Theory for Adaptive Systems: Collective Robustness of Genotype-Phenotype Evolution

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The investigation of mutually coupled dynamics, involving many degrees of freedom on two separated timescales, one for fast changes of state variables and another for the slow adaptation of parameters controlling the former's dynamics is crucial for understanding biological evolution and learning. We develop a general theory for such dynamics by extending dynamical mean field theory. We then apply our framework to biological systems whose fate is determined by the evolution of genotype-phenotype relationship. Here phenotypic evolution is shaped by stochastic gene-expression fast dynamics and is coupled to selection-based slow changes of genotypes encoding the network of gene regulations. We find *dynamically robust patterns* of phenotypes can be achieved under an intermediate level of external noise where the genotype-phenotype relation evolves in such a way that results in intrinsic out-of-equilibrium fluctuations of phenotypes even in the absence of that noise.

In a wide class of biological or neural systems one type of degrees of freedom (dofs) often slowly changes and plays a role for the rule of the faster dynamics of state variables, so that they can make *adaptation*. Such coupled multiple timescale dynamical systems include cellular adaptation [1–4], cell differentiation with slower epigenetic changes [5–9], neural network with synaptic changes [10], eco-evolutionary dynamics [11, 12], as well as extensive studies in adaptive network models [13, 14]. On one hand, singular perturbation theory or quasi-steady-state approximation [15] often applied to systems of fast/slow timescales are generally difficult to analyse high-dimensional systems with multiple sources of stochasticity. On the other hand, dynamical mean-field theory (DMFT) [16–19], a powerful tool to study large random systems [20–37], is limited to the case of quenched disorder, i.e, without considering changes in the slow dofs (i.e. the interactions among system's components or any parameter controlling their dynamics). One hence needs a new framework towards those systems in which the parameters are also dynamical variables with their own dynamics. Such systems are given by:

$$\begin{cases} d\mathbf{x}/dt = -\mathbf{x} + F(\mathbf{x}, \mathbf{J}) + \boldsymbol{\xi}(t) \\ \tau \, d\mathbf{J}/dt = G(\mathbf{x}, \mathbf{J}) + \tilde{\boldsymbol{\xi}}(t) \end{cases} \quad (1)$$

where $\mathbf{x}$ are the state variables of interest and $\mathbf{J}$ are the parameters controlling the dynamics of $\mathbf{x}$, such as the set of interaction couplings among $\mathbf{x}$'s components. Further, $\boldsymbol{\xi}(t)$ and $\tilde{\boldsymbol{\xi}}(t)$ are the level of stochasticity in the dynamics of $\mathbf{x}$ and $\mathbf{J}$, respectively. Here τ denotes the characteristic timescale for changes in $\mathbf{J}$, which is assumed to be much larger than 1 in case $\mathbf{J}$ are considered as slow variables.

One of the most important issues in adaptation is biological evolution. In evolution, phenotypes are shaped by the fast dynamics of states as captured by the first of Eq. (1), while the rule of the dynamics are determined by genotypes which change slowly through the selection,

depending on how adapted the shaped phenotypes are. This slow change is given by the second of Eq. (1). Such adapted phenotypes also need to be robust to perturbations induced by the noise terms of Eq. (1). Both the dynamics here are stochastic; the phenotype is under developmental noise [38–44] and genotype changes with mutation. At the heart of evolutionary biology hence is the question of which features of the genotype-phenotype relation give rise to phenotypic robustnesses to noise and mutation [45–47]. A full answer to this question yet remains elusive.

To this end, gene-expression dynamics, where $\mathbf{x}$ represents the expression level of multiple genes that mutually influence according to a network of regulations specified by $\mathbf{J}$, is commonly adopted. By integrating the gene-expression dynamics into network dynamics under adaptive evolution through the selection by a fitness defined as a function of $\mathbf{x}$, a recent work shown the loss of phenotypic robustness with decreasing noise level [44]. This observation is rather counter-intuitive as noise may be an obstacle to maintain a fitted state. Numerical results therein suggest that this loss of robustness may occur as a transition to a spin-glass-like phase where the dynamical system shaped by evolution turns to have multiple fixed-points as noise is decreased. Still, how this occurs is not well understood. As this kind of systems is neither in thermal equilibrium, nor described by Hamiltonian dynamics, equilibrium spin-glass theory cannot be applied here. A deeper understanding of this transition in particular, and the genotype-phenotype relation in general requires a new analytical framework.

In this Letter, we develop an extension of the standard DMFT, which we term adaptive DMFT (ADMFT), to include the evolution of couplings, thus leveraging its original use in systems with quenched disorder to stochastic adaptive systems. As a straighforward application of our framework to evolution of gene-expression dynamics, we demonstrate the three phases with regards to the pheno-

typic robustness and fitness, against changes in the noise strength. The ADMFT analysis thus is able to unveil the transition leading to the loss of phenotypic robustness.

The key point of our approach is to derive an effective dynamics for a representative gene expression x that becomes exact in the limit $N \to \infty$ [48] from a saddle-point approximation of the moment generating functional of the joint trajectories of $\mathbf{x}$ and $\mathbf{J}$. When $\mathbf{J}$ is nothing else than the matrix capturing the interactions among the N components of $\mathbf{x}$, e.g. J_{ij} denotes the regulation of gene j on i, this can be done by writing the first of Eq. (1) as

$$dx_k/dt = -x_k + F\Big(\sum_j J_{kj}x_j\Big) + \xi_k(t), \quad k = 1, \cdots, N.$$

Under an assumption (which is biologically motivated but does not limit the generality of our methodology) that each entry J_{kj} of this interaction matrix needs to evolve so as to increase a "fitness" function $\Psi = h_{kj}(\mathbf{x})$ whose expression is model-dependent, we can consider a discrete-time update for J_{kj} [49]

$$J_{kj}(\tau+1) = \frac{1}{\sqrt{N}} \text{sign}\left(h_{kj}\big(\mathbf{x}(\tau)\big) + \beta^{-1}\tilde{\xi}(\tau)\right) \quad (2)$$

where the factor $1/\sqrt{N}$ is to ensure a sensible thermodynamic limit [50] and β is the selection pressure that controls the variations of genotypes. Here the distribution of noise is $\mathbb{P}(\tilde{\xi}) = \left[1 - \tanh^2(\tilde{\xi})\right]/2$, see [51] for details. For the entire genotype, the dynamics of Eq. (2) can be formulated as a discrete-time master equation for the joint distribution $P(\mathbf{J})$, see SM.

The form of Eq. (2) captures the fact that due to selection a new genotype $\mathbf{J}(\tau+1)$ will be chosen with a probability proportional to the exponential of $\mathbf{J}(\tau)\mathbf{h}(\mathbf{x}(\tau))$. If assumed that the optimal phenotype is attained when only a subset of genes called target and denoted by $\mathcal{T}$ are on, the fitness can be defined as a function of the mean expression level of the target genes. Accordingly, $\mathbf{h} = \mathbf{h}(x_{i\in\mathcal{T}})$ is a function of only the target-gene levels. Those genes that do not contribute to the fitness are called non-target, their set is denoted by $\mathcal{O}$. From now on we consider only a fully-connected network with N_t target and $N_o = N - N_t$ non-target genes, respectively. We distinguish the interactions $J_{ij}^{(tt)}$ for $i \in \mathcal{T}$ and $j \in \mathcal{T}$; $J_{ij}^{(oo)}$ for $i \in \mathcal{O}$ and $j \in \mathcal{O}$; $J_{ij}^{(to)}$ for $i \in \mathcal{T}$ and $j \in \mathcal{O}$. In correspondece to these notations, we introduce $h^{(tt)}$, $h^{(to)}$ and $h^{(oo)}$ for $J_{ij}^{(tt)}$, $J_{ij}^{(to)}$ and $J_{ij}^{(oo)}$, respectively.

