (\Lambda/\Lambda_c)^{2/3}$, collapsing the potential barriers for all species. In this regime, the distinction between dominant and subdominant species vanishes. Removal is dominated by drift, and the lifetimes of all components degrade as $T \approx \pi/(2\sqrt{h}) \sim \Lambda^{-1/3}$.

These results establish self-tuning by competition as a proofreading mechanism acting on steady-state composition. Competition pins the shared environment to the marginal stability threshold of the most persistent species, concentrating occupancy in maximally stable components while depleting less stable ones. In this way, heterogeneity in intrinsic stability is converted into a sharp separation in representation. The mechanism selects for stability rather than function directly and therefore implements proofreading only when the processes that generate the repertoire confer greater stability on components of higher functional quality. When the aggregate drive exceeds the pinning capacity, this selectivity is lost and the repertoire becomes nondiscriminating as all components enter a drift-driven turnover regime.

Sequential assembly—The compositional proofreading mechanism described so far concerns the properties of the system at steady state. I therefore proceed to examine the system's relaxation to steady state from an initially empty configuration, $N_r(0) = 0$ for all r .

For a single species, the effective barrier is initially large ($z = \mu > 0$), suppressing decay. The population grows linearly, $N(t) \approx \lambda t$, until it reaches the bifurcation threshold at the accumulation timescale $t_{\text{acc}} \approx \mu/(\gamma\lambda)$. In the multi-species case, all populations initially grow linearly, driving a collective, monotonic increase in the global field $h(t) = \sum_r \gamma_r N_r(t)$ (Supplemental Material, Sec. S4 [28]). However, this collective accumulation is punctuated by a sequence of instabilities that result in a sawtooth-like trajectory for the individual populations {Fig. 3(a), Supplemental Material, Sec. S5 [28]}.

To gain analytical insight into this sawtooth-like trajectory, consider the limiting case of strong separation of accumulation timescales between species. In this limit, a subcritical species k initially approaches its single-species capacity, $N_k^{\text{peak}} \approx \mu_k/\gamma_k$, before the collective field triggers

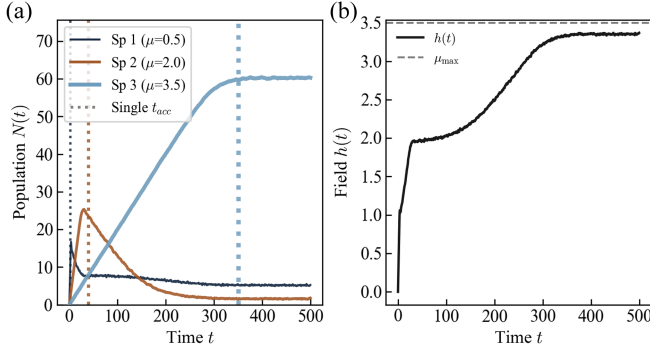


FIG. 3. Sequential assembly from an empty state. Dynamics for $\lambda \in \{5.0, 1.0, 0.2\}$, corresponding to $\mu \in \{0.5, 2.0, 3.5\}$. (a) Species populations: low-stability, high-flux species transiently overshoot and collapse as more stable species accumulate. Dotted lines mark $t_{acc} = \mu_r/(\gamma\lambda_r)$. (b) The shared field $h(t)$, which rises monotonically despite population collapses.

the bifurcation. Upon crossing the threshold, the population declines toward its drift-driven steady state, $N_k^{ss} \approx \lambda_k \tau(-\Delta_k)$.

While the individual population N_k collapses, the global field $h(t)$ remains monotonic [Fig. 3(b)]. The collective field is sustained by the continued linear accumulation of the more stable species ($j > k$). However, the loss of species k reduces the aggregate driving flux contributing to the growth of $h(t)$ to $\Lambda_{k+1} = \sum_{j=k+1}^R \gamma_j \lambda_j$. The time required to drive the field from μ_k to the next barrier μ_{k+1} thus scales inversely with Λ_{k+1} . The global field therefore progressively purges low-stability components, leaving only the most stable species to drive the system toward its final steady state.

Application to immune memory—Humoral immune memory is a system in which competition has recently been proposed to tune component persistence near a tipping point [9], and in which the conditions for compositional proofreading are plausibly met. Long-lived plasma cells (LLPCs), which reside in the bone marrow and can secrete antibodies for years to decades in humans, are generated following infection or vaccination alongside a far larger population of short-lived plasma cells (SLPCs) [7,9]. LLPC enrichment is preferentially induced by immune challenges bearing strong pathogen-associated or inflammatory features, and is associated with antibodies that confer durable protection [49–51], so that plasma-cell intrinsic stability μ is plausibly correlated with functional quality. Although the flux of SLPCs into the marrow greatly exceeds that of LLPCs ($\lambda_s \gg \lambda_l$), the steady-state repertoire is dominated by LLPCs ($N_l > N_s$) [52,53]. Below I examine the resulting signatures in steady-state composition and assembly dynamics, and suggest that characteristic pathologies may correspond to failures of pinning.

