PNAS RESEARCH ARTICLE | BIOPHYSICS AND COMPUTATIONAL BIOLOGY
EVOLUTION

Simple biological controllers drive the evolution of soft modes

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Edited by Kunihiko Kaneko, Kobenhavns Universitet, Copenhagen, Denmark; received August 21, 2025; accepted March 7, 2026 by Editorial Board Member Mehran Kardar

Biological systems, with many interacting components, face high-dimensional environmental fluctuations, ranging from diverse nutrient deprivations to toxins, drugs, and physical stresses. Yet, many biological control mechanisms are "simple," i.e., restoring homeostasis through low-dimensional representations of the system's high-dimensional state. How do low-dimensional controllers maintain homeostasis in high-dimensional systems? We develop an analytically tractable model of integral feedback for complex systems in fluctuating environments. We find that selection for homeostasis leads to the emergence of a soft mode that provides the dimensionality reduction required for the functioning of simple controllers. Our theory predicts that simple controllers that buffer environmental perturbations (e.g., stress response pathways) will also buffer mutational perturbation, an equivalence we test using experimental data across 5,000 strains in the yeast knockout collection. We also predict, counterintuitively, that knocking out a simple controller will decrease the dimensionality of the response to environmental change; we outline transcriptomics tests to validate this. Our work suggests an evolutionary origin of soft modes, with implications ranging from cryptic genetic variation to global epistasis.

soft modes | dimensionality reduction | stress response

Significance

Biological systems respond to environmental challenges through surprisingly simple control mechanisms despite their enormous complexity, yet how low-dimensional controllers can regulate high-dimensional networks remains unclear. We develop a theoretical framework showing selection for environmental robustness drives evolution of "soft modes" in biological state space which enable simple controllers to function effectively. Our model predicts soft-mode mediated environmental stress-response systems also buffer mutations, confirmed using fitness data from yeast strains subject to environmental and mutational perturbations. We also validate the counterintuitive prediction that eliminating controllers reduces stress response dimensionality. This work helps explain the ubiquity of low-dimensional control observed across biological systems and provides testable insights for understanding robustness, with implications for evolutionary biology and the molecular biology of stress response.

How can a complex system be maintained at homeostasis without a controller that is as complex as the system itself? Biological organisms have many possible internal degrees of freedom—even single celled organisms have thousands of genes that interact via complex regulatory networks (1). These organisms are able to survive in face of diverse environmental fluctuations that perturb them in a high dimensional way; for example, environmental perturbations can involve different toxins, drugs, and physical stresses like temperature, pH, or osmolarity or the deprivation of different combinations of nutrients.

Naively, homeostasis of such complex systems subject to high-dimensional fluctuations would require a complex controller. For example, a controller might need to monitor many specific aspects of the system state. This could include separately sensing the impacts of amino acid deprivation, carbon limitation, nitrogen limitation, and ribosome-targeting antibiotics, while taking distinct restorative actions for each. However, such a complex controller might be prohibitively costly for an organism to maintain.

In contrast, many low-dimensional controllers have been documented across biology—these controllers project the high-dimensional state of the organism to much lower dimensional space and take restorative actions based on this projection (Fig. 1*A*). For example, in bacteria, while uncharged tRNAs for the distinct amino acids, carbon and phosphate deficiency, and temperature stress represent distinct types of environmental stress, they all converge to modulate the concentration of a single molecule, (p)ppGpp; this low-dimensional representation of the high-dimensional stresses then determines the 'stringent response', regulating transcription, translation, replication, and other aspects of bacterial physiology (2–4) (Fig. 1*C*).

Similarly, diverse aspects of the environment experienced by yeast—glucose levels, amino acid abundance, nitrogen state, and osmotic stress—are integrated into the level of cAMP (5, 6) (Fig. 1*B*). While distinct receptors are dedicated to sensing these different environmental perturbations, their downstream signals are projected down onto a low dimensional variable, the level of cAMP. The integrated cAMP variable then influences diverse downstream processes including transcriptional regulation, metabolic adjustments, and cell cycle control. In the innate immune system, the cAMP pathway homologously senses diverse immune signaling molecules and controls complex immune behavior, including phagocytosis and antimicrobial activity (7, 8).

Here, we build a theoretical framework to understand conditions where simple controllers control complex high-dimensional systems. We define "simple" controllers as

The authors declare no competing interest.

This article is a PNAS Direct Submission. K.K. is a guest editor invited by the Editorial Board.

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This article contains supporting information online at https://www.pnas.org/lookup/suppl/doi:10.1073/pnas.2523032123/-/DCSupplemental.

Published April 21, 2026.

integral feedback mechanisms that regulate a high-dimensional system by first projecting its state onto a low-dimensional representation before sensing and acting. In contrast, "complex" controllers directly monitor and respond to multiple independent aspects of the system's state without such dimensionality reduction. Using simulations of gene regulatory networks and an analytically tractable model of integral feedback control, we show that selection for homeostasis leads to the evolution of a soft mode (alternatively called a dynamical slow mode or slow manifold) in the organism's dynamics if the controller is constrained to be simple. A soft or slow mode is a mode that relaxes slowly; when a system with a soft mode or modes is perturbed in the absence of a control mechanism, some components of the perturbation will decay quickly (stiff directions) while others decay much more slowly (soft directions). That the mode is soft means that arbitrary perturbations will tend to push the system along that mode (9–12). First described by Ginzburg and Anderson in the context of ferroelectricity, soft or slow modes are a common feature of dynamical systems, from condensed matter physics to biological systems (13, 14).

Our framework makes surprising predictions that we test with empirical data. Our model predicts that proteins mediating environmental robustness, such as stress response factors, also facilitate mutational robustness, a prediction we test using data from 5,000 strains in a yeast knockout collection (15, 16). Our framework predicts that knocking out a controller will reduce the dimensionality of environmental perturbation effects, a prediction supported by yeast transcriptomic data, with further experiments suggested.

Prior works have presented explanations that invoke soft modes for the widely observed low dimensional nature of biological systems. These works predict soft modes with a specific structure—for example, the soft mode facilitates communication through allostery in proteins (17–21) or is an internal model of low-dimensional structure in the external world (22, 23). In contrast, in our framework, the soft mode does not need to point in any particular direction in state space, as we do not assign any specific function to the direction of the soft mode. Instead, the presence of any soft mode leads to dimensionality reduction that can be exploited by simple feedback controllers. Large-scale datasets increasingly reveal low-dimensional structure in biological systems across different scales. Our work provides a scale-independent mechanistic explanation for this phenomenon while offering testable predictions for future studies examining both environmental and genetic variation.

Results

In-Silico Evolution Simulations. How are simple controllers able to regulate high dimensional biological systems in the face of diverse challenges? To address this question, we consider a model of a complex gene regulatory network that has a stable point and can be disturbed by high-dimensional environmental perturbations acting on different network nodes (Fig. 2*A*):

$$\frac{dn_a}{dt} = f_a(n) = \sum_b k_{ab}\frac{n_b}{n_b + K_{ab}} + \delta e_a(t) n_a, \qquad [1]$$

where n_a is the expression level of gene a and k_{ab} and K_{ab} define the interactions between genes a and b, e_a represents environmental fluctuations that act on different genes a of the network.