Let $\mathbb{E}[\cdot]$ denote the ensemble average over trajectories in the joint space of x and $\mathbf{J}$. We introduce the average activity $m(t,\tau)$, the autocorrelation $C(t,t',\tau)$; the response $G(t,t',\tau)$ generated by adding an external perturbation $\theta(t')$ to $F(\cdot)$; the mean value of the target-target couplings $\hat{\mu}(\tau)$; and the mean value of the target-

vs non-target couplings $\hat{\lambda}(\tau)$ as follows

$$m(t,\tau) = \mathbb{E}\big[x(t,\tau)\big] \tag{3a}$$

$$C(t,t',\tau) = \mathbb{E}\big[x(t,\tau)x(t',\tau)\big] \tag{3b}$$

$$G(t,t',\tau) = \mathbb{E}\left[\frac{\partial x(t,\tau)}{\partial \theta(t')}\right] \tag{3c}$$

$$\hat{\mu}(\tau)/N_t = \mathbb{E}\left[J_{ij}^{(tt)}(\tau)\right] \tag{3d}$$

$$\hat{\lambda}(\tau)/\sqrt{N_t} = \mathbb{E}\left[J_{ij}^{(to)}(\tau)\right] \tag{3e}$$

We derive an effective process describing the state of target genes x and that of $J^{(tt)}$ and $J^{(to)}$ (see SM for detailed calculations) in the limit $N \to \infty$ [52]:

$$\begin{cases} \hat{\mu}(\tau+1) = \tanh\big(\beta h^{(tt)}(\tau)\big) \\[2mm] \hat{\lambda}(\tau+1) = \tanh\big(\beta h^{(to)}(\tau)\big) \\[2mm] \dot{x} = -x + F\left(\hat{\mu}m + \alpha\hat{\lambda}^2 \int_0^t dt' G(t,t')x(t') + \eta(t)\right) + \xi(t) \end{cases}$$
$$\tag{4}$$

where $\alpha = N_o/N_t$ and the self-consistency noise is

$$\mathbb{E}\Big[\eta(t,\tau)\eta(t',\tau)\Big] = \alpha\,\hat{\lambda}^2 C(t,t',\tau) = \alpha\hat{\lambda}^2\mathbb{E}\Big[x(t,\tau)x(t',\tau)\Big] \tag{5}$$

Time-dependent solutions to the last ODE can be found using Monte Carlo methods [53, 54].

We now apply the present theoretical framework specifically to the adaptation of a gene regulatory network, where the dynamics of the gene expression level x_k is given by [44, 55–59]

$$\frac{dx_k}{dt} = -x_k(t) + \tanh\Big(\sum_j J_{kj} \cdot x_j(t)\Big) + \xi_k(t), \tag{6}$$

where $\langle \xi(t)\xi(t')\rangle = 2\sigma^2\delta(t-t')$ and $J_{kk} = 0$. Here all the couplings J_{ij} are regarded as *fixed* over the course of this gene dynamics because they are assumed to evolve on much slower timescale τ than that of the genes t. For target genes $k, j \in \mathcal{T}$, the $\mathbf{x}$-dependence of $h_{kj}^{(tt)}(\tau)$ can be derived as follows. From the identity

$$\sum_{k\neq j\in\mathcal{T}} x_kx_j = \Big(\sum_{k\in\mathcal{T}} x_k\Big)^2 - \sum_{k\in\mathcal{T}} x_k^2 \simeq \Big(\sum_{k\in\mathcal{T}} x_k\Big)^2,$$

where we have neglected the second term in comparison to the first one in the $N_t \to \infty$ limit, we obtain $\big(N_t\Psi\big)^2 \simeq \sum_{k\neq j\in\mathcal{T}} x_kx_j$ for $\Psi = N_t^{-1}\sum_{i\in\mathcal{T}} x_i$ as specified in [44] (this choice is not unique though and does not limit the use of our approach in general). This summation suggests that for each pair of target genes j and k, $h_{kj}^{(tt)}$ needs to depend on the product of their states. At each generation τ, due to the time scale separation between the phenotype- and the genotype dynamics, the gene levels can be assumed to reach stationary

$x_k(\tau) = \lim_{t\to\infty} x_k(t|\mathbf{J}(\tau))$. Therefore, $h_{kj}^{(tt)}(\tau)$ is determined by the steady-state correlation between x_k and x_j, following a generalised Hebbian-like rule [60] [61]:

$$h_{kj}^{(tt)}(\tau) \propto \langle x_k(\tau) x_j(\tau)\rangle^{1/2}, \quad k,j \in \mathcal{T} \qquad (7)$$

Now for $J_{kj}^{(tt)} \to J_{kj}^{(tt)} + \Delta J_{kj}$ we consider $\Psi \to \Psi + \Delta\Psi$. At steady state, $\partial x_k/\partial J_{kj}^{(tt)} \simeq x_j(1-x_k^2)$, so to the first order approximation,

$$\Delta\Psi := \frac{1}{N_t}\sum_{k\in\mathcal{T}}\Delta x_k \simeq \frac{1}{N_t}\sum_{k\in\mathcal{T}}\left(\sum_{j=1(\neq k)}^{N_t}\frac{\partial x_k}{\partial J_{kj}^{(tt)}}\cdot\Delta J_{kj}\right)$$

$$\simeq \frac{1}{N_t}\sum_{k\neq j\in\mathcal{T}} x_j(1-x_k^2)\cdot\Delta J_{kj} \qquad (8)$$

Moreover, for a pair $k,j \in \mathcal{T}$, ΔJ_{kj} can be regarded as the perturbation that is induced by the joint effect of $J_{k\ell}^{(to)}$ and $J_{\ell j}^{(ot)}$ on the coupling $J_{kj}^{(tt)}$. In fact, assuming that $\forall \ell \in \mathcal{O}$, $|x_\ell| \ll 1$ and $\left(\sum_{j=1}^N J_{\ell j} x_j\right) \ll 1$, we have

$$\arctan(x_k) = \sum_{j\in\mathcal{T}} J_{kj}^{(tt)} x_j + \sum_{\ell\in\mathcal{O}} J_{k\ell}^{(to)} x_\ell$$
$$\simeq \sum_{j\in\mathcal{T}} J_{kj}^{(tt)} x_j + \sum_{\ell\in\mathcal{O}} J_{k\ell}^{(to)}\left(\sum_{j\in\mathcal{T}} J_{\ell j}^{(ot)} x_j\right)$$
$$\simeq \sum_{j\in\mathcal{T}} x_j\left[J_{kj}^{(tt)} + \sum_{\ell\in\mathcal{O}} J_{k\ell}^{(to)} J_{\ell j}^{(ot)}\right]$$

