

Learning Principle for the Adaptive Shaping of Epigenetic Memory Repertoires

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Biological systems maintain long-term memories that guide future behavior but face the challenge of retaining beneficial memories while eliminating harmful ones. This challenge is exemplified in gene silencing mechanisms, which must suppress deleterious genetic elements without affecting essential genes. These systems face a fundamental credit assignment problem, as the fitness consequences of individual memory units are revealed only through aggregate physiological outcomes such as cellular growth or DNA damage. We propose that eukaryotic gene silencing mechanisms address this challenge through fluctuation-driven feedback. Silenced genomic regions are memory units whose stability depends on fluctuating residual transcription, and different genomic regions are coupled through shared epigenetic modifiers that respond to global stress signals. Our analysis shows that this feedback loop preferentially stabilizes the silencing of harmful elements, enabling adaptive refinement of the memory repertoire over time. The model explains the paradoxical reliance of stable silencing on residual transcription and the adaptive role of stress-induced desilencing, makes specific testable predictions, and illustrates how fluctuation-driven feedback can shape memory repertoires in biological systems.

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I. INTRODUCTION

Eukaryotic genomes contain many transposable elements and other potentially harmful sequences alongside essential genes and regulatory regions [1,2]. Only a small fraction of these elements remain functionally active and potentially deleterious at any given instant, while many have been co-opted over evolutionary timescales into regulatory roles such as enhancers [3,4]. Eukaryotes suppress harmful elements through specialized silencing mechanisms based on DNA and chromatin modifications and small RNA molecules [5–11]. These silencing states are not permanent but are established and lost in response to environmental, developmental, and spontaneous cues, generating long-term epigenetic variation [4,6,12,13].

The plasticity of silencing introduces significant risks. Aberrant activation of harmful elements such as retrotransposons can compromise genomic integrity and has been implicated in aging and disease [14–17], while inappropriate silencing of beneficial or co-opted loci can be similarly deleterious. Although genomic features such as sequence composition influence the initiation and maintenance of silencing [18–20], these features alone may not reliably distinguish harmful elements from benign or beneficial ones, particularly when environmental conditions shift the costs and benefits of expression.

How, then, does the silencing machinery determine which states to keep and which to discard? Silencing a single locus

may be beneficial, neutral, or harmful, but this consequence is not observable at the locus itself. It emerges only indirectly through aggregate physiological outcomes such as growth rate or genomic integrity. Assigning credit or blame to individual silencing decisions based on these global signals is an instance of the credit assignment problem, a challenge that arises broadly in memory and learning systems [21,22], and it is the central question of this paper.

A striking feature of epigenetic silencing systems across eukaryotes is their high sensitivity to stress signals, which can trigger rapid and widespread desilencing of numerous loci [23–28]. This phenomenon was central to the discovery of transposable elements, as Barbara McClintock first observed their activation and transposition in maize under genotoxic stress [29,30]. Mechanistically, stress-induced changes in cellular physiology, such as during heat shock or DNA damage, can disrupt silencing by modulating the activity of maintenance enzymes [25,31,32]. For example, in mammals the retrotransposon-repressing factor SIRT6 translocates rapidly, on the timescale of seconds to minutes, in response to DNA damage, leading to the de-repression of transposable elements [15,28,33–35]. Upon return to normal conditions, silencing is typically reestablished, though this process may occur gradually over a prolonged timescale [24,32,36].

This stress sensitivity is puzzling, given that de-repression of silenced elements is typically deleterious. The paradox is particularly evident for transposable elements, whose activation is triggered by DNA damage signaling, even though retrotransposons themselves induce DNA damage and genome instability [3,26,37]. One hypothesis suggests that stress-induced desilencing increases population-level variation for natural selection [26], but this is difficult to reconcile with the harmful effects of transposon activation in somatic tissues [28,38].

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Here, we propose stress-mediated desilencing functions as an adaptive learning or proofreading mechanism that enables silencing systems to selectively retain the repression of harmful elements and reactivate beneficial ones. Our analysis is based on the observation that across many eukaryotic gene silencing systems, the maintenance of gene silencing requires active, low-level transcription from the silenced loci [7,8,11,20,39–61]. This “leaky” expression is crucial for recruiting silencing-associated enzymes and producing silencing-associated factors, including small RNAs and silencing chromatin modifications, yet it also permits fluctuating, low-level activity of the silenced loci [62–66]. We will show that this paradoxical regulation produces markedly different silencing fates for harmful versus beneficial or neutral elements.