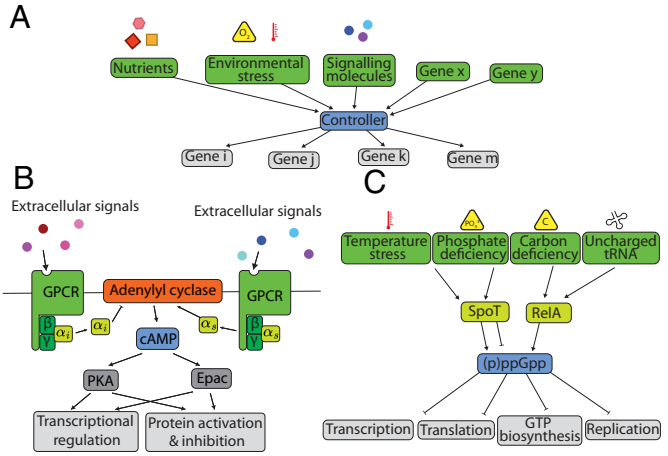

Fig. 1. (*A*) Low-dimensional controllers—controllers that project the high-dimensional state of the organism and the environment to much lower dimensional space and take restorative actions based on this projection—are found throughout biological systems. (*B*) The cAMP pathway is a low-dimensional controller across eukaryotes: in yeast, diverse environmental inputs (glucose levels, amino acid abundance, nitrogen state, osmotic stress) are integrated into a single cAMP concentration, which then coordinates transcriptional regulation, metabolic adjustments, and cell cycle control. (*C*) The stringent response is a prokaryotic low-dimensional controller: multiple stress signals (including carbon deficiency, phosphate deficiency, and temperature stress) are integrated into the concentration of (p)ppGpp, which accordingly reprograms the entire cellular physiology.

We now add an integral feedback controller that tries to restore homeostasis—to return the system to its fixed point x_0, despite environmental fluctuations $\vec{e}(t)$. Integral feedback control mechanisms are widely implemented at the cellular level in organisms for maintaining homeostasis and responding robustly to environmental conditions (24–27).

Integral feedback is often formulated for a single variable $n(t)$ and is based on computing an integrated error signal,

$$I(t) = c_i \int^t \delta n(t')dt' + c_p \delta n(t), \qquad [2]$$

where $\delta n(t) = n(t) - n_0$ is the error signal, i.e., deviation from the fixed point n_0 (Fig. 2*B*); c_i, c_p are the gain parameters for the integral and proportional parts of the feedback control. This integrated error signal is then used to take restorative action for $n(t)$, e.g., $dn/dt = f(n) - I(t)$.

For our high-dimensional system, we consider an integral feedback controller that measures d independent integrated error signals $I_i, i = 1, \ldots d$, each of which measures the deviation of a different linear combination $\vec{s}_i \cdot \vec{n} = \sum_a s_i^a n_a$ of the nodes n_a from their set points,

$$I_i(t) = c_p\left(\vec{s}_i \cdot \vec{\delta n}(t)\right) + c_i \int \left(\vec{s}_i \cdot \vec{\delta n}(t)\right)dt. \qquad [3]$$

Integral feedback controllers allow restoration to the original fixed point despite constant forcing, while proportional-only controllers incompletely restore toward the fixed point (24). When the number of measurements (d) equals the total number of nodes (N), the controller can monitor the complete state of the system, sensing N combinations $\vec{s}_i \cdot \vec{\delta n}$ of deviations. However, if $d < N$, the controller must work with incomplete information, monitoring only a simplified version of the system's full state, a d-dimensional projection of the N dimensional state

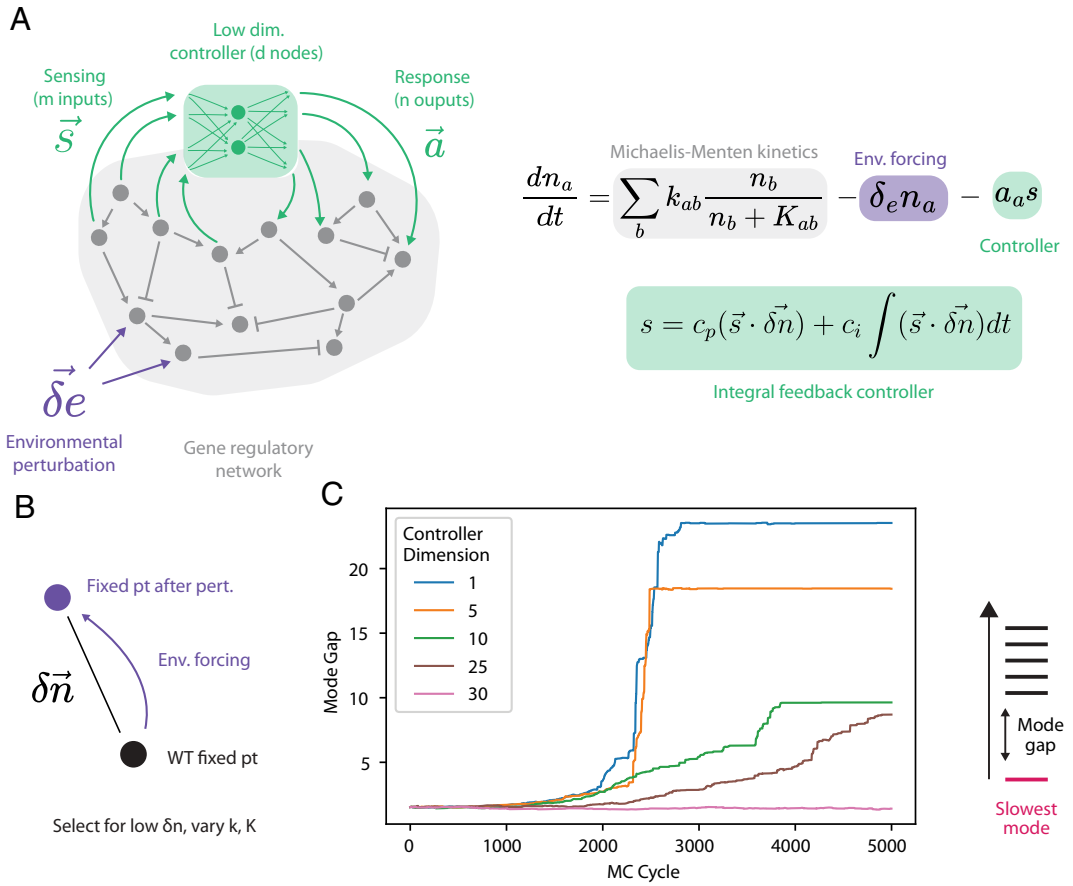

Fig. 2. Selection for environmental robustness in a system with a low complexity controller leads to the evolution of a dynamical soft mode. (*A*) We simulate a simple model of a gene regulatory network. In gray, Michaelis–Menten kinetics govern interactions between genes, while the controller mechanism and environmental forcing terms are highlighted in green and purple, respectively. The controller measures *N* nodes, projects them down to *d* random and independent combinations, and then acts on m nodes based on that project. $d = 1$ resembles the simple controllers found in biology while large *d* correspond to more complex controllers. (*B*) Selection for robust networks, quantified by the normalized average deviation from the WT fixed point in the presence of a low or intermediate complexity controller (*C*) leads to an increase in the mode gap of the system ($d = 1, 5, 10, 25$). Selection for robustness in the presence of a high complexity controller does not lead to an increase in mode gap ($d = 30$).

of the system. Intuitively, d can be understood as the internal complexity of the controller as shown in Fig. 2*A*. The simplest case, $d = 1$, represents a controller like those often seen in biological systems—where diverse signals are compressed into a single measure like cAMP or ppGpp levels.