Therefore, $\Delta J_{kj} = \sum_{\ell\in\mathcal{O}} J_{k\ell}^{(to)} J_{\ell j}^{(ot)}$. Substituting this into Eq. (8) results in a fitness change

$$\Delta\Psi \simeq \frac{1}{N_t}\sum_{k\neq j\in\mathcal{T}} x_j(1-x_k^2)\cdot\left(\sum_{\ell\in\mathcal{O}} J_{k\ell}^{(to)} J_{\ell j}^{(ot)}\right)$$

This change affects the selection of $J_{k\ell}^{(to)}$ in such a way that can be accounted for by assigning

$$h_{k\ell}^{(to)}(\tau) \propto \left\langle \frac{(1-x_k^2(\tau))J_{k\ell}^{(to)}(\tau)}{N_t}\left(\sum_{j\in\mathcal{T}} J_{\ell j}^{(ot)}(\tau) x_j(\tau)\right)\right\rangle. \qquad (9)$$

If the system reaches stationary states with time-translational symmetry, then $\forall s > 0$

$$\lim_{t'\to\infty} C(t=t'+s, t', \tau) = C(s,\tau) = \hat{q}(\tau)$$
$$\lim_{t'\to\infty} G(t=t'+s, t', \tau) = G(s,\tau)$$
$$\lim_{t\to\infty} G(t, t', \tau) = 0, \forall t' \qquad (10)$$

We define the intrinsic variance $q_0 = q - \sigma^2$ for $q = \lim_{\tau\to\infty}\hat{q}(\tau)$ and the integrated response

$$\hat{\chi}(\tau) = \int_0^\infty ds\, G(s,\tau)$$

that remains finite in this case. As x reaches a stationary state, so does η: $\lim_{t\to\infty}\eta(t) = \eta_0 = J_0\sqrt{q}\tilde{z}$, where η_0 is a Gaussian random number with mean zero and variance $J_0^2 q$, $J_0 = \lambda\sqrt{\alpha}$ and $\tilde{z} \sim \mathcal{N}(0,1)$, the standard normal distribution. Likewise, at stationary, the effect of the white noise ξ is equivalent to adding a static random number $\xi_0 = \sigma z$ to the dynamics specified by the first two terms of the second Eq. (4), for $z \sim \mathcal{N}(0,1)$. Let

$$\mu = \lim_{\tau\to\infty}\hat{\mu}(\tau), \quad \lambda = \lim_{\tau\to\infty}\hat{\lambda}(\tau), \quad x_* = \lim_{\tau,t\to\infty} x(t,\tau)$$

denote the fixed point of the effective dynamics Eq. (4). Such *random* fixed point obeys

$$x_*(\tilde{z}, z) = \tanh\left(\mu m_\infty + J_0^2\chi x_* + J_0\sqrt{q}\tilde{z}\right) + \sigma z. \quad (11)$$

where $\chi = \lim_{\tau\to\infty}\hat{\chi}(\tau)$ and $m_\infty = \langle\langle x_*\rangle_{\tilde{z}}\rangle_z$. Assuming that $x_*(\tilde{z}, z)$ does not depend on initial conditions, i.e. it is the unique for any given realisation of z and $\tilde{z}$, the stationary state can be characterised by solutions to a closed set of self-consistency equations for m_∞, q, χ, μ and λ, obtained by averaging over the ensemble of fixed points

$$(12)\quad\begin{cases} \mu = \tanh\left(\beta m/\sqrt{q}\right) \\[2mm] \lambda = \tanh\left(\beta\lambda^2 m/\sqrt{q}(1-m/\sqrt{q})\right) \\[2mm] m_\infty = \int_{-\infty}^\infty Dz \int_{-\infty}^\infty D\tilde{z}[f_0 + \sigma z] \\[2mm] q = \sigma^2 + \int_{-\infty}^\infty Dz \int_{-\infty}^\infty D\tilde{z} f_0^2 \\[2mm] \chi = \int_{-\infty}^\infty Dz \int_{-\infty}^\infty D\tilde{z}\frac{1-f_0^2}{1-J_0^2\chi\cdot(1-f_0^2)} \end{cases}$$

where $f_0 := x_*(\tilde{z}, z) - \sigma z$ and $Dz := dz e^{-z^2/2}/\sqrt{2\pi}$ is the Gaussian measure. The solutions are obtained as stable attractors of an iteration dynamics started with an initial condition that has a sufficiently large values of m_∞, q, χ, μ and λ. A local stability analysis of x_* using an ansatz $x(t) = x_* + \varepsilon x_1(t)$, $\eta(t) = J_0\sqrt{q}\tilde{z} + \varepsilon\nu(t)$, $\langle\nu(t)\nu(t')\rangle = J_0^2\langle x_1(t)x_1(t')\rangle$, where $\varepsilon \ll 1$, allows us to conclude $x_*(\tilde{z}, z)$ is the unique stable fixed point if

$$\Sigma := \left[1 - J_0^2\chi(1-f_0^2)\right]^2 - J_0^2(1-f_0^2)^2 > 0. \quad (13)$$

We realise that $\Sigma = 1 > 0$ for $(\mu,\lambda,x_*) = (0,0,0)$ and such $(\mu,\lambda,x_* \neq 0)$ that $f_0^2 = 1$. The latter case, however, can only happen if $\chi \to \infty$.

Let us recall the meaning of the steady-state order parameters m_∞, q_0, λ, μ and χ. m_∞ is the average of the *random* fixed point x_* as the latter depends on the realisation of both z and $\tilde{z}$; q_0 is the variance of x_* subtracted from σ^2, so that q_0 measures only the intrinsic fluctuation in x_* that is not due to the external noise σ. χ is

(A) ... **(B)** ... **(C)** m_∞ ... **(D)** λ ... **(E)** q_0 ... **(F)** μ
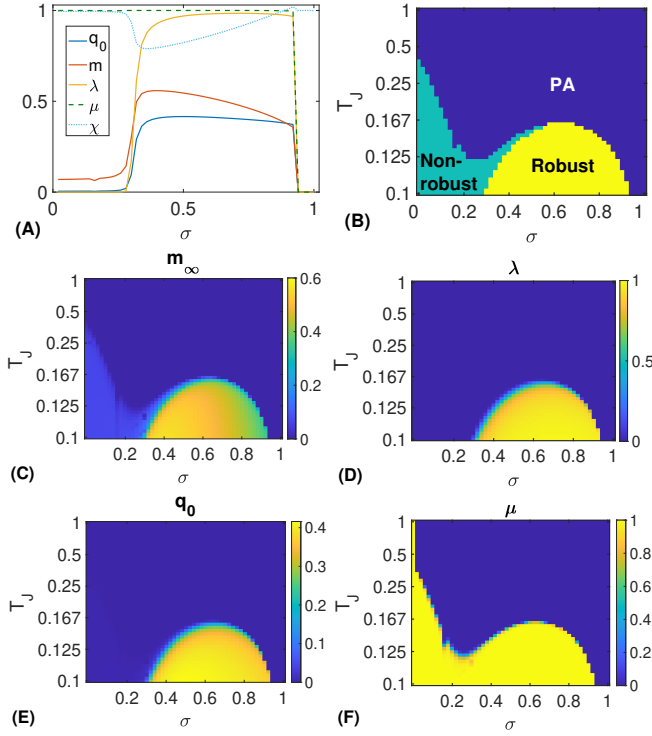
FIG. 1. **(A)** Order parameters as function of σ for $\beta = 10$. In the non-robust phase $m > 0$ and $\mu = 1$ but $\lambda = q_0 = 0$, while in the robust phase $m, q_0, \lambda, \mu > 0$. In the para-attractor phase **(PA)** $m = q_0 = \lambda = \mu = 0$. **(B)** The phase diagram in terms of σ and $T_J = \beta^{-1}$. **(C)** Averaged activity of target genes m. **(D)** The average of target vs non-target coupling λ. **(E)** The intrinsic variance in the target gene's activity q_0. **(F)** The average of target vs target coupling μ. Here $\alpha = 0.5$.

the response of x_* wrt perturbation induced by z; μ and λ are the steady-state mean value of $J^{(tt)}$ and $J^{(to)}$.