Intuitively, within this framework, fluctuations in the leaky expression of a silenced gene affect its silencing stability through two channels. Locally, such fluctuations modulate the maintenance of the gene’s own silencing machinery. Globally, they alter the stress signal that destabilizes silencing across the genome. For a harmful element whose expression increases stress, these two channels act in opposing directions and partly cancel each other out, as a fluctuation that locally reinforces silencing simultaneously raises stress and destabilizes silencing elsewhere. This cancellation buffers the silencing machinery of harmful genes against expression noise, rendering it more stable. For a beneficial element whose expression reduces stress, the two channels reinforce, as a sustained drop in expression both weakens local silencing maintenance and, by raising stress, destabilizes silencing globally. The resulting amplification of fluctuations in the silencing barrier makes beneficial genes more susceptible to desilencing. We formalize this observation through a general modeling framework and demonstrate how this mechanism refines silencing repertoires over time, leading to the selective retention of silencing for harmful genetic elements.

II. CREDIT ASSIGNMENT PROBLEM IN GENE SILENCING

We model a system of N genetic elements, indexed by $i \in \{1, \dots, N\}$, with expression levels $y_i \in [0, y_{\max}]$, where $y_i = y_{\max}$ signifies full expression and $y_i = 0$ indicates complete silencing. To gain analytical insight, we initially consider a simple model for gene expression with fluctuations captured by a Brownian motion-like process. The expression of each gene is regulated by silencing mechanisms such as siRNAs or chromatin modifications, with dynamics governed by

$$\eta_y^{-1} dy_i = [y_{\max}(1 - \theta_i) + \epsilon \theta_i - y_i]dt + \sigma_y dW_{y,i}, \quad (1)$$

where $\theta_i \in \{0, 1\}$ denotes the silencing state of the gene, $\epsilon \in [0, y_{\max}]$ quantifies the leakiness of the silencing mechanism, σ_y represents the noise intensity in gene expression, η_y^{-1} is the timescale of the dynamics, and $W_{y,i}$ is a Wiener process capturing stochastic fluctuations.

We define an objective function V , given by

$$V = \sum_{j=1}^N \alpha_j y_j, \quad (2)$$

where the coefficients $\alpha_j \in \mathbb{R}$ weight the contribution of each gene’s expression. The function V may represent biologically relevant quantities, such as DNA damage or growth measurements, and is assumed to be measurable by the cell through its impact on biochemical pathways. The additive form is well suited to the setting of long-term silencing of harmful genomic elements, such as autonomous retrotransposons, whose activity contributes largely additively to genomic stress, or of elements that encode essential functional components. For instance, if V corresponds to DNA damage, genetic elements like active retrotransposons that exacerbate damage will have positive coefficients ($\alpha_i > 0$), whereas if V relates to growth rate, elements that enhance growth will have negative coefficients ($\alpha_i < 0$).

To minimize V , the system must selectively silence genes with positive coefficients ($\alpha_i > 0$) while preserving the expression of those with negative coefficients ($\alpha_i < 0$), as the latter reduce V . However, the system can only measure the aggregate value of V without direct access to the individual coefficients α_i . This presents a fundamental credit assignment problem, where the cell must determine how to assign credit or blame to individual loci for their contribution to a global signal.

III. SELECTIVE RETENTION OF SILENCING MEMORIES

To investigate how gene silencing systems may resolve the credit assignment problem, we introduce an explicit model describing the interaction between the objective function V and the silencing machinery. For this purpose, we presuppose a mathematical form for the desilencing process. Heterochromatin in genomic regions typically exhibits bistability, and its dissolution represents a discontinuous (all-or-none) transition [11,67–72]. From the perspective of dynamical systems theory, such transitions are typically low dimensional and can be captured by the stochastic normal form of a saddle-node bifurcation [11,73,74]:

$$dx_i = (x_i^2 + \mu_i)dt + \sigma_x dW_{x,i}, \quad (3)$$

where x_i indexes the stability of the silencing machinery for gene i (more precisely, it captures progression along the slow manifold of the bifurcation), and μ_i measures the distance of the dynamics from the bifurcation point. The parameter σ_x denotes the noise intensity, and $W_{x,i}$ is a Wiener process accounting for stochastic fluctuations. This normal form is universal in the sense that it governs the dynamics near typical destabilization transitions, regardless of the specific molecular nonlinearities (e.g., cooperative binding) in the underlying regulatory network (Appendix A [75]). The system is subcritical when $\mu_i < 0$, with a stable fixed point at $-\sqrt{|\mu_i|}$ representing persistent silencing of locus i . Desilencing, where trajectories diverge as $x \rightarrow \infty$, may occur either through stochastic fluctuations or via crossing into the supercritical state ($\mu_i > 0$) after a typical timescale $\tau_i(\mu_i)$ [76–78].

To map these dynamics to a learning framework [79], we define $\lambda_{i,+}$ as the silencing initiation rate (“on” rate) and $\lambda_{i,-} \sim 1/\tau_i$ as the desilencing rate governed by Eq. (3) (the “off” rate). While initiation is likely determined by fixed genomic features, adaptive shaping of the silencing repertoire depends on modulating the off-rate $\lambda_{i,-}$. Specifically, the sys-

tem must minimize $\lambda_{i,-}$ for harmful elements to ensure their persistent suppression while maximizing it for beneficial elements to permit rapid reactivation. This modulation optimizes both the long-term (equilibrium) silenced fraction $\frac{\lambda_{i,+}}{\lambda_{i,+} + \lambda_{i,-}}$ and the system's robustness in nonequilibrium regimes, where even a single desilencing event of a harmful element, or prolonged silencing of a beneficial one, may have severe fitness consequences.