Plasma cells compete for shared survival factors, so the bone marrow niche is modeled as a two-species system

[7,9,54–56]. I set $\mu_l = 1$ and $\mu_s = 1 - \Delta$, where $\Delta > 0$ is the stability gap, and use physiological estimates of plasma-cell influx and niche capacity [9] (Supplemental Material, Sec. S6 [28]). Fixing the coupling by the capacity normalization $\gamma = \mu_l/N_{\text{niche}}$ gives an aggregate flux $\Lambda = \gamma(\lambda_s + \lambda_l)$, with $\Lambda^{\text{hum}} \approx 10^{-2}$ and $\Lambda^{\text{mice}} \approx 10^{-1}$. Both estimates lie below the depinning threshold, placing healthy bone marrow in the proofreading regime. The natural drift-turnover time maps approximately to a physiological timescale of days [9].

In the pinned regime, the steady-state population of the dominant species decouples from its production rates. The dominant LLPC population fills most of the niche, while the subdominant SLPC population is suppressed [Fig. 4(a)]. The residence times reflect this separation, with $T_s \sim \mathcal{O}(1)$ (days) versus $T_l \approx \mu_l/(\gamma\lambda_l)$, which corresponds to years in humans and months in mice [Fig. 4(b)].

The model produces transient dynamics consistent with repertoire assembly during ontogeny or recovery from plasma cell depletion, including after measles infection [57–59], Fig. 4(c)}. Starting from an empty niche, the global field grows rapidly as $h(t) \approx \gamma\lambda_s t$. This early phase is dominated by the high-flux SLPCs, which subsequently collapse due to the sawtooth instability described previously. The purging of these lower-stability components is

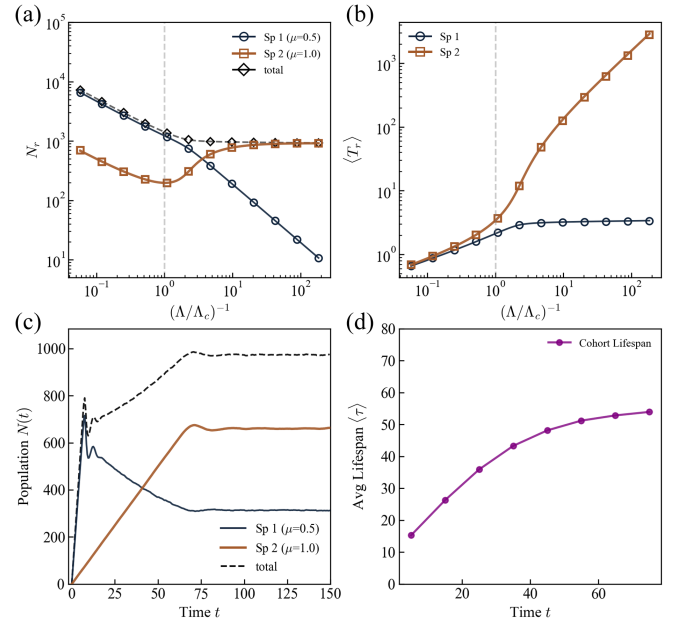


FIG. 4. Compositional proofreading in humoral memory. Two-species simulations with SLPCs (Sp1, $\mu = 0.5$) and LLPCs (Sp2, $\mu = 1.0$). (a)–(b) Populations and residence times across the depinning transition; symbols show simulations and solid lines the self-consistent theory. (c) Assembly from an empty niche, showing transient SLPC accumulation followed by LLPC enrichment. (d) Mean lifespan of cells present at the indicated time, followed until removal or end of the simulation. Parameters correspond to a representative murine microniche; mapping is given in Supplemental Material [28].

driven by the slow, linear accumulation of LLPCs over a timescale T_I (several months in mice, several years in humans), progressively extending the average plasma cell lifespan [Fig. 4(d)]. This two-phase remodeling is consistent with accumulation dynamics in mice [53,54,60–63], where SLPC numbers rise over days before a months-long transition toward an LLPC-enriched phenotype that tracks age and total plasma-cell number, is accompanied by progressive lifespan extension, and is recapitulated after depletion. In humans the predicted timescale is several years, comparable to the period over which antibody repertoires are built in early childhood and rebuilt after measles-associated depletion of humoral memory [58,64]. Competitive LLPC enrichment may therefore serve as a dynamical signature of compositional proofreading, and T_I as a constraint on how quickly durable protection can be established.