The following result is presented for $\alpha = 0.5$, similar behaviour is observed for other $\alpha \geq 0.08$ (see SM for the dependence of the order parameters on α). At sufficiently high selection pressure, such as for $\beta = 10$, we find that upon increasing the noise σ, two transitions happen between three different types of solutions in Fig. 1 **(A)**. The first solution is $q_0 = \lambda = 0$ and $m_\infty, \mu > 0$, the second one corresponds to $q_0, m_\infty, \lambda, \mu > 0$ and the last one – to $q_0 = m_\infty = \lambda = \mu = 0$. We call them non-robust, robust and para-attractor, respectively. Figure 1 **(B)** shows the full phase structure in terms of $T_J = 1/\beta$ and σ, supported by detailed behaviour of the order parameters in Fig. 1 **(C)**- **(F)**. At low noise, a high fitness-selection effect ($\beta > 2$) leads to a small but non-zero steady-state mean expression level ($m_\infty > 0$) due to a positive feedback (ensured by Hebbian-learning in Eq. (7)) between the positivity of μ and m_∞. The structure of this non-robust region is similar to that of a spin-glass phase at low-temperature because of the randomness in $J^{(to)} \sim \pm 1$ with the mean $\lambda = 0$ acting on the target.

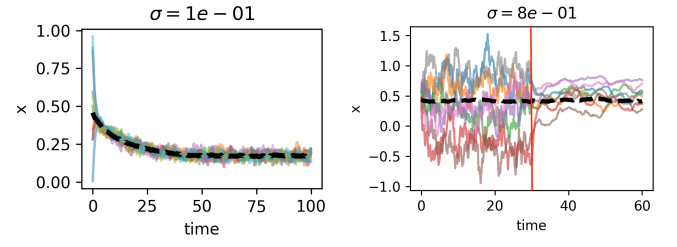The robust region always exists within an intermediate

FIG. 2. Timeseries of the gene-expression level in the non-robust phase at low noise $\sigma = 0.1$ (left) and in the robust one at intermediate noise $\sigma = 0.8$ (right). In the plot with $\sigma = 0.8$ the vertical red line marks the two stages of phenotypic evolution. Here the timeseries for time $\in [0, 30]$ are first generated at $\sigma = 0.8$, and then continued after time = 30 by decreasing σ to zero. In all panels the thick dashed lines denote the mean expression level $m(t, \tau \to \infty)$ over 1000 trajectories.

range of noise strength σ, $\sigma \in [\sigma_c^{(1)}(T_J), \sigma_c^{(2)}(T_J)]$ below some T_J. This phase can emerge if a sufficiently large noise destabilises those stable fixed points observed at low noise. Here phenotypes with high fitness are achieved through the support of robust genotypes $J^{(tt)}$ and $J^{(to)}$, both, on average, remain close to 1, indicating the dominance of positive regulations [62]. If noise is increased further so that the diffusive term becomes much larger than the first term in Eq. (6), then the loss of robustness occurs via a transition from the robust to para-attractor phase. In the para-attractor region, both phenotypic and genotypic values are zero, indicating the unique state is one that is neither robust nor functional.

The observed transitions are consistent with those reported in the numerical evolution for finite systems [44] where the robustnesses to noise and mutation that evolved at intermediate noise, lost at lower noise, resulting in a less fitted frozen state. Likewise, we here find that the integrated response χ is reduced and proportional to the response to mutation [63] in the robust phase, while it is larger at low noise regime. Timeseries of x in Eq. (4) in the robust and non-robust regions are given in Fig. 2, where the prediction of our fixed-point equations is found to be consistent with the timeseries in both regions. In particular, at low noise the deterministic system relaxes to a unique fixed point for any initial condition, while the small perturbation induced by $\sigma = 0.1$ results only in the proximity of random trajectories. The dynamics at intermediate noise $\sigma = 0.8$ exhibit intrinsic fluctuations that exist even when the external noise is removed. Nevertheless, despite of high variations in this case ($q_0 \simeq 0.4$), the phenotypes remain robust as shown by the dashed line indicating the mean expression level $m(t, \tau \to \infty)$.

To sum up our ADMFT demonstrated a robust-to-nonrobust transition with decreasing noise, quantified by the set of order parameters. The similarity between the nonrobust phase and spinglass, while noted, needs future

scrutiny. From an evolutionary perspective, the term in Eq. (9) can be considered as what gives rise to epistasis [64]. Moreover, when subjected to a time-dependent environment, the fitted phenotypes need to change over time, resulting in a more complicated relationship between fitness and phenotypes such as a nonlinear dependence of Ψ on m due to a tradeoff between the cost and benefit [65].

The present ADMFT, beyond the genotype-phenotype evolution, can be applied to a wide class of adaptive systems, in which slow adaption of one type of degrees of freedom occurs in response to changes in the state of the other. Such reciprocal evolution is not captured by the standard DMFT that deals only with fixed, i.e. "quenched" coupling constants. Other extensions of DMFT have been done recently for neural dynamics with activity-dependent plasticity [66] and with modification of synaptic weights by external temporal patterns [67]. These approaches, however, are different from ours, where a 'learning' rule for the **J** variables was derived from a global fitness-maximization requirement. The ADMFT further suggests the relevance of noise to shape robust memory by generating those evolved network structures that allow for the existence of an ensemble of intrinsically fluctuating trajectories with constant mean.

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[48] The effective dynamics is expected to yield the same statistics as that of the original dynamics, in an analogous manner to what has been rigorously proven for spin glasses [68].

[49] Note that h_{kj} differs from the local field typically used in spin-models and neural networks, where for a spin (neuron) i its local field is the sum over the states σ_j of its neighbors $h_i = \sum_{j \neq i} J_{ij}\sigma_j$.

[50] Note that when all the interactions between target genes become positive, another rescaling applies for $J_{ij}^{(tt)}$, namely $J_{ij}^{(tt)} \to J_{ij}^{(tt)}/N_t$, while for the couplings between target- and non-target genes $J_{ij}^{(to)} \to J_{ij}^{(to)}/\sqrt{N_t}$.

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[52] If we consider a sequential dynamics for the couplings then the first two equations are $d\mathbf{Y}(\tau)/d\tau = -\mathbf{Y}(\tau) + \tanh\big(\mathbf{H}(\tau)\big)$, where $\mathbf{Y} = (\hat{w}, \hat{\lambda})$ and $\mathbf{H}(\tau)$ is given by the same expressions as in (4).

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[61] This square-root form of the original Hebbian rule is due to the definition of fitness Ψ.