To capture how destabilization depends on the cellular state, we note that Eq. (3) represents a linearization around a critical transition of a high-dimensional regulatory network. The control parameter μ_i is therefore influenced by multiple physiological variables. Here, we focus on three well-established interactions: (i) the dependence of silencing stability on active transcription from the target gene (see also Appendix B) [7,8,11,20,45–48,58]; (ii) nonspecific competition for shared enzymatic resources required for silencing maintenance, including SIR proteins [10,11,80]; and (iii) modulation by a global control signal V , such as a DNA damage response [15,81]. Linearizing the response around the critical point (Appendix A), we have that

$$\begin{aligned}\mu_i &= \mu_0 + \gamma_1 \sum_{j=1}^N \theta_j + \gamma_2 V + \gamma_3 y_i \\ &= \mu_0 + \gamma_1 \sum_{j=1}^N \theta_j + \gamma_2 \sum_{j=1}^N \alpha_j y_j + \gamma_3 y_i,\end{aligned}\quad (4)$$

where $\mu_0, \gamma_1, \gamma_2, \gamma_3 \in \mathbb{R}$ are constants describing sensitivities of the bifurcation parameter to its inputs. The term $\gamma_1 \sum_{j=1}^N \theta_j$ models resource competition ($\theta_j = 1$ for silenced loci, $\theta_j = 0$ otherwise), $\gamma_2 V$ encodes the global contribution of the objective function, and $\gamma_3 y_i$ represents feedback from the transcriptional output of gene i (see Appendix A for derivation details). Both the local term $\gamma_3 y_i$ and the global term $\gamma_2 V$ depend on expression levels y_j , so they are temporally correlated through shared transcriptional fluctuations, either directly or indirectly via shared chromatin accessibility [82–84]. This correlation is the only structural requirement of the model (see Appendix B). A transient increase in leaky transcription at a silenced locus both reinforces local silencing maintenance (e.g., through siRNA amplification or recruitment of chromatin-modifying enzymes) and contributes to the global signal V (e.g., through aberrant protein expression that triggers a stress response). The biological mechanism behind Eq. (4) is illustrated in Fig. 1.

To understand how Eq. (4) resolves the credit assignment problem, we consider at first a simplified scenario where the silencing states of all genes are fixed and new silencing or desilencing events are ignored (that is, $\sum_{j=1}^N \theta_j = n$ where n is constant). Since y_i are random variables governed by Eq. (1), μ_i is also a random variable. The mean of μ_i for a silenced gene is

$$\hat{\mu} := \mathbb{E}[\mu_i] = \mu_0 + \gamma_1 n + \gamma_2 \left(\sum_{j=1}^n \alpha_j \epsilon + \sum_{j=n+1}^N \alpha_j y_{\max} \right) + \gamma_3 \epsilon,\quad (5)$$

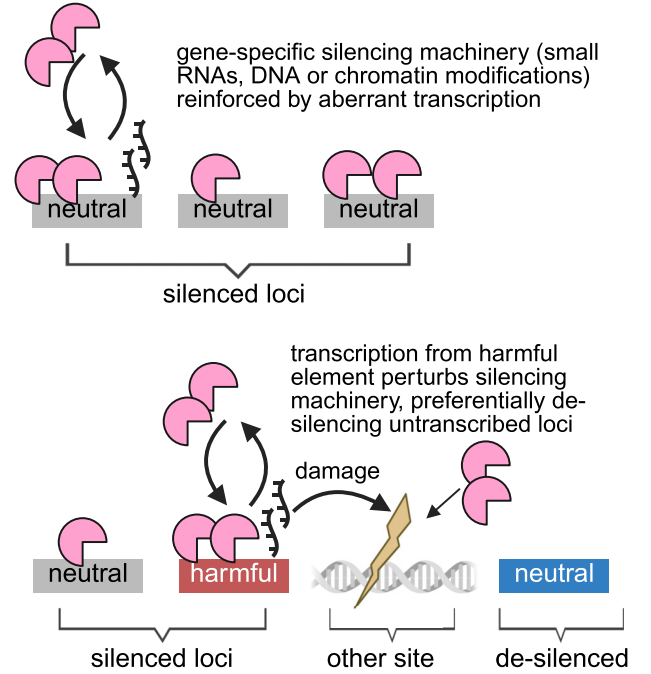


FIG. 1. A stress-feedback loop for the selective retention of gene silencing. The maintenance of gene-specific silencing machinery (e.g., small RNAs, chromatin modifications) depends on low-level, leaky transcription from silenced genetic elements. If an element is harmful, its leaky transcripts can also activate a cellular stress response, such as DNA damage. This stress signal acts globally to perturb and destabilize silencing at many other loci. The harmful element that initiated the response is relatively protected, as its leaky transcription reinforced its own silencing machinery.