To understand how controllers with low d values could ever be effective, we turn to in silico evolution of genetic networks under fluctuating environmental conditions (Fig. 2*A*). We vary the controller complexity ($d = 1, 5, 10, 25, 30$) and evolved parameters of the underlying dynamical system (here, k_{ab} and K_{ab})

$$\frac{dn_a}{dt} = \sum_b k_{ab}\frac{n_b}{n_b + K_{ab}} + \delta e_a(t)n_a - \sum_{i=1}^{m} a_a I_i. \qquad [4]$$

We add a controller that tries to restore the system to the wild type fixed point in the face of environmental challenges:

$$\frac{dn_a}{dt} = \sum_b k_{ab}\frac{n_b}{n_b + K_{ab}} - a_a s + \delta e_a n_a, \qquad [5]$$

$$s = c_p(\vec{s}\cdot\vec{\delta n}) + c_i\int(\vec{s}\cdot\vec{\delta n})dt, \qquad [6]$$

where $\vec{s}, \vec{a}$ are parameters that determine the behavior of the controller and $\vec{\delta n}$ is $\vec{n}_{WT} - \vec{n}$, the deviation from the WT fixed point (Fig. 2*B*). We define the fitness cost of the system as the failure to maintain homeostasis. We quantify this by computing the residual deviation from the fixed point—the absolute value of $\vec{\delta n}$, normalized by the overall stiffness of the system, averaged over many different values of environmental fluctuations $\vec{\delta e}_{env}$. We simulate the evolution of the network parameters k, K, selection for higher fitness using a simulated annealing Markov Chain Monte Carlo protocol (*SI Appendix*).

We find different results for low and high d: low and intermediate controller complexity ($d = 1, 5, 10, 25$) leads to dimensionality reduction in the controlled system itself while high d ($d = 30$) controllers allow the system to retain a high dimensional response to perturbations (Fig. 2*C*). Selection for robustness with a low complexity controller leads to a reduction in the system's mode gap—the ratio of the second and first eigenmodes of the system around its fixed point, $\frac{\lambda_1}{\lambda_0}$, which corresponds to the emergence of a soft mode that channels perturbations—when arbitrarily perturbed, the system tends to move along this mode, making it easier for the simple controller to detect and correct deviations.

A single soft mode is not in principle necessary for low complexity controllers with more than one dimension to re-

spond to environmental perturbations, as they could channel perturbations across a number of soft modes that correspond to the dimensionality of the controller. However, our simulations, which use annealing protocols to simulate evolution, still lead to the emergence of a single soft mode in such systems. A single soft mode may be more entropically favored than a more diffuse channeling of environmental perturbations across controller nodes. Intermediate complexity controllers that develop a single soft mode see marginal benefit to additional complexity; imposing a modest cost on controller complexity could lead to degeneration of complex controllers into simple ones. Our simulations also show that lower complexity controllers typically achieve relative robustness gains more rapidly during evolution than higher complexity controllers (*SI Appendix*, Fig. S1*B*). We also note that our result—simple controllers select for soft modes—is not dependent on our choice of control architecture—simple proportional controllers can also leverage soft mode mediated low dimensionality (*SI Appendix*, Fig. S1*C*).

We further analyzed the implications of this emergent redundancy for the evolution of controller complexity (*SI Appendix*, section 1.3). We find that because additional controller nodes offer only marginal robustness benefits once a dominant soft mode has evolved, even modest metabolic costs are sufficient to make one-dimensional controllers optimal. This suggests that low-dimensional biological controllers like the ppGpp and cAMP pathways may represent evolutionary endpoints where controller complexity has been trimmed to match the effective dimensionality of soft-mode-mediated control.

In this work, we propose one possible origin for soft modes in biological systems. Indeed, it is possible that soft modes may evolve for one reason but then acquire new roles in the cell, including for adaptive adjustment of the internal state along the soft mode in response to the environment . The case of ppGpp perhaps reflects both selection pressures (28, 29). To address this, we perform simulations on our already-evolved soft mode mediated low complexity controlled networks, but varying the homeostatic optimum (corresponding to different environmental contexts over time), showing that soft mode mediated homeostatic control can easily evolve to vary state along the soft mode (*SI Appendix*, Fig. S2).

Analytic Theory for a Low Complexity Controller. Here we use a simple analytically tractable model of integral feedback control to build intuition about the fitness value of a mode gap and the resulting soft mode. Consider a system with dynamics f in the absence of any control but is subject to environmental perturbations

$$\frac{d\vec{x}}{dt} = \vec{f}(\vec{x}) + \vec{e}_{env}, \quad [7]$$

where $\vec{e}_{env}$ represents high-dimensional environmental perturbations to the state of the system $\vec{x}$.

In such a system, the impact $\delta\vec{x}$ of environment perturbation on the state of the system will be of the form,

$$\delta\vec{x} = J_x^{-1}\delta\vec{e}_{env}, \quad [8]$$

where $J_x = \{\frac{tialf_i}{tialx_j}\}$ is the Jacobian with respect to the state x of the system.

The distribution of eigenvalues $\{\lambda_0, \lambda_1 \ldots \lambda_n\}$ of J_x affects the behavior of the system in response to environmental perturbations.

We find that the impact of environmental perturbations $\delta\vec{x}$ will be as high dimensional as the environmental perturbations $\delta\vec{e}_{env}$ in the absence of a mode gap but can be much lower dimensional with a mode gap.

Concretely, if we consider an ensemble of environmental perturbations $\{\vec{\delta e}_{env}\}$, we can quantify its effective dimensionality using effective rank (30):

$$\text{rank}_{\text{eff}}(\{e_{env}\}) = \exp\Big(-\sum p_i \log(p_i)\Big), \quad [9]$$

where p_i is the fraction of variance explained by the ith principal component.

We can in the same way compute the effective rank of the ensemble of the impacts of these environmental perturbations $\text{rank}_{\text{eff}}(\{\vec{\delta x}\})$ We can show that it has the same effective rank as the ensemble of the environmental perturbations that caused them:

$$\text{rank}_{\text{eff}}(\{\vec{\delta x}\}) \approx \text{rank}_{\text{eff}}(\{\vec{\delta e}_{env}\}),$$

with the assumption that all eigenvalues of J_x are the same value, λ (Fig. 3*A*).

On the other hand, if the eigenvalues show a mode gap (i.e., $\frac{\lambda_1}{\lambda_0} \gg 1$), the effective rank $\text{rank}_{\text{eff}}(\{\vec{\delta x}\})$ can be lower than that of $\text{rank}_{\text{eff}}(\{\vec{\delta e}_{env}\})$. If we consider a system with a single soft mode λ_0 and all other modes λ, with a mode gap $\frac{\lambda}{\lambda_0}$ and an ensemble of perturbations where each entry $\delta e_{env,i} \sim N(0, \sigma)$

$$\text{rank}_{\text{eff}}(\{\vec{\delta e}_{env}\}) \gg \text{rank}_{\text{eff}}(\{\vec{\delta x}\}) \quad [10]$$

The effective rank $\text{rank}_{\text{eff}}(\{\vec{\delta x}\})$ is greatly reduced from $\text{rank}_{\text{eff}}(\{\vec{\delta e}_{env}\})$ (see *SI Appendix* for full derivation).