[62] Note that since our calculations are restricted to the mean values of $J^{(tt)}$ and $J^{(to)}$, they can not be used to study how similar the evolved genotypes are in the robust phase.

[63] In case where the system has a non-zero averaged activity $m > 0$, as $t, \tau \to \infty$, $\chi \propto \chi_m := \sum_{\tau'=0}^{\tau} G_m(t, \tau, \tau')$, where $G_m(t, \tau, \tau') := \partial\langle x(t, \tau)\rangle/\partial\hat{\mu}(\tau')$ is the response to mutation. Such proportionality between the two responses that implies a correlation between phenotypic changes due to genetic variation and those in response to environmental perturbations, as suggested by [44, 45, 59, 69–75], does not exist if $m \simeq 0$.

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SUPPLEMENTAL MATERIAL

A. Derivation of the effective dynamics in Eq. (4)

Applying the Fourier transform to the probability distribution of paths $\{x_k(t,\tau)\}$ generated by the gene-expression dynamics in Eq. (6)

$$\mathbb{P}_{\text{traj}}\Big(\{x_k(t,\tau)\}\Big) := \mathbb{P}_{\text{traj}}\Big[\{\mathbf{x}(0),\cdots,\mathbf{x}(t)\}_{\tau=0}, \{\mathbf{x}(0),\cdots,\mathbf{x}(t)\}_{\tau=1},\cdots,\{\mathbf{x}(0),\cdots,\mathbf{x}(t)\}_{\tau=T}\Big],$$

with T being the total number of generations (discrete time steps) of the J's dynamics, we have the following identity

$$1 = \int D[x\hat{x}]D[f\hat{f}]\exp\left\{i\cdot\sum_{\tau=0}^{T-1}\sum_{k=1}^{N}\int dt\Big[\hat{x}_k(t,\tau)(\partial_t+1)x_k(t,\tau)+i\sigma^2\hat{x}_k^2(t,\tau)-\gamma_k(t,\tau)\hat{x}_k(t,\tau)+\hat{f}_k(t,\tau)\big(f_k(t,\tau)-z_k(t,\tau)\big)\Big]\right\}$$

$$= \int D[x\hat{x}]D[f\hat{f}]\exp\left\{i\cdot\sum_{\tau=0}^{T-1}\sum_{k=1}^{N}\int dt\Big[E_k(t,\tau)-\sum_{j=1}^{N}J_{kj}(\tau)\cdot\hat{f}_k(t,\tau)\cdot x_j(t,\tau)\big)\Big]\right\} \tag{14}$$

where $J_{kk}=0$ and

$$z_k(t,\tau) = \tilde{h}_k(t) + \sum_{j(j\neq k)} J_{kj}(\tau)\cdot x_j(t,\tau) \tag{15a}$$

$$\gamma_k(t,\tau) = \tanh\big(f_k(t,\tau)\big) \tag{15b}$$

$$\int D[x\hat{x}] = \lim_{t_{\max}\to\infty}\int\prod_{k}^{N}\prod_{t}^{t_{\max}}\prod_{\tau}^{T-1} dx_k(t,\tau)d\hat{x}_k(t,\tau) \tag{15c}$$

$$E_k(t,\tau) = \hat{x}_k(t,\tau)(\partial_t+1)x_k(t,\tau)+i\sigma^2\hat{x}_k^2(t,\tau)-\gamma_k(t,\tau)\hat{x}_k(t,\tau)+\hat{f}_k(t,\tau)\big(f_k(t,\tau)-\tilde{h}_k\big) \tag{15d}$$

Note that, in the above expressions, $D[x\hat{x}]$ means a measure over all the generations $\tau = 0,\cdots,T$ of the J's dynamics and over all the possible paths of $x_k(t,\tau)$ and $\hat{x}_k(t,\tau)$ for all the genes at each of these generations, i.e. $D[x_k(t,\tau),\hat{x}_k(t,\tau)]$, $k = 1,\cdots,N$. We also used an integral representation of the probability $P(\xi)$ of the noise $\xi(t)$ with correlation $C_\xi = \langle\xi(t)\xi(t')\rangle = 2\sigma^2\delta(t-t')$:

$$P(\xi) \sim \exp\left[-\frac{1}{2}\int dt dt'\cdot\xi(t)\big[C_\xi(t,t')\big]^{-1}\xi(t')\right]$$

to write

$$1 = \int Dx D\hat{x} D\xi P(\xi)\exp\left[i\int dt\,\hat{x}(t)\big[\partial_t x+x-\gamma(x(t),\tilde{h}(t))-\xi(t)\big]\right]$$

$$= \int Dx D\hat{x}\exp\left[-\frac{1}{2}\int dt dt'\,\hat{x}(t)C_\xi\hat{x}(t')+i\int dt\,\hat{x}(t)\big[\partial_t x+x-\gamma(x(t),\tilde{h}(t))\big]\right]$$

In equivalent to the dynamics of a single coupling in Eq. (2) in case of synchronous update, the joint distribution $P(\mathbf{J})$ for the entire genotype satisfies a discrete-time master equation

$$P\big(\mathbf{J}(\tau+1)\big) = \sum_{\mathbf{J}(\tau)} W_\tau\big[\mathbf{J}(\tau+1);\mathbf{J}(\tau)\big]P\big(\mathbf{J}(\tau)\big)$$

$$W_\tau\big[\mathbf{J}(\tau+1);\mathbf{J}(\tau)\big] = \prod_{k\neq j} W_\tau\big[J_{kj}(\tau+1);J_{kj}(\tau)\big]$$

$$W_\tau\big[J_{kj}(\tau+1);J_{kj}(\tau)\big] = \frac{e^{\beta J_{kj}(\tau+1)h_{kj}(\mathbf{x}(\tau))}}{2\cosh\big[\beta h_{kj}(\mathbf{x}(\tau))\big]}. \tag{16}$$

Without considering the x's dynamics the moment generating functional of the trajectories $\{\mathbf{J}(\tau)\}$, $\tau = 0, \cdots, T$, according to Eq. (16) reads

$$Z_J[\mathbf{\Psi}] = \sum_{\{\mathbf{J}(0)\}} \cdots \sum_{\{\mathbf{J}(T)\}} \int D[h\hat{h}] \exp\left\{ \sum_{\tau=0}^{T-1} \sum_{k \neq j} A_{kj}(\tau) \right\} \tag{17a}$$

$$A_{kj}(\tau) = i\hat{h}_{kj}\big(h_{kj} - \theta_{kj}\big) + J_{kj}(\tau+1)\big(\Psi_{kj}(\tau+1) + \beta h_{kj}(\tau)\big) - \ln\big(2\cosh\big[\beta h_{kj}(\tau)\big]\big) \tag{17b}$$

$$\theta_{kj}^{(tt)}(\tau) = \lim_{t\to\infty} \big\langle x_k(t,\tau) x_j(t,\tau) \big\rangle \tag{17c}$$

$$\theta_{kj}^{(to)}(\tau) = \lim_{t\to\infty} \left\langle \big(1 - x_k^2(t,\tau)\big) J_{kj}^{(to)} \Big(\sum_{\ell \in \mathcal{T}} J_{j\ell}^{(ot)} x_\ell(t,\tau) \Big) \right\rangle \tag{17d}$$