and the variance, using $\text{Var}[y_i] = \frac{\sigma_y^2 \eta_y}{2}$, is

$$\hat{\sigma}_i^2 := \text{Var}[\mu_i] = \left((\gamma_2 \alpha_i + \gamma_3)^2 + \sum_{j \neq i} \gamma_2^2 \alpha_j^2 \right) \frac{\sigma_y^2 \eta_y}{2}. \quad (6)$$

The bifurcation parameters μ_i for silenced genes share the same mean ($\hat{\mu}$), but their variances ($\hat{\sigma}_i^2$) differ due to the gene-specific term $(\gamma_2 \alpha_i + \gamma_3)^2$, which depends on the coefficient α_i .

When $\hat{\mu} < 0$, the system is on average bistable, and the silencing duration τ_i reflects the escape time from a fluctuating potential well. In the regime where fluctuations in μ_i dominate, this timescale is

$$\tau_i \approx A_{\hat{\sigma}_i, \hat{\mu}} \exp \left(\frac{C \hat{\mu}^a}{\hat{\sigma}_i^2} \right), \quad (7)$$

where $A_{\hat{\sigma}_i, \hat{\mu}}$ is a prefactor with polynomial dependence on $\hat{\sigma}_i$ and $\hat{\mu}$ (with $a = 2$ for a slow fluctuating barrier and $a = 3/2$ for a fast fluctuating barrier) and C is a constant (see Appendix B). Letting τ_0 denote the silencing duration for a neutral gene ($\alpha = 0$), we obtain the scaling (Appendix C):

$$\tau_i \approx \tau_0 \frac{B_i + \alpha_i^2 + \kappa^2}{B_i + 2\kappa \alpha_i + \alpha_i^2 + \kappa^2}, \quad (8)$$

where $B_i = \sum_{j \neq i} \alpha_j^2$ and $\kappa = \gamma_3/\gamma_2$. This expression shows that τ_i is modulated by α_i : it decreases when α_i and κ share the same sign and increases otherwise. Amplification peaks at

$$\alpha_i = \pm \sqrt{B_i + \kappa^2}, \text{ yielding } \tau_i = \tau_0 \frac{1 \pm \frac{\kappa}{\sqrt{B_i + \kappa^2}}}{\sqrt{B_i + \kappa^2}}.$$

This modulation is asymmetric, as shortening is bounded (with $\tau_i \geq \tau_0^{1/2}$), while extension is unbounded. Taken together, Eq. (8) illustrates how the interplay between global interactions with V and local gene-specific feedback enables the system to resolve the credit assignment problem, selectively stabilizing silencing based on a gene's functional impact.

From the perspective of adaptively retaining silencing memories associated with harmful genetic elements, the key requirement is that their coefficients α_i (i.e., their contribution to the objective function V) have the opposite sign to κ , which governs the interaction between gene transcription and silencing stability.

In known mechanisms, κ is negative, as stable silencing depends on active transcription. This feature likely encodes a core constraint, namely, that silencing memories must correspond to actively transcribed loci, thereby preventing the accumulation of spurious or biologically irrelevant silencing. As a consequence, the system is constrained to interpret harmful genetic elements as those that increase V ; in other words, V must represent a signal of *damage* or *stress*, and this signal must act to destabilize silencing memories. Thus, from first principles, we propose that the classical experimental observation of stress-induced desilencing emerges as a necessary by-product of a mechanism that selectively stabilizes the silencing of harmful elements.

IV. SENSITIVITY OF LEARNING TO SIZE OF THE SILENCED REPERTOIRE

To examine how the size of the silenced repertoire influences the sensitivity of selective retention, we observe that the amplification capacity of gene i is primarily governed by the parameter B_i . This parameter encapsulates the cumulative interaction strength between other silenced genetic elements and the regulatory variable V . Most silenced elements in organisms are typically nonfunctional and contribute minimally to this interaction. For example, the human genome harbors over 500 000 L1 transposable elements, the only autonomous retrotransposons in humans, of which only about 80–100 retain retrotransposition potential [85], with a small fraction, typically fewer than a dozen, exhibiting significant activity in any given cell type [86–88]. Consequently, despite the large number of genetic elements that could serve as targets for silencing mechanisms (large N), only a small subset is likely to have significant positive α_i coefficients within our modeling framework.