Intuitively, the effective rank (or dimensionality) of $\{\vec{\delta x}\}$, the impact of environmental perturbations, can be much lower dimensional than the environmental perturbations $\{\vec{\delta e}_{env}\}$ if the system's Jacobian J_x has a soft mode that dominates the effect of perturbations (Fig. 3*B*).

We now show that integral feedback can exploit this reduced dimensionality of impacts δx to function effectively despite the high dimensional nature of environmental fluctuations e_{env}. We consider integral feedback of low complexity, i.e., a single sensing vector $\vec{s}$ compresses information about the state of the system into a one-dimensional scalar (Fig. 3*E*). Integral feedback tries to restore the system based on this scalar s by acting along an action vector $\vec{a}$, determining the direction the integral feedback restores along. k_i and k_p are the integral and proportion terms, respectively.

$$\frac{d\vec{x}}{dt} = f(\vec{x}) + \vec{\delta e}_{env} - \vec{a}\Big[k_p(\vec{s}\cdot\vec{\delta x}) + k_i\int(\vec{s}\cdot\vec{\delta x})dt\Big]. \quad [11]$$

We consider the linear regime about the fixed point. Solving for the impact vector $\vec{\delta x}$ in the presence of a controller, we find,

$$\vec{\delta x} = \vec{\delta e} - \left(\frac{\vec{\delta e}\cdot\vec{s}}{\vec{a}\cdot\vec{s}}\right)\vec{a}, \quad [12]$$

with rescalings $\tilde{\delta e}_i = \delta e_{env,i}/\lambda_i$, and $\tilde{\delta a}_i = \delta a_i/\lambda_i$.

As before, we consider a system with one soft mode λ_0 and other modes of faster and equal λ. We consider sensing $\vec{s}$ and action $\vec{a}$ unit vectors that sense and act on a direction that is a

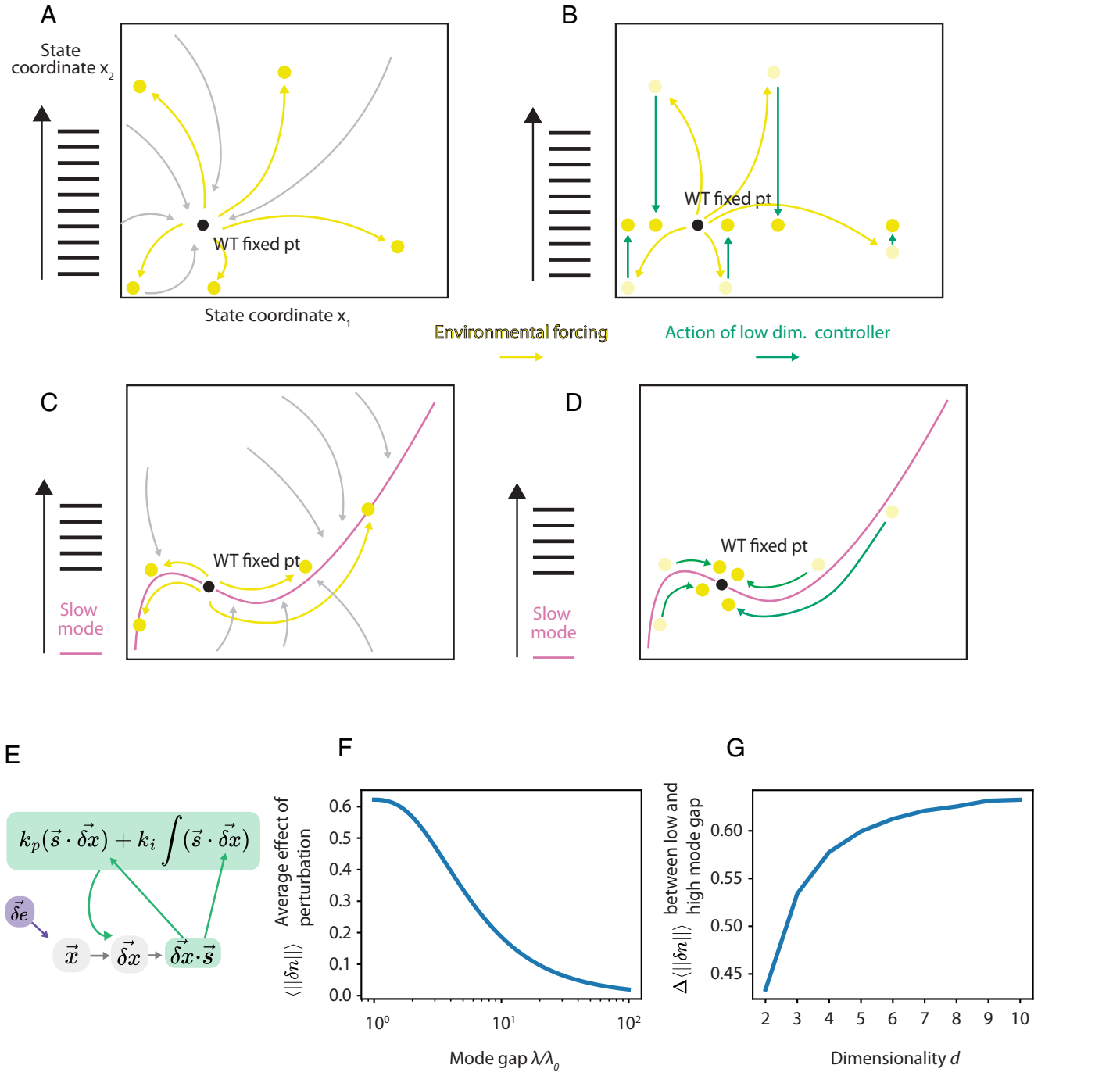

Fig. 3. (*A*) In systems with no significant mode gap, relaxation trajectories are diverse, and perturbations push the system in arbitrary directions. (*B*) A low complexity controller is not effective in the face of diverse perturbations. (*C*) In systems with a significant mode gap, a quick relaxation to the soft mode is followed by slow relaxation along the soft mode. Environmental and mutational perturbations push the system largely along the soft mode. (*D*) A simple controller can nevertheless be effective because all it needs to do is sense and act on the soft mode. (*E*) In a linear model of a simple controller with integral feedback, as mode gap increases, (*F*) As mode gap increases, the normalized average effect of a perturbation $\langle||\delta x||\rangle$ decreases, see Eq. **14**. (*G*) As dimensionality of the system increases, the difference in normalized $\langle||\delta x||\rangle$ between a system with a small mode gap and a large mode gap increases.