Plugging Eq. (14) into (17a) leads to

$$Z_J[\mathbf{\Psi}] = \int D[x\hat{x}f\hat{f}h\hat{h}] \sum_{\{\mathbf{J}(0)\}} \cdots \sum_{\{\mathbf{J}(T)\}} \exp\left\{ \sum_{\tau=0}^{T-1} \left[i \cdot \sum_{k=1}^{N} \int dt E_k(t,\tau) + \sum_{k\neq j} \left[A_{kj}(\tau) - i J_{kj}(\tau) \int dt \hat{f}_k x_j \right] \right] \right\} \tag{18}$$

Denoting the J-independent and J-dependent part of the exponential in Z_J by $\mathcal{L}_0$ and $\mathcal{L}$, respectively. We have

$$Z_J[\mathbf{\Psi}] = \int D[x\hat{x}f\hat{f}h\hat{h}]e^{\mathcal{L}_0} \cdot \left(\sum_{\{\mathbf{J}(0)\}} \cdots \sum_{\{\mathbf{J}(T)\}} e^{\mathcal{L}_J} \right) \tag{19a}$$

$$\mathcal{L}_0 = \sum_{\tau=0}^{T-1} L(\tau) \tag{19b}$$

$$L(\tau) = i \cdot \sum_k \int dt E_k(t,\tau) + \sum_{k\neq j} i\hat{h}_{kj}\big(h_{kj} - \theta_{kj}\big) - \sum_{k\neq j} \ln\big(2\cosh\big[\beta h_{kj}(\tau)\big]\big) \tag{19c}$$

$$\mathcal{L}_J = \sum_{\tau=0}^{T-1} \left[\sum_{k\neq j} J_{kj}\Big(\Psi_{kj} + \beta h_{kj} - i \int dt \hat{f}_k x_j \Big) \right] \tag{19d}$$

So far we have made no distinction between target and non-target genes. Now we consider the following ansatz for any pair of target genes k and j:

$$J_{kj} = J_{kj}^{(tt)} + \Delta J_{kj} \tag{20}$$

where $J_{kj}^{(tt)}$ is the direct interaction between k and j and ΔJ_{kj} indicates the effective coupling between them that is induced by all the non-target genes l via $J_{kl}^{(to)}$ and $J_{lj}^{(to)}$. In analogy to the standard quenched disorder case, where the coupling J_{kj} is characterised by a distribution whose mean and variance, both need to be scaled as $1/N_t$ for a sensible thermodynamic limit, we use

$$J_{kj} = \frac{J_{kj}^{(tt)}}{N_t} + \Delta J_{kj} \tag{21}$$

where $J_{kj}^{(tt)} \in \{-1, 1\}$ and $\Delta J_{kj} = N_t^{-1} \sum_{l \notin \mathcal{T}} J_{kl}^{(to)} J_{lj}^{(to)}$, with $J_{kj}^{(to)} \in \{-1, 1\}$. The sum over $\{\mathbf{J}(\tau)\}$ in Eq. (18) can now be performed to obtain

$$S := \ln\left\{ \sum_{\{J_{kj}^{(tt)}\}} \sum_{\{J_{kl}^{(to)}\}} \exp(\mathcal{L}_J) \right\} = \sum_{\tau=0}^{T-1} S(\tau), \qquad S(\tau) = B(\tau) + D(\tau) \tag{22}$$

where, by defining the order parameters

$$w_{kj}(\tau) = \frac{1}{N_t} \int dt \, \hat{f}_k(t,\tau) x_j(t,\tau) \tag{23a}$$

$$m(t,\tau) = \frac{1}{N_t} \sum_j x_j(t,\tau) \tag{23b}$$

$$g(t,\tau) = \frac{1}{N_t} \sum_k \hat{f}_k(t,\tau) \tag{23c}$$

$$q(t,t',\tau) = \frac{1}{N_t} \sum_k x_k(t,\tau) x_k(t',\tau) \tag{23d}$$

$$Q(t,t',\tau) = \frac{1}{N_t} \sum_k \hat{f}_k(t,\tau) \hat{f}_k(t',\tau) \tag{23e}$$

$$K(t,t',\tau) = \frac{1}{N_t} \sum_k x_k(t,\tau) \hat{f}_k(t',\tau) \tag{23f}$$

and using the identity $\sum_{k \neq j} w_{kj}(\tau) = N_t \int dt \cdot m(t,\tau) \cdot g(t,\tau)$, we can compute

$$B(\tau) = \ln \left\{ \int D[\hat{\mu} wmg] \exp \left(i\hat{\mu}(\tau) \left[N_t \int dt \cdot m(t,\tau) g(t,\tau) + \sum_{k \neq j} w_{kj}(\tau) - \sum_k \int dt \Big[g(t,\tau) x_k(t,\tau) + m(t,\tau) \hat{f}_k(t,\tau) \Big] \right] \right) \right\}$$
$$+ \sum_{k \neq j \in \mathcal{T}} \ln 2\cosh \left(\frac{\Psi_{kj}(\tau+1) + \beta h_{kj}(\tau)}{N_t} - i w_{kj}(\tau) \right) \tag{24}$$

$$D(\tau) = \ln \left\{ \sum_{\left\{ J_{kl}^{(to)} = \pm 1 \right\}} \exp \left\{ \sum_{k \in \mathcal{T}, l \notin \mathcal{T}} J_{kl}^{(to)} \big(\Psi_{kl} + \beta h_{kl} \big) - i \sum_{k \neq j \in \mathcal{T}} \left[\int dt \Big(\frac{1}{N_t} \sum_{l \notin \mathcal{T}} J_{kl}^{(to)} J_{lj}^{(to)} \Big) \hat{f}_k x_j \right] \right\} \right\}$$

$$= \ln \left\{ \sum_{\left\{ J_{kl}^{(to)} = \pm 1 \right\}} \exp \left\{ \sum_{k \in \mathcal{T}, l \notin \mathcal{T}} J_{kl}^{(to)} \big(\Psi_{kl} + \beta h_{kl} \big) - i \sum_{l \notin \mathcal{T}} \int dt \left[\Big(\sum_{k \in \mathcal{T}} \frac{J_{kl}^{(to)}}{\sqrt{N_t}} \hat{f}_k \Big) \cdot \Big(\sum_{j \in \mathcal{T}} \frac{J_{lj}^{(to)}}{\sqrt{N_t}} x_j \Big) \right] \right\} \right\}$$

$$= \ln \left\{ \sum_{\left\{ J_{kl}^{(to)} \right\}} \prod_{l \notin \mathcal{T}} \left[\int Dy_l Dz_l \cdot \exp \left\{ -i \int dt \, y_l z_l + \sum_{k \in \mathcal{T}} J_{kl} \frac{\Psi_{kl} + \beta h_{kl}}{\sqrt{N_t}} \right\} \cdot \int dt \, \delta \Big(z_l - \sum_{k \in \mathcal{T}} \frac{J_{kl}}{\sqrt{N_t}} \hat{f}_k \Big) \cdot \delta \Big(y_l - \sum_{j \in \mathcal{T}} \frac{J_{jl}}{\sqrt{N_t}} x_j \Big) \right] \right\}$$