To assess the sensitivity of silencing amplification to the size of the silenced repertoire, we consider a symmetric case where genes $i \in \{1, \dots, m\}$ have interaction coefficients of magnitude $\alpha_i = \alpha$, while all other genes have zero coefficients. The amplification factor is then given by

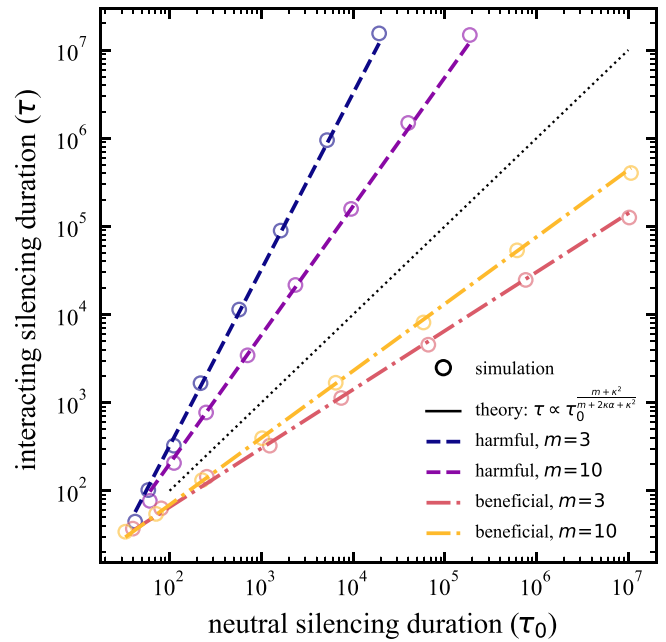


FIG. 2. Amplification and suppression of silencing duration follow a scaling law. Silencing duration of interacting genes (τ) vs neutral silencing duration (τ_0) on logarithmic axes for systems with m interacting genes of a single type. The baseline bifurcation parameter μ_0 is varied to sweep τ_0 across several orders of magnitude while all other parameters are held fixed (Table S1). Open circles show simulation results; lines show the analytical scaling prediction. Harmful genes correspond to $\alpha = -1$ while beneficial genes correspond to $\alpha = 1$.

$\tau_i = \tau_0 \frac{m\alpha^2 + \kappa^2}{m\alpha^2 + 2\kappa\alpha + \kappa^2}$ (Appendix C). This expression achieves maximal amplification when $\kappa = \sqrt{m}|\alpha|$, yielding

$$\tau_i = \tau_0 \frac{\sqrt{m}}{\sqrt{m \pm 1}}. \quad (9)$$

Amplification sensitivity therefore decreases as the number of interacting elements m increases, with the exponent approaching 1 for large m . However, due to the power-law form of Eq. (9), increasing the baseline silencing duration τ_0 enhances the relative change τ_i/τ_0 , resulting in stronger amplification for longer-lived silencing. We tested this by simulating systems with m interacting genes of a single type while sweeping μ_0 to vary τ_0 across several orders of magnitude (Fig. 2, parameters were fixed across different values of m , full simulation parameters are given in Appendix E 1). For both harmful and beneficial genes, the simulated silencing durations follow the predicted scaling across the full range of τ_0 , confirming that the exponents capture the essential dependence on repertoire composition.

Equation (9) highlights a fundamental constraint on gene silencing systems, limiting efficient amplification when the number of active elements (m) is large, as the amplification exponent approaches 1. However, for a small number of active elements, such as the active L1 elements in human cells,

which are silenced for extended periods (large τ_0), the stress-responsive amplification system can be highly effective.

V. EVOLUTION OF SILENCED REPERTOIRES

We now consider how selective retention of silenced genomic elements is maintained within a dynamic silencing repertoire. Previous sections assumed a static repertoire; however, silencing repertoires evolve dynamically, with new silencing events triggered by environmental cues or spontaneous activity. We model this by introducing a flux of new silencing events at a baseline per-gene rate λ_+ . The amplification and maintenance of silencing machineries are coupled through shared biochemical pathways, where the accumulation of silenced genomic elements drives their destabilization [11]. This is captured in Eq. (4) by the global feedback term $\gamma_1 \sum_{j=1}^N \theta_j$, where $\gamma_1 > 0$. Over time, the production of new silenced genomic elements is balanced by desilencing, resulting in a dynamic steady-state repertoire.

The steady-state balance between the creation and desilencing of silenced genomic elements is described by Little's law, given by $\mathbb{E}[n] = \mathbb{E}[\sum_{j=1}^N \theta_j] = \lambda_{\text{total}} \mathbb{E}[\tau]$, where n is the magnitude of the silencing repertoire, $\mathbb{E}[\tau]$ is the expected silencing duration, and λ_{total} is the total influx of silenced genomic elements [$\lambda_{\text{total}} = \lambda_+(N - n)$] [11,89–91]. Due to the high sensitivity of silencing duration near the critical point, the steady-state magnitude of the silencing repertoire can be approximated by identifying the value of n that satisfies $\hat{\mu} = 0$ in Eq. (5), denoted as $\hat{n}$. Thus, the average silencing duration is approximately $\mathbb{E}[\tau_i] \approx \frac{\hat{n}}{\lambda(N - \hat{n})}$, assuming most silenced elements are neutral. Therefore, competition among silenced loci can stabilize a finite mean silencing duration, even in the presence of the strong sensitivity of Eq. (3) near the critical point.