linear combination of the soft mode itself $\hat{v_0}$ and a unit vector in the direction of the mean perturbation $\hat{\mu}$: $\vec{a} = \beta\hat{v_0} + \sqrt{1-\beta^2}\hat{\mu}$, $\vec{s} = \alpha\hat{v_0} + \sqrt{1-\alpha^2}\hat{\mu}$. We find the expectation value $\langle||\vec{\delta x}||^2\rangle$ over a normally distributed $\vec{\delta e}$ as a function of mode gap λ/λ_0, the variance and mean of the normal distribution $\vec{\sigma}_{env}$ and $\vec{\mu}_{env}$ and the parameters α, β. We find that in the limit of a large mode gap $\lambda/\lambda \gg 1$, the optimal values of α, β are both 1. As the mode gap λ/λ_0 increases, the optimal $\vec{a}, \vec{s}$ vectors (that is, those that minimize $\langle||\vec{\delta x}||\rangle$) align with the soft mode $\hat{v_0}$ (see *SI Appendix* for a full derivation). With optimal controller parameters α, β, in this limit the expectation value of the effect of a perturbation reduces to

$$\langle||\vec{\delta x}||\rangle = \frac{1}{\lambda}\langle||\vec{\delta e}_{\perp\hat{v_0}}||\rangle = \frac{1}{\lambda}\sqrt{\sum_{i\neq 0}(\mu_i^2+\sigma_i^2)}. \quad [13]$$

The soft mode is completely canceled, and all that is left is the effect on the uncontrolled fast modes. The expectation value $\langle||\vec{\delta x}||\rangle$ with optimal $\vec{a}, \vec{s}$ normalized by the effect of an uncontrolled perturbation decreases as mode gap increases—a higher mode gap leads to a more robust system, given a low dimensional controller (Fig. 3*E*).

$$\langle||\vec{\delta x}||\rangle_{norm} = \frac{\sqrt{\sum_{i\neq 0}(\mu_i^2+\sigma_i^2)}}{\sqrt{\sum_{i\neq 0}(\mu_i^2+\sigma_i^2)+(\lambda/\lambda_0)^2(\mu_0^2+\sigma_0^2)}}. \quad [14]$$

The fitness benefit of a high mode gap—$\langle||\vec{\delta x}||\rangle_{\lambda/\lambda_0=1} - \langle||\vec{\delta x}||\rangle_{\lambda/\lambda_0=100}$—increases with the overall dimensionality of the system N (Fig. 3*G*, see *SI Appendix* for full derivation). Our simple analytic model above shows how soft modes can reduce the effective dimensionality of the effect of perturbations on a system, and in turn how simple controllers can thus select for soft modes to facilitate robustness.

Environmental Buffers Are Mutational Buffers.

Theory. Our model of soft mode mediated response to environmental challenges in living systems predicts dual buffering—mechanisms that buffer environmental perturbations should also buffer mutational perturbations. This dual ability to buffer environmental stressors as well as mutations has been noted since the 1990s in the case of the heat shock system in *Drosophila* (31, 32), and more recently in the context of yeast (33) and *Escherichia coli* (34). In a simple linear model, the change in state due to environmental perturbation $\delta\vec{e}$ is $\delta_e\vec{x} \approx \sum_i \frac{\mathbf{J}_e\delta\vec{e}\cdot\vec{v}_i}{\lambda_i}\vec{v}_i$. The change to the cell state due to mutation $\delta\vec{g}$ is $\delta_g\vec{x} \approx \sum_i \frac{\mathbf{J}_g\delta\vec{g}\cdot\vec{v}_i}{\lambda_i}\vec{v}_i$. If $\lambda_1 \gg \lambda_{i>1}$ then

$$\delta_g\vec{x} \approx \frac{\mathbf{J}_g\delta\vec{g}\cdot\vec{v}_1}{\lambda_1}\vec{v}_1, \quad [15]$$

and

$$\delta_e\vec{x} \approx \frac{\mathbf{J}_e\delta\vec{e}\cdot\vec{v}_1}{\lambda_1}\vec{v}_1. \quad [16]$$

Both kinds of perturbations will tend to be aligned. This alignment between the effects of mutational and environmental perturbation has also been observed empirically in proteins (35, 36).If a controller restores homeostasis by sensing the position of the system and restoring it along this mode, it will thus be able to buffer both kinds of challenges (Fig. 4*A*).

We use our simulations from above to explore dual buffering. We simulate the effect of mutational perturbations by introducing small changes to the interaction parameters of our Michaelis–Menten network, and test how low complexity controllers buffer the effects of mutations. We reuse controller parameters selected for environmental robustness. When there is a large mode gap, a controller that has evolved to buffer the effects of mutational forcing is able to buffer the effects of mutations as well (Fig. 4*B*). Our model of stress response and low dimensionality thus makes a prediction testable in perturbative experiments.

Empirical Results. In light of the aforementioned prior studies that have argued that mechanisms that facilitate environmental robustness also buffer mutations, and in the context of our theory, we reanalyze the data from two experiment studies which collected high-throughput fitness data on yeast grown subject to different kinds of mutational and environmental perturbations. Two experimental studies collected high-throughput fitness data on yeast grown subject to different kinds of mutational and environmental perturbations, shedding light on dual buffering in living cells (15, 16). A library of yeast strains with all nonessential gene knockouts had previously been assembled (37). In one experiment, this library was used to create a library of all possible pairwise double knockouts, which we term GxG (essential gene knockdowns were also assayed, as well as a subset of triple gene knockouts and knockdowns, but we do not analyze them in this work) (15). The fitness of the yeast strains in the GxG library was then assayed using an automated colony size protocol (Fig. 4*C*). In another experiment by the same group, each strain from the same single gene knockout library was subject to 14 diverse environmental perturbations (GxE). The fitness of each strain-environment combination was then assayed using the same colony size quantification protocol (16). In these experiments, the fitnesses of the single knockouts (G) and WT subject to environmental stresses (E) were also quantified using the same protocol.

To identify genes that buffer environmental or mutational perturbations, we first identify pairs of knockouts (in the GxG experiment) or knockout-environment pairs (in the GxE experiment) where there is a significant negative nonadditive effect of the pair of perturbations (beyond the independent effects of the knockouts or the knockout and the environment, known from the G and E datasets). We use the same significance test as the authors of the original studies for identifying significant negative interactions (*SI Appendix*). In the GxG experiment, this is equivalent to identifying significant negative epistatic interactions. Genes which have many negative epistatic interactions with other genes are buffering many genes—the absence of the buffering gene increases the fitness cost of many other mutations. Similarly, genes with many significant negative interactions with environmental conditions buffer the effect of the environments—the absence of the gene increases the fitness cost of many environments.

We find that genes that buffer many environmental conditions are more likely to buffer the effects of many mutational perturbations. We show this with a plot of histograms of genes by the number of knockouts the buffer, binned by the number of environmental conditions they buffer (Fig. 4*D*). Genes that buffer 6 or 7 environmental conditions are much more likely to buffer the effects of 300 or more genes than genes that buffer only 1 or 2 environmental conditions. One of the environmental challenges was subjecting the cells to Rapamycin, which is an mTOR inhibitor (38). If we treat this as equivalent to an mTOR knockdown and apply the same analysis as above, we find that mTOR is buffering over the effect of over 400 knockouts.

These experiments show that genes that are able to buffer many environmental challenges are more likely to buffer many mutational challenges, in line with our theoretical predictions.