$$= \ln \left\{ \int D[y\hat{y}] D[z\hat{z}] \cdot e^{i \int dt \sum_{l \notin \mathcal{T}} [z_l \hat{z}_l + y_l \hat{y}_l - z_l y_l]} \sum_{\left\{ J_{kl} \right\}} \exp \left\{ \sum_{k \in \mathcal{T}, l \notin \mathcal{T}} \frac{J_{kl}}{\sqrt{N_t}} \left[\Psi_{kl} + \beta h_{kl} - i \int dt \, \big(\hat{z}_l \hat{f}_k + \hat{y}_l x_k \big) \right] \right\} \right\}$$

$$= \ln \left\{ \int D[y\hat{y}] D[z\hat{z}] \cdot \exp \left\{ i \int dt \sum_{l \notin \mathcal{T}} [z_l \hat{z}_l + y_l \hat{y}_l - z_l y_l] + \sum_{k,l} \ln \left[\cos \left(i \cdot \frac{\Psi_{kl} + \beta h_{kl}}{\sqrt{N_t}} + \int dt \frac{\hat{z}_l \hat{f}_k + \hat{y}_l x_k}{\sqrt{N_t}} \right) \right] \right\} \right\}$$

$$= \ln \left\{ \int D[y\hat{y}] D[z\hat{z}] D[q\hat{q}] D[Q\hat{Q}] D[K\hat{K}] \cdot \exp \left(N_t \Big[i\psi + \Phi + \Omega \Big] + \int dt \sum_{l \notin \mathcal{T}} [z_l \hat{z}_l + y_l \hat{y}_l - z_l y_l] \right) \right\} \tag{25}$$

where

$$\psi = \int dtdt' \left\{ q \cdot \left[\hat{q} + \frac{i}{2N_t} \sum_{l \notin \mathcal{T}} \hat{y}_l(t)\hat{y}_l(t') \right] + Q \cdot \left[\hat{Q} + \frac{i}{2N_t} \sum_{l \notin \mathcal{T}} \hat{z}_l(t)\hat{z}_l(t') \right] + K \cdot \left[\hat{K} + \frac{i}{N_t} \sum_{l \notin \mathcal{T}} \hat{y}_l(t)\hat{z}_l(t') \right] \right\}$$

$$\Phi = -\frac{i}{N_t} \sum_k \int dtdt' \left[\hat{q} \cdot x_k(t)x_k(t') + \hat{Q} \cdot \hat{f}_k(t)\hat{f}_k(t') + \hat{K} \cdot \hat{f}_k(t')x_k(t) \right]$$

$$\Omega = \frac{1}{N_t^2} \sum_{k \in \mathcal{T}, l \notin \mathcal{T}} \left[\frac{(\Psi_{kl} + \beta h_{kl})^2}{2} - i(\Psi_{kl} + \beta h_{kl}) \int dt \cdot (\hat{z}_l \hat{f}_k + \hat{y}_l x_k) \right]$$

Substituting $\hat{y} = z$ and $\hat{z} = y$, those that are obtained by varying the action wrt y and z, respectively, we get

$$\psi = \int dtdt' \left\{ q \cdot \left[\hat{q} + \frac{i}{2N_t} \sum_{l \notin \mathcal{T}} z_l(t)z_l(t') \right] + Q \cdot \left[\hat{Q} + \frac{i}{2N_t} \sum_{l \notin \mathcal{T}} y_l(t)y_l(t') \right] + K \cdot \left[\hat{K} + \frac{i}{N_t} \sum_{l \notin \mathcal{T}} z_l(t)y_l(t') \right] \right\}$$

$$\Omega = \frac{1}{N_t^2} \sum_{k \in \mathcal{T}, l \notin \mathcal{T}} \left[\frac{(\Psi_{kl} + \beta h_{kl})^2}{2} - i(\Psi_{kl} + \beta h_{kl}) \int dt \cdot (z_l x_k + y_l \hat{f}_k) \right]$$

Saddle-point conditions for $(\psi + \Phi)$ wrt q, Q and K; $\hat{q}, \hat{Q}$ and $\hat{K}$ lead to

$$
\begin{cases}
\dfrac{\partial \psi}{\partial q} = 0, & \rightarrow \hat{q}_* = -\dfrac{i\alpha}{2} \cdot \langle z(t)z(t') \rangle_* \\[2mm]
\dfrac{\partial \psi}{\partial Q} = 0, & \rightarrow \hat{Q}_* = -\dfrac{i\alpha}{2} \cdot \langle y(t)y(t') \rangle_* \\[2mm]
\dfrac{\partial \psi}{\partial K} = 0, & \rightarrow \hat{K}_* = -i\alpha \cdot \langle z(t)y(t') \rangle_*
\end{cases}
\qquad
\begin{cases}
\dfrac{\partial(\psi + \Phi)}{\partial \hat{q}} = 0, & \rightarrow q = \langle x(t)x(t') \rangle_* \\[2mm]
\dfrac{\partial(\psi + \Phi)}{\partial \hat{Q}} = 0, & \rightarrow Q = \langle \hat{f}(t)\hat{f}(t') \rangle_* \\[2mm]
\dfrac{\partial(\psi + \Phi)}{\partial \hat{K}} = 0, & \rightarrow K = \langle x(t)\hat{f}(t') \rangle_*
\end{cases}
\qquad (28)
$$

where $\alpha = N_o/N_t$ and we have introduced a measure for the effective dynamics of a single gene x that evolves under all realizations of $(x, \hat{x}, f, \hat{f}, h, \hat{h}, w, \hat{w})$ as

$$\left\langle O(x, \hat{x}, f, \hat{f}, h, \hat{h}, w, \hat{w}) \right\rangle = \frac{\int DyDzD[x\hat{x}f\hat{f}h\hat{h}w\hat{w}] \cdot O \cdot e^L}{\int DyDzD[x\hat{x}f\hat{f}h\hat{h}w\hat{w}] e^L}, \qquad L = \sum_{\tau=0}^{T-1} L(\tau) + S(\tau) \qquad (29)$$

where

$$L(\tau) + S(\tau) = \sum_{k \neq j \in \mathcal{T}} W_{kj} + \sum_{k \in \mathcal{T}, l \notin \mathcal{T}} \tilde{W}_{kl} + i \sum_k \left(\int dt E_k(t, \tau) - M_k^{(\mathrm{sd})}(\tau) \right) \qquad (30\mathrm{a})$$

$$M_k^{(\mathrm{sd})}(\tau) = \hat{\mu}(\tau) \int dt [g_* x_k + m_* \hat{f}_k] + \int dtdt' \left[\hat{q}_* \cdot x_k(t)x_k(t') + \hat{Q}_* \cdot \hat{f}_k(t)\hat{f}_k(t') + \hat{K}_* \cdot \hat{f}_k(t')x_k(t) \right] \qquad (30\mathrm{b})$$

$$W_{kj} = i\hat{h}_{kj}^{(tt)}\left(h_{kj}^{(tt)} - \theta_{kj}\right) + \ln \left[\frac{2\cosh\left(\dfrac{\Psi_{kj}(\tau+1) + \beta h_{kj}^{(tt)}(\tau)}{N_t} - iw_{kj}(\tau) \right)}{2\cosh\left[\beta h_{kj}^{(tt)}(\tau)/N_t \right]} \right] \qquad (30\mathrm{c})$$

$$\tilde{W}_{kl} = \frac{\left(\Psi_{kl} + \beta h_{kl}^{(to)}\right)^2}{2N_t} - i\frac{\Psi_{kl} + \beta h_{kl}^{(to)}}{N_t} \int dt \left[y\hat{f}_k + zx_k \right] + i\hat{h}_{kl}^{(to)}\left(h_{kl}^{(to)} - \tilde{\theta}_{kl}\right) - \ln \left[2\cosh\left(\frac{\beta h_{kl}^{(to)}}{\sqrt{N_t}} \right) \right] \quad (30\mathrm{d})$$