The stochastic nature of silencing and desilencing events introduces noise in the barrier height, driven by fluctuations in the silencing repertoire size n . In a standard birth–death process with a constant removal rate, the variance of n equals its expected value, resulting in small relative fluctuations for large repertoires. Here, however, the removal rate fluctuates due to variations in the barrier height. Additionally, in biological contexts, the expression of silenced loci (e.g., protein or RNA abundance) is likely dominated by small-number fluctuations. These stochastic processes can, in principle, modulate the amplification of silencing duration.

To investigate how a silencing repertoire is learned and refined, we simulated a system of $N = 1000$ genes comprising eight harmful genes ($\alpha_i = +1$), representing elements such as active retrotransposons, two beneficial genes ($\alpha_i = -1$), whose silencing is disadvantageous, and 990 neutral genes ($\alpha_i = 0$), using a Gillespie algorithm [92] for the expression dynamics; full simulation parameters are provided in Appendix E.2. The system was initialized with $n = 500$ genes silenced, chosen near the expected steady-state repertoire size.

The simulation confirms that the repertoire self-organizes around a homeostatic steady state [Fig. 3(a)]. Within this dynamically evolving repertoire, feedback interactions between the global stress signal and local gene expression enable the selective retention of silencing for harmful genes. This

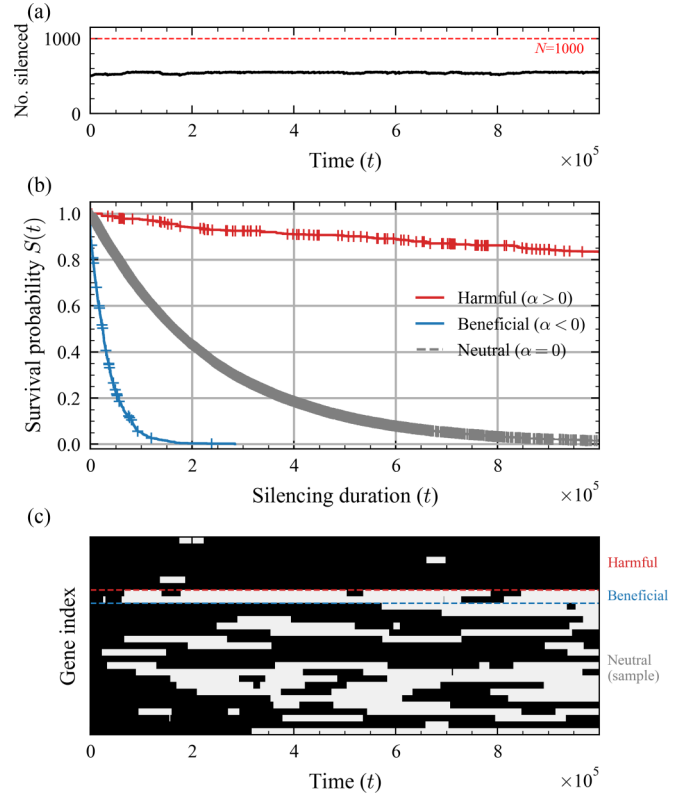


FIG. 3. Learning and selective retention of the silencing repertoire. Results from stochastic simulations of a system of $N = 1000$ genes, starting with $n = 500$ genes silenced. The system comprises eight harmful ($\alpha = 1$), two beneficial ($\alpha = -1$), and 990 neutral ($\alpha = 0$) elements, all with uniform resilencing rates. (a) The total number of silenced genes evolves toward a dynamical steady state as the repertoire is refined. (b) Right-censored Kaplan–Meier survival curves for the duration of silencing events, grouped by functional category and pooled across 100 simulation runs (+ marks indicate censored observations). (c) Kymograph of silencing states (black = silenced) for a single representative run, showing all harmful and beneficial genes together with a random sample of neutral genes. The harmful gene cohort (top block) maintains near-continuous silencing, in contrast to the transient episodes observed for other gene types. Full simulation parameters are given in Appendix E2 (Tables S2 and S3).

is quantified by Kaplan–Meier survival curves of silencing duration [93], pooled across 100 realizations [Fig. 3(b)]: silencing of harmful genes is dramatically more stable than that of neutral or beneficial genes, with a median duration exceeding the full observation window of 10^6 time units. In contrast, silencing of beneficial genes is short-lived, with a median duration approximately an order of magnitude shorter than that of neutral genes. The kymograph of individual gene states provides a complementary view [Fig. 3(c)]. The harmful gene cohort (top rows) maintains near-continuous silencing throughout the simulation, whereas neutral and beneficial genes exhibit transient, intermittent episodes. Together, these results demonstrate that the system can refine its silencing repertoire to preferentially suppress harmful genetic elements without requiring parameter fine-tuning or prior specification of target loci.

VI. EXPERIMENTAL SIGNATURES OF FLUCTUATION-DRIVEN LEARNING

The fluctuation-driven mechanism makes several predictions that distinguish it from alternative explanations for the selective retention of gene silencing.