Dimensionality Increase by Controllers. We simulate the effects of diverse environmental perturbations in our system with and without the controller knocked out, using our coevolved controller and soft-mode containing network. We apply many high dimensional environmental perturbations to the system, and then perform principal component analysis (PCA) on the resulting states (Fig. 5*A*). We show that the effective dimensionality is in fact lower once the controller is knocked out—the first principal component captures a much larger share of the variation caused by environmental challenges in the absence of the controller. In our model, the system evolves a soft mode, but because the mode is effectively buffered by a controller, the controlled system does not have an exposed soft mode. If the controller that listens to

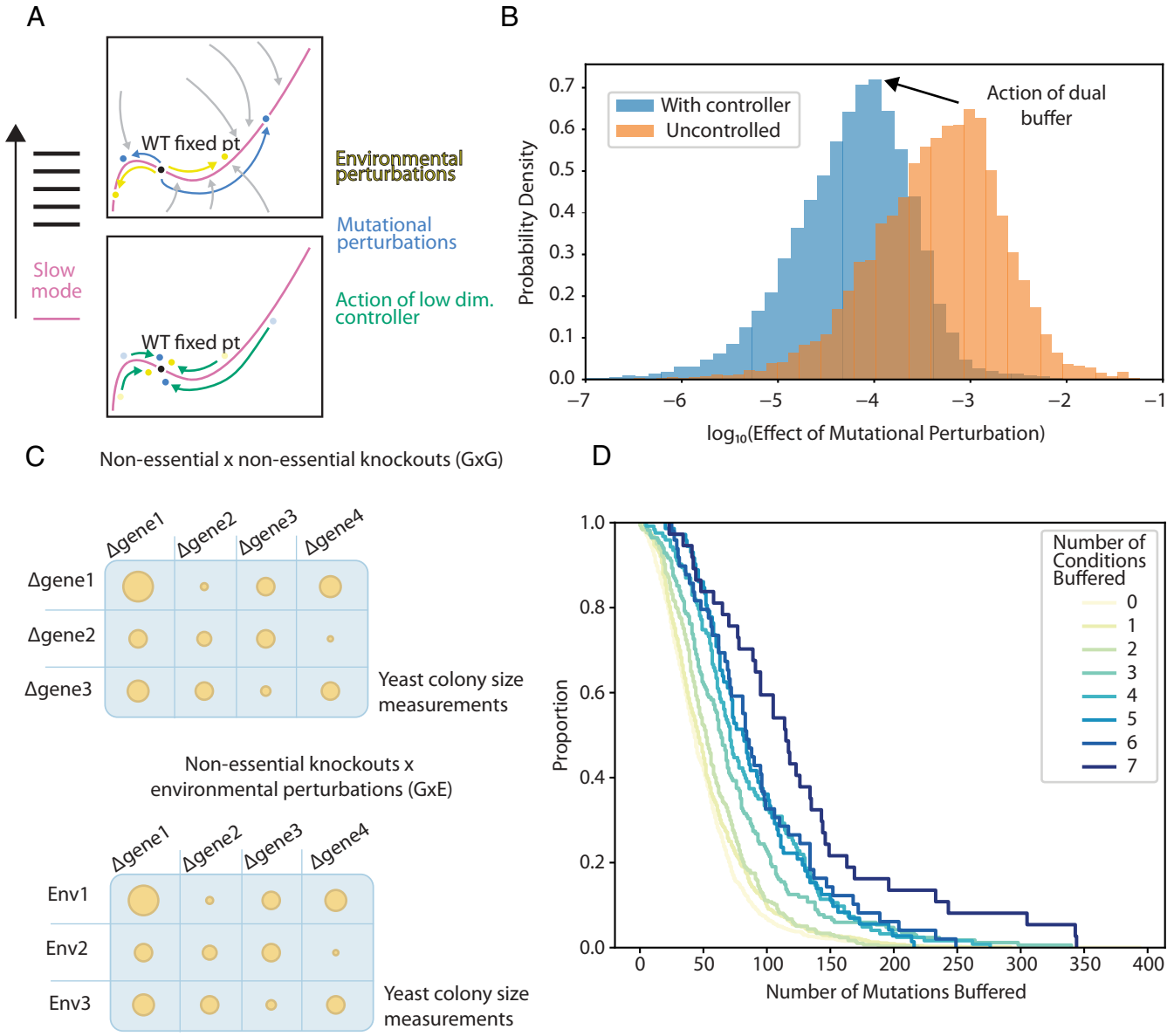

Fig. 4. Soft modes allow controllers of environmental perturbations to also buffer mutational perturbations (dual buffering). (*A*) Soft modes channel all perturbations, regardless if they are environmental or mutational, along that mode; accordingly, a controller that senses and restores the state of the system along that mode is effective against both kinds of challenges. (*B*) Our simulations demonstrate that low complexity controllers,with controller parameters selected for environmental robustness, can buffer mutational perturbations in networks with a large mode gap. The "uncontrolled" distribution in orange corresponds to the effects of mutational perturbations on the network in the absence of the controller; the "controlled" distribution in blue corresponds to the effects of the same set of mutational perturbations, but in the presence of the soft mode mediated controller. (*C*) Two experimental studies measured yeast fitness: one using a library of all possible pairwise nonessential gene knockouts (GxG) (15) and another exposing single gene knockout strains to 14 diverse environmental perturbations (GxE) (16), both quantified via automated colony size measurements. (*D*) Significant GxE and GxG interactions were identified from the dataset. Genes are binned by the number of significant negative GxE interactions, and the cdf histograms of significant negative GxG interactions are plotted. Genes buffering multiple environmental conditions are significantly more likely to buffer numerous mutational perturbations, with genes buffering 6 to 7 environmental conditions much more likely to buffer 300+ gene knockouts than those buffering only 1 to 2 conditions, supporting our theoretical predictions of dual buffering.

and restores homeostasis along the soft mode is knocked out, however, the knockout will expose the soft mode (Fig. 5*B*). This has the counterintuitive effect of reducing the dimensionality of the effects of environmental perturbations. Since the soft mode is soft, but uncontrolled with the controller knocked out, environmental stresses will disproportionately push the system along that mode in the absence of the controller.

Empirical Results. In another experimental study, the effects of kinase inhibition and environmental stresses on gene expression in yeast were investigated (39). Given that Tpk123 mediates the cyclic AMP system in yeast, a system which we have identified as system with a low dimensional controller architecture, we use these data to interrogate whether disabling Tpk123 leads to dimensionality reduction. A panel of 32 mutant kinase strains, which allow for selective inhibition of the mutant kinase, along with wild-type replicates were grown to exponential phase in rich media (Fig. 5*C*). The 32 yeast strains were subjected to 10 different environmental conditions: rich media (YPD), synthetic media (SDC), heat shock (39 °C), hyperosmotic shock (0.5 M NaCl), glucose depletion, endoplasmic reticulum stress (tuni-

camycin), oxidative stress (menadione), proteotoxic stress (AZC), TOR inhibition (rapamycin), and antifungal drug exposure (fluconazole). After 20 min of exposure to each condition, cells were harvested and bulk transcriptomic datasets were collected. In this work, we will focus on a comparison of Tpk123 inhibition with the WT controls.