Saddle-point conditions for $\tilde{W} = \sum_{k,l} \tilde{W}_{kl}$ wrt $h_{kl}^{(to)}$ and $\hat{h}_{kl}^{(to)}$ in the limit $\Psi_{kl} \rightarrow 0$ lead to

$$\hat{\lambda}(\tau+1) := \sqrt{N_t}\left\langle J_{kl}^{(to)}(\tau+1) \right\rangle = \sqrt{N_t}\left(\lim_{\Psi \to 0} \frac{\partial Z}{\partial \Psi_{kl}} \right) = \tanh\left(\frac{\beta}{\sqrt{N_t}} h_{kl}^{(to)}(\tau) \right) \qquad (31)$$

Similar saddle-point calculations for $W = \sum_{k,j} W_{kj}$ yield $h_{kj}^{(tt)}(\tau) = \theta_{kj}(\tau)$ and

$$\left\langle J_{kj}^{(tt)}(\tau+1) \right\rangle := \lim_{\Psi \to 0} \frac{\partial Z}{\partial \Psi_{kj}} = \frac{1}{N_t} \tanh\left(\frac{\beta}{N_t} h_{kj}^{(tt)}(\tau)\right) , \qquad \to \hat{\mu}(\tau+1) = \tanh\left(\frac{\beta}{N_t} h_{kj}^{(tt)}(\tau)\right) \tag{32}$$

The final step consists of evaluating these $\hat{q}_*, \hat{Q}_*, \hat{K}_*$ as follows

$$\hat{q}_* = -\frac{i\alpha}{2} \left\langle \left(\sum_{\ell' \in \mathcal{T}} J_{\ell'}^{(to)} \hat{f}_{\ell'}(t)\right) \left(\sum_{\ell \in \mathcal{T}} J_{\ell}^{(to)} \hat{f}_{\ell}(t')\right) \right\rangle_* = -\frac{i\alpha}{2} \left(\sum_{\ell' \neq \ell} J_{\ell'}^{(to)} J_{\ell}^{(to)} \left\langle \hat{f}_{\ell'}(t)\hat{f}_{\ell}(t')\right\rangle_* + \sum_{\ell \in \mathcal{T}} [J_{\ell}^{(to)}]^2 \left\langle \hat{f}_{\ell}(t)\hat{f}_{\ell}(t')\right\rangle_*\right) = 0$$

$$\hat{Q}_* = -\frac{i\alpha}{2} \left\langle \left(\sum_{\ell'} J_{\ell'}^{(to)} x_{\ell'}(t)\right) \left(\sum_{\ell} J_{\ell}^{(to)} x_{\ell}(t')\right) \right\rangle_* = -\frac{i\alpha}{2} \left(\sum_{\ell' \neq \ell} J_{\ell'}^{(to)} J_{\ell}^{(to)} \left\langle x_{\ell'}(t) x_{\ell}(t')\right\rangle_* + \sum_{\ell} [J_{\ell}^{(to)}]^2 \left\langle x_{\ell}(t) x_{\ell}(t')\right\rangle_*\right)$$

$$= -\frac{i\alpha\lambda^2}{2} C(t,t')$$

$$\hat{K}_* = -i\alpha \left\langle \left(\sum_{\ell'} J_{\ell'}^{(to)} \hat{f}_{\ell'}(t)\right) \left(\sum_{\ell} J_{\ell}^{(to)} x_{\ell}(t')\right) \right\rangle_* = -i\alpha \left(\sum_{\ell' \neq \ell} J_{\ell'}^{(to)} J_{\ell}^{(to)} \left\langle \hat{f}_{\ell'}(t) x_{\ell}(t')\right\rangle_* + \sum_{\ell} [J_{\ell}^{(to)}]^2 \underbrace{\left\langle \hat{f}_{\ell}(t) x_{\ell}(t')\right\rangle_*}_{K(t',t)}\right)$$

$$= -i\alpha\lambda^2 \left(i \underbrace{\frac{\partial \langle x(t')\rangle_*}{\partial \tilde{h}(t)}}_{G(t',t)}\right) \tag{33}$$

The effective single-gene dynamics is generated by the following path probability, introducing the notation, $\hat{\mu} = \hat{w}$,

$$P(x(t)) = \int D\left[x\hat{x}f\hat{f}\right] \prod_{\tau=0}^{T-1} \left[\exp\left\{i \cdot \int dt\left[\hat{x}(\partial_t + 1)x + i\sigma^2 \hat{x}^2 - \hat{x}\gamma(f) + \hat{f}\left(f - m_*\hat{\mu}(\tau) - \tilde{h}\right)\right]\right.\right.$$
$$\left.\left. - \alpha\hat{\lambda}^2(\tau) \int dt dt'\left[\frac{C(t,t')}{2}\hat{f}(t)\hat{f}(t') + iG(t',t)x(t)\hat{f}(t')\right]\right\}\right] \tag{34}$$

This equation results in the equivalent SDE form of Eq. (4). In addition to the results in the main text, here we present the model phase diagrams in terms of α and σ in Fig. 3.
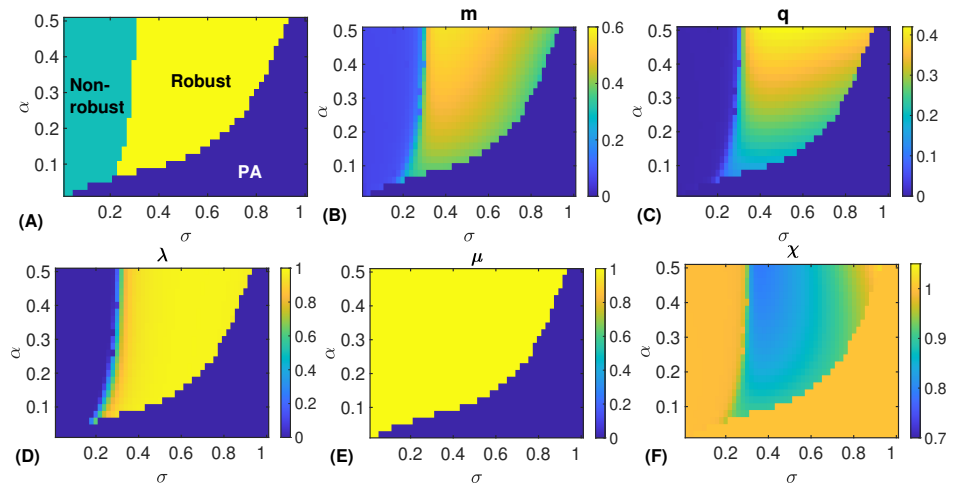

FIG. 3. Order parameters as function of $\alpha = N_o/N_t$ and σ at $\beta = 10$. **(A)** The model phase diagram. **(B)** Averaged activity of target genes m. **(C)** The variance in the activity of target genes q. **(D)** The average of target vs non-target coupling λ. **(E)** The average of target vs target coupling μ. **(F)** The integrated response of target spins χ.