A key prediction is that the silencing duration of a given genetic element is competitively modulated by other elements in the genome. A harmful element can prolong its own silenced state by triggering a broad stress response that leads to the desilencing of other, less-protected loci. This could be tested by comparing the silencing stability of a reporter gene engineered to interact with a specific stress pathway against an otherwise identical control, under conditions where the stress response is triggered either by the reporter's own leaky transcription or by an exogenous signal. The model predicts a counterintuitive outcome, namely, that activating a stress response through a harmful element's leaky transcription should confer relative protection to that element compared to the global desilencing observed when the same stress pathway is activated directly by an exogenous signal. In contrast, a model in which harmful elements are recognized purely by specific molecular features would predict selective retention regardless of how the stress signal originates.

A further consequence of Eq. (8) is that the silencing duration of a given locus depends on the interaction coefficients of all other silenced loci. Introducing additional elements that interact strongly with the stress response reduces the amplification of existing elements and shortens their silencing duration relative to neutral genes. Similarly, the model predicts that the silencing advantage of a given harmful element should diminish as more stress-interacting elements are added to the system. This could be tested by titrating the number of active harmful elements, for example, by selectively introducing copies of L1 retrotransposons into a mammalian cell line and monitoring the silencing stability of a focal reporter.

Finally, the scaling law of Eq. (9) predicts a specific quantitative relationship between the silencing duration of interacting elements and that of comparable neutral elements, with an exponent that depends only on the number of interacting genes. This relationship can be probed experimentally by modulating the availability of shared silencing factors to vary the baseline silencing duration and measuring the corresponding change in reversion rates for non-neutral elements. On a log-log plot, the slope would directly yield the amplification exponent (Fig. 2).

VII. DISCUSSION

We propose that stress-induced desilencing, a widely observed phenomenon in eukaryotic gene regulation, may function as an adaptive learning mechanism for refining silencing repertoires. This widespread loss of silencing, often triggered by cellular stressors such as DNA damage, has long been puzzling given its typical harmful effects on the cell. Our mathematical framework unifies this paradox with other known features of gene silencing systems, including their reliance on leaky transcription from silenced genes. This framework demonstrates how a dynamic feedback loop enables the system to continuously evaluate the consequences

of gene expression. Through this process, the silencing of elements that increase cellular stress is preferentially retained, driving the dynamic and selective refinement of epigenetic silencing repertoires over time.

The selective silencing of genetic elements is profoundly important for eukaryotic cells, which have vast genomes containing millions of potential regulatory targets. Only a small fraction of these, such as active transposable elements, are harmful, yet their erroneous desilencing can severely impair cellular integrity [3]. In contrast, many elements, such as mutated transposons, may be repurposed as beneficial components, such as regulatory sequences [3,94,95]. For these elements to evolve adaptively and enhance cellular function, their expression is essential. However, distinguishing harmful from beneficial elements is complex, as they often share genomic features and their functional impact shifts with cellular and environmental contexts. Our proposed mechanism addresses this by dynamically linking gene silencing to functional outcomes.

Our fluctuation-driven feedback mechanism complements other, well-studied structural recognition mechanisms that stabilize silencing at specific loci based on genomic features such as sequence composition, repeat density, or chromatin context. Within our framework, such structural features would act primarily on the mean bifurcation parameter $\bar{\mu}_i$, effectively deepening the potential barrier for particular loci independently of their functional consequences. The fluctuation-driven mechanism we describe is complementary, operating on the variance of the bifurcation parameter $\hat{\sigma}_i^2$ and modulating the rate at which stochastic fluctuations drive barrier crossing. These two modes of stabilization are therefore largely independent and act synergistically. Structural recognition sets a baseline silencing propensity, while fluctuation-driven feedback refines the repertoire by selectively tuning silencing persistence according to functional impact.

Theoretically, our mechanism relies on the feedback control of fluctuations. For harmful elements, local feedback reinforces silencing while global stress signals oppose it, forming a negative feedback loop that suppresses fluctuations and extends silencing duration. For beneficial elements, these signals align, creating positive feedback that amplifies fluctuations and shortens silencing duration. While we analyzed this phenomenon using the general framework of a saddle-node bifurcation [11], our conclusions are broadly applicable. The differential effect on stability is a generic feature of stochastic systems with barrier crossing dynamics [96], suggesting our conclusions generalize to a wide class of biological circuits.

For the mechanism to work, the consequences of gene expression must be measurable on a timescale compatible with the expression fluctuations themselves. Eukaryotic gene expression is inherently bursty, with fluctuations occurring on timescales of minutes to hours, providing the dynamic signal the system needs to evaluate [97,98]. Harmful effects due to such fluctuations should then be rapidly evaluated. Consider human L1 retrotransposons as an example: L1 expression rapidly induces DNA double-strand breaks, triggering a DNA damage response that serves as a potent stress signal [99]. This signal subsequently causes the swift translocation of chromatin factors such as SIRT6 from silenced loci to sites

of damage, thereby globally modulating silencing stability [15,34]. The rapid nature of this feedback loop enables the system to correlate specific instances of leaky expression with their harmful consequences and strengthen silencing mechanisms accordingly.