To investigate the effect of knocking out a low dimensional controller, we analyze the processed data from the original study—DESeq2 had been used to generate normalized expression values (40), and then the log2 fold change of each gene in each sample with respect to wild type cells in YPD was calculated. The original study computed t-distributed stochastic neighbor embedding (t-SNE) (41) analysis (following PCA) of the data from the original study.

We find that diverse environmental challenges lead to a stereotyped transcriptional response in the context of Tpk123 inhibition. The t-SNE analysis shows that the diverse environmental challenges tend to push the transcriptional state of the yeast cells in idiosyncratic ways in the absence of Tpk123 inhibition (even when other kinases are inhibited)—samples cluster on the basis of environmental perturbation. In contrast, Tpk123 inhibited cells cluster together, across diverse perturbations (Fig. 5 *D*–*F*). Note that following normalization, which was conducted on the transcriptomic data, we expect low dimensional data to cluster, instead of showing a single dominant PC, as a consequence of projection onto the simplex (42).

If indeed a simple controller is buffering environmental challenges by listening to and restoring the cell state along a soft mode, inhibiting the controller will expose a soft mode. Diverse challenges in the absence of the controller will tend to push the system along the soft mode, and the observed dimensionality of the state of the cell will be lower across perturbations than in the presence of the controller. In the presence of the controller, the soft mode is controlled, and environmental perturbations appear distinct across genetic contexts, as they have idiosyncratic effects not canceled by the control mechanism.

This prediction is specific to our framework for explaining the function and origin of soft modes. If the soft mode is mediating plasticity, instead of facilitating return to a homeostatic fixed point, we should expect the state of the system to vary along the soft mode across environmental states, and do not necessarily expect as strong a dimensionality reduction following controller knockout.

Discussion

We developed a theoretical framework linking the complexity of biological controllers to the emergence of soft modes in the systems they regulate. Using an analytically tractable model and simulations of high-dimensional nonlinear gene regulatory networks, we show that when controllers are constrained to be simple, selection for robustness drives the formation of a dominant soft mode that channels perturbations into a low-dimensional subspace the controller can sense and correct. Conversely, when controller complexity is unconstrained, co-evolution naturally produces hierarchical mode structures that render most controller nodes redundant; any nonzero cost to controller complexity then selects for simple controllers. Our framework predicts that environmental buffers should also buffer mutations and that controller knockouts should reduce the dimensionality of stress responses; we tested and found support for both predictions in large-scale yeast fitness and transcriptomic data.

Low effective dimensionality in naively high-dimensional biological systems has been observed across scales, from proteins to gene expression to neural activity (10, 43–49). The adaptive immune system is perhaps one exceptional example of a high dimensional controller, if one conceptualizes the distribution and behavior of antigen-specific clonotypes in the immune repertoires as an internal representation mediating a control process. It has been argued that soft modes may mediate this low dimensionality in many contexts (10, 12, 20), but generic reasons for the emergence of such dimensionality reduction have been actively sought (11, 50, 51). Mathematical results like the Johnson–Lindenstrauss lemma demonstrate that high-dimensional data can in principle be embedded in lower dimensions without significant distortion but they do not specify how a physical system would implement such projection. Our work shows an evolutionary pathway by which biological systems come to achieve this dimensionality reduction through soft mode formation.

Others have proposed alternative origins for soft modes. Selection for allosteric communication can lead to soft modes (18, 20), as can the need for low-dimensional internal models of the external world (22, 23). In prior work on modularity, low-dimensional external perturbations become reflected in internal dimensionality (22, 50). In contrast, our model does not assume low-dimensional external perturbations; the system itself evolves low-dimensional internal effects so that a simple controller can be effective. Yet others have argued that evolvability, an indirect function subject to second-order selection, has led to the evolution of soft modes (21, 23, 52, 53). These origins need not be mutually exclusive; soft modes evolved for one reason may be co-opted for others. Indeed, the duality between environmental and mutational robustness means it may not be possible to distinguish whether soft modes originally arose from selection for stress response or for enhancing genetic variation available for natural selection to act on.

Our framework makes testable predictions about biological systems where robustness is mediated by a soft mode. We predict that if a controller senses and acts on a soft mode, even if evolution selected exclusively for environmental robustness, such a controller would also facilitate mutational robustness. This suggests that genes buffering mutations tend to buffer environmental stresses as well. We test this prediction using fitness data from high-throughput yeast experiments exploring interactions between mutations and environmental stresses, finding support for this dual buffering (15, 16). We also predict that knocking out a controller exposes a soft mode to perturbations, counterintuitively reducing the dimensionality of environmental responses. We find preliminary support for this prediction in yeast kinase knockout transcriptomic data, where Tpk123 inhibition leads to stereotyped transcriptional responses across diverse environmental conditions (39).

Several open questions remain. While we focus on homeostatic controllers that restore a fixed point, real controllers like ppGpp also mediate adaptive plasticity (28, 29), adjusting the target state along the soft mode in response to environmental context (54). Our simulations suggest soft modes selected for homeostasis can evolve to facilitate such plasticity (*SI Appendix*, Fig. S4), but a fuller treatment of soft mode-mediated control for both adaptive plasticity and homeostasis awaits future work. Relatedly, our prediction that controller knockout reduces response dimensionality is specific to homeostatic control; if a soft mode instead mediates adaptive plasticity, knockout may produce different phenotypes, a distinction that could guide experimental tests.