The framework points to two distinct ways proofreading can fail in this setting. The first is loss of pinning. When the aggregate flux exceeds the threshold, $\Lambda \gg \Lambda_c$, the effective barriers collapse and all components, including LLPCs, enter the drift-driven regime. Warts, hypogammaglobulinemia, infections, and myelokathexis syndrome [9,65–67] may reflect such a failure, where despite large-scale plasma-cell production and high marrow cellularity, long-term memory is impaired, consistent with a crowded but rapidly turning-over niche.

The second mode preserves pinning but redirects it toward a pathological state, and may manifest in multiple myeloma, a malignancy of bone-marrow plasma cells typically associated with the emergence of clones with enhanced sensitivity to survival factors [68]. Such clones have larger effective stability than healthy LLPCs, $\mu_{\text{cancer}} > \mu_I$, and the model predicts that they pin the shared field to their own marginal stability, depleting the healthy plasma-cell population. This is the clinical hallmark of multiple myeloma, in which malignant clones progressively replace normal plasma cells and other niche-dependent populations, producing severe immunoparesis [69–71]. The two routes need not be exclusive, as highly proliferative clones could additionally drive immunoparesis through depinning. Importantly, the two failure modes make distinct perturbative predictions. In the model, flux-driven depinning is preferentially reversed by lowering aggregate drive, whereas pathological repinning is preferentially affected by perturbations that reduce the malignant clone's access or sensitivity to survival signals.

Conclusion—This Letter proposes a compositional proofreading mechanism fundamentally distinct from classical kinetic proofreading. Whereas classical models rely on biochemical kinetic rates, compositional proofreading operates through competition among high-dimensional dynamical memory units coupled via shared control parameters. In such systems, critical self-tuning implements proofreading by pinning the shared environment

to the marginal stability of the most persistent species, selectively retaining stable components while driving sub-optimal variants into a drift-driven regime of rapid turnover.

The framework reveals an intrinsic speed-fidelity trade-off in compositional proofreading. While repertoire assembly accelerates with aggregate influx [$t_{\text{acc}} \sim \mu_{\text{max}}/(\gamma_r^* \lambda_r^*)$, which scales as Λ^{-1} at fixed composition], efficient proofreading requires $\Lambda \ll \Lambda_c$, and selectivity degrades as the transition is approached. This tension parallels the speed-accuracy trade-off in classical kinetic proofreading [1,2,72], where additional irreversible steps sharpen substrate discrimination at the cost of time and energy dissipation. In this setting, the cost of a high-fidelity repertoire is an extended formation timescale.

Proofreading mechanisms differ in the physical basis and scale of selectivity. Classical kinetic proofreading enhances molecular discrimination through a chemically driven, effectively irreversible step that gives incorrect intermediates additional opportunities to dissociate [1,2]. Conformational proofreading exploits structural mismatch and can improve specificity without a dedicated nonequilibrium cycle [73]. Compositional proofreading differs from both in that no additional step is applied to any single component; selectivity is tuned collectively, by the continual influx and removal of components competing through a shared environmental field. It therefore describes an open, driven population, sustained out of equilibrium by continual energy input. It is also distinct from models of self-organized criticality [74–77], in that the critical point is local to each component rather than a collective property of the bulk, so that what diverges is the lifetime of individual components, and with it the separation between component lifetimes (Supplemental Material, Sec. S7 [28]).

The framework may also apply to eukaryotic genome silencing. Repetitive elements and retrotransposons are repressed by heterochromatin whose maintenance depends on limiting pools of shared silencing factors, including sirtuins [78–80]; competition and redistribution of these factors among silenced loci [81] realize the coupling of Eq. (2). Pinning would then confer durable repression on the elements that most strongly recruit this machinery, provided recruitment cues track deleterious potential, as suggested by the preferential recognition of intronless and other non-self elements [82–85]. Age-associated erosion of heterochromatin, which derepresses repetitive elements and contributes to age-related dysfunction [86,87], is a candidate depinning failure. As silencing capacity declines [79,88,89], the model predicts a progression from persistent repression through intermittent silencing, with shortening silent-state residence times, to broad loss of silencing; intermittent rDNA-silencing losses during yeast replicative aging are consistent with such a precursor state [90].

Compositional proofreading, and its failure through depinning, may arise well beyond the systems considered here. Because the pinning transition threshold is coarse grained, fidelity can fail through increased influx, altered

coupling, or reduced maximal stability. The essential ingredients are component influx, threshold-limited persistence, and competition through a shared control field. Wherever these co-occur, dominant components should become buffered against their production rates, while compositional fidelity declines with increasing aggregate drive.

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Data availability—The code used to generate all figures is available at [91].

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