An important consideration is that harmful elements which escape silencing are not symmetrically stabilized in the active state because the system operates in a fundamentally nonequilibrium regime. Retrotransposon activation can trigger DNA damage, cell death, or senescence [16,33], meaning that cells in which a harmful element escapes silencing may be eliminated before the active state can persist. Moreover, the model predicts a self-correcting feature, whereby the activation of a harmful element raises the global stress signal, driving desilencing of other loci and thereby reducing competition for shared silencing maintenance factors. Once the harmful element is resilenced, it encounters a larger pool of available maintenance enzymes, effectively deepening its silencing barrier relative to the pre-escape state.

Because the learning mechanism leverages fluctuations in the leaky expression of silenced loci, it is most effective when a limited number of elements strongly interact with the stress response. A high abundance of harmful elements can diminish the amplification of their silencing duration. For beneficial elements that may be inappropriately silenced, their rapid reversion to full expression allows them to disengage from this fluctuating interaction with the stress response, thereby posing less of an issue for the cell. Consequently, strong evolutionary pressure likely maintains low copy numbers of actively harmful elements, such as retrotransposons, as observed in humans [2,100,101]. In species with more active retrotransposons, like mice, this mechanism may primarily prolong the silencing of only the most potent elements [102]. At the same time, evolution would favor specialized cellular sensors for specific threats, enhancing the precision of credit assignment by partitioning interactions among silenced elements.

While this mechanism can refine silencing repertoires in a closed-loop system, it may be detrimental when stress signals arise from external sources. In somatic tissues, stress signals can induce retrotransposon expression, leading to further DNA damage and cellular senescence [16,103]. Furthermore, our model predicts that an increase in baseline cellular stress reduces silencing duration and steady-state silencing repertoire magnitude (that is, in mathematical terms, an increase in V in Eq. (4) forces a decrease in steady-state n , leading to a decrease in silencing duration τ_0). This effect strongly amplifies the desilencing of harmful elements due to the power-law form of Eq. (8). This effect may underlie the increased retrotransposition observed during aging and under environmental stressors [16,28]. Stress-induced desilencing can therefore be both an adaptive learning tool and a potential driver of cellular and organismal pathology.

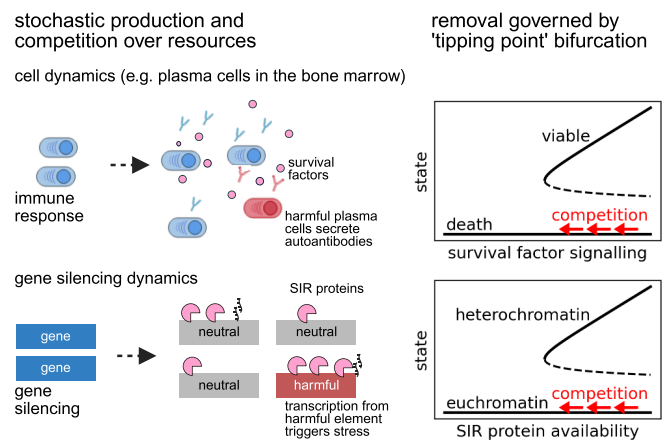


FIG. 4. Control architectures in immune memory and gene silencing. Top: Plasma cell survival depends on competition for limiting survival factors, with loss governed by a tipping-point bifurcation in signaling strength. Bottom: Gene silencing is similarly controlled by competition for limiting SIR proteins, with desilencing transitions governed by analogous bistable dynamics. In both systems, a fluctuation-driven feedback mechanism based on the interaction of memory unit activity with the effective potential barrier (survival factors, SIR proteins) can drive adaptive shaping of the memory repertoire.

Finally, although our analysis has focused on gene silencing, the proposed framework is general and may extend to other biological memory systems shaped by similar feedback dynamics. A natural example is immune memory in the adaptive immune system (Fig. 4). Following infection or vaccination, long-term protection depends on the survival of antibody-producing plasma cells, whose persistence is governed by a bistable switch controlled by niche-secreted survival factors [89]. Competition for these factors resembles the shared-resource dynamics of chromatin modifiers, while plasma cell death parallels desilencing transitions. In this context, autoreactive plasma cells could be preferentially eliminated [104]. Such selective refinement could occur if niche cells targeted by autoantibodies reduce their production of survival factors. Our analysis suggests this mechanism would be particularly effective if antibody secretion fluctuates in concert with susceptibility to elimination, amplifying the removal of autoreactive plasma cells. More broadly, this highlights how fluctuation-driven feedback loops may provide a principle for shaping adaptive memory repertoires across diverse biological systems.

DATA AVAILABILITY

The data that support the findings of this article are openly available [105].

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