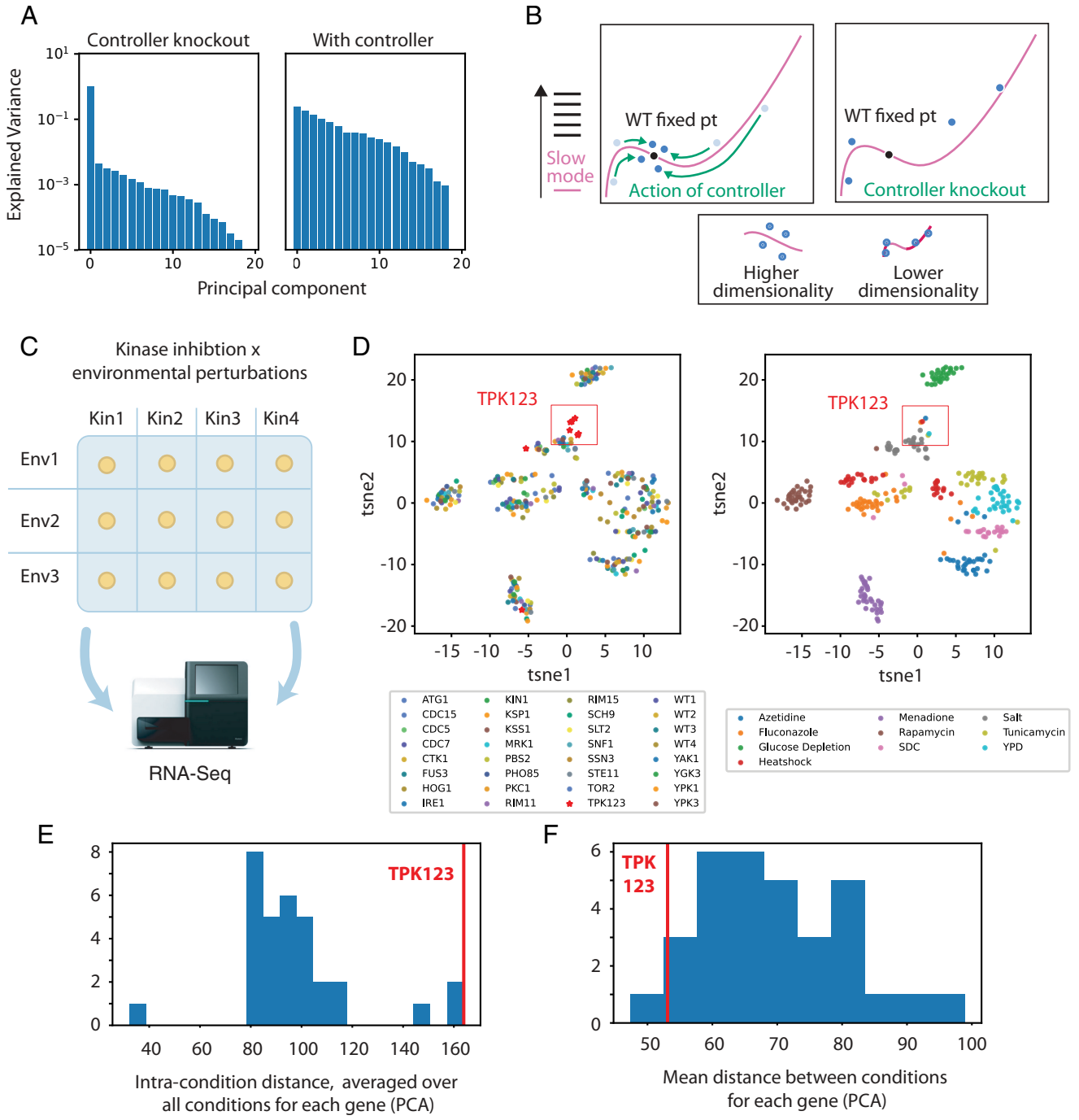

Fig. 5. Soft modes imply that knocking out a controller will, counterintuitively, reduce the dimensionality of an environmental perturbation. (*A*) We simulated the effects of diverse environmental perturbations on our coevolved network and soft mode mediated simple controller with and without the controller knocked-out. We apply PCA to the simulation results, showing the reduction of dimensionality due to the knockout. (*B*) Without a controller, perturbations largely push the system along the soft mode, leading to a lower observed dimensionality. (*C*) Yeast cells subject to inhibition of 28 different kinases were grown in 10 different environmental conditions, and transcriptomic data were collected (39). (*D*) Clustering of RNA-seq samples following dimensionality reduction by t-SNE plotted in two dimensions. Colors indicate different kinase inhibitions or environmental conditions, respectively. Tpk123 inhibited samples cluster, regardless of environmental conditions. For other conditions, samples generally cluster on the basis of environmental perturbation, regardless of kinase knock-down. Tpk123 knock-down leads to stereotyped effect across environmental conditions; for other knockdowns, different environmental conditions have distinct effects. (*E*) The average distance in PCA space (first three components) to all other GxE samples of the same condition was computed, and then an average of averages was computed for each genetic background and is plotted. The TPK123 value is highlighted. (*F*) The average distance in PCA space (first three components) to all other GxE samples of the same genetic background was computed and is plotted, and the TPK123 value is highlighted.

Further, unlike explanations of soft modes based on functions such as allostery, our framework does not require the soft mode to point in a specific direction; however, the direction that emerges may subsequently be co-opted for cellular function, a possibility that remains to be investigated. Real cells also employ multiple low-dimensional controllers (e.g., both ppGpp and cAMP systems); how such controllers interact and whether they select for shared or distinct soft modes invites further inquiry.

More generally, the de novo origin of controller topology, i.e., how a cell evolves from a state with no active control to any controller architecture, remains an open question for further theoretical inquiry.

Finally, theoretical and experimental work on the dynamic responses after controller knockouts could provide further support for our framework. In the presence of a controller, our framework generally implies that trajectories from diverse perturbations should diverge over time (reflecting distinct stresses), as the controller quickly restores the system along the soft mode. But following a controller knockout, trajectories should remain displaced along the soft mode, and tend to converge along the soft mode over time as faster modes decay more quickly. The transcriptomic data we analyzed represent steady-state snapshots, but time-resolved measurements following perturbation would provide a more stringent test. At the molecular scale, time-resolved X-ray crystallography can now capture such dynamics with atomic resolution (55, 56); at the cellular scale, time-resolved phosphoproteomics (57, 58) and live-cell imaging of signaling dynamics could similarly reveal the timescales of mode separation and the direction of soft modes in cellular state space.

Materials and Methods

We briefly review the methods employed in this study, which were implemented in Python. For a more detailed description, please refer to the appropriate section in *SI Appendix*. Simulation code and analysis scripts are publicly available on GitHub at https://github.com/GeroyUsilov/simple-biological-controllers.

In Silico Evolution of Genetic Networks. We modeled gene regulatory networks using Michaelis–Menten kinetics subject to high-dimensional environmental perturbations. To simulate selection for homeostasis, we evolved network interaction parameters (k_{ab} and K_{ab}) using a simulated annealing Markov Chain Monte Carlo (MCMC) protocol. Fitness was defined by the system's ability to minimize deviations from a wild-type fixed point, normalized by overall stiffness. We varied the internal complexity of the controller ($d = 1, 5, 10, 25, 30$) to observe how the number of available control nodes influences the emergence of soft modes.

Analytic Theory of Low-Dimensional Control. To quantify the effective dimensionality of environmental perturbations and their impacts, we utilized the effective rank metric. We developed a linear model of integral feedback to analytically derive the relationship between the system's mode gap (the ratio of the fastest to slowest eigenvalues) and the effectiveness of a simple controller. This model allowed us to calculate the expectation value of perturbation effects as a function of dimensionality and mode gap.

Yeast Fitness and Transcriptomic Data Analysis. We reanalyzed high-throughput yeast fitness data from GxG (gene–gene) and GxE (gene–environment) interaction studies to test for dual buffering. Significant interactions were identified using intermediate confidence thresholds ($P < 0.05$ and $|\epsilon| > 0.08$), established in prior high-throughput studies, to bin genes by their buffering capacity. For transcriptomic analysis, we utilized processed RNA-seq data of 32 kinase mutants across 10 environmental conditions. We performed PCA and t-SNE to quantify how the inhibition of Tpk123 (cAMP pathway) impacts the observed dimensionality of the stress response.

Data, Materials, and Software Availability. Previously published data were used for this work (15, 16, 39).

ACKNOWLEDGMENTS. We are grateful to Abigail Skwara, Pankaj Mehta, Mikhail Tikhonov, Terry Hwa, Shenshen Wang, Ariel Amir, Maryn Carlson, Annisa Dea, Lauren McGough, Marcos Viera, Manon Ragonnet, Alex Byrnes, Joshua Sodicoff, the Murugan lab, the Chan-Zuckerberg theory group for helpful discussions. This work was supported by the Chan-Zuckerberg Initiative, NSF through the Center for Living Systems (Grant No. 2317138) and DMR-2239801, the NIGMS of the NIH under Award No. R35GM151211, and the NSF-Simons National Institute for Mathematics and Theory in Biology under NSF Award DMS-2235451 and Simons Foundation Award MPS-NITMB-00005320.

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