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Double-replica theory for evolution of genotype-phenotype interrelationship

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The relationship between genotype and phenotype plays a crucial role in determining the function and robustness of biological systems. Here the evolution progresses through the change in genotype, whereas the selection is based on the phenotype, and the genotype-phenotype relation also evolves. The theory for such phenotypic evolution remains poorly developed, in contrast to evolution under the fitness landscape determined by genotypes. Here we provide a statistical-physics formulation of this problem by introducing replicas for genotype and phenotype. We apply it to an evolution model in which phenotypes are given by spin configurations; genotypes are an interaction matrix for spins to give the Hamiltonian, and the fitness depends only on the configuration of a subset of spins called the target. We describe the interplay between the genetic variations and phenotypic variances by noise in this model by our approach that extends the replica theory for spin glasses to include a spin replica for phenotypes and a coupling replica for genotypes. Within this framework we obtain a phase diagram of the evolved phenotypes against the noise and selection pressure, where each phase is distinguished by the fitness and overlaps for genotypes and phenotypes. Among the phases, a robust fitted phase, relevant to biological evolution, is achieved under the intermediate level of noise (temperature), where robustnesses to noise and to genetic mutation are correlated, as a result of replica symmetry. We also find a tradeoff between maintaining a high fitness level of phenotype and acquiring a robust pattern of genes as well as the dependence of this tradeoff on the ratio between the size of the functional (target) part to that of the remaining nonfunctional (non-target) one. The selection pressure needed to achieve high fitness increases with the fraction of target spins.

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I. INTRODUCTION

Evolution under given fitness landscape in the space of genotypes has been studied extensively [1,2]. Here genotypes are changed (mutated) in the reproduction process, and those that have higher fitness, i.e., higher offspring-production rate, are selected to the next generation. The fitness, however, is not directly determined by the genes, but rather by phenotypes, that are the characteristics of a biological system and are also modulated by environmental effects, such as thermal noise [3]. Examples of phenotypes include the shape of folded proteins, a set of intracellular chemical concentrations, specific functions of an organism, and so forth. These phenotypes are shaped as a result of dynamical process, whose rule is determined by genes. The evolution of phenotypes is thus shaped by the genetic evolution.

In addition to the variations of phenotypes induced by genetic mutations during the evolution, phenotypes of isogenic individuals are also generally variable under noise, resulting in their stochastic dynamics. Cells involve stochastic gene expression dynamics, whereas protein folding dynamics to give the protein shape is under thermal noise [4–7]. Fitted phenotypic states hence are better preserved under noise, i.e., they keep robustness to noise, while robustness to mutation will also be required. The achievement of robustness of phenotypes to noise and to mutation is important to evolution, as was discussed recently [8–11]. Now, considering stochastic dynamics of phenotypes, a general formulation of the evolution of such genotype-phenotype mapping and phenotypic robustness is hence wanted.

Underlying such stochastic dynamics are the interactions among a vast number of elements that constitute a biological system. A cell consists of a huge variety of interacting molecules, and its constituent polymers (proteins) are composed of many monomers (residues). Statistical physics [12,13] provides an appropriate description of the states of such interacting elements under noise, and hence it can be adopted to yield a proper formulation of the mapping from genotype to phenotype as a dynamical process that shapes the phenotypes. To this kind of study, use of spin models is relevant, as it has been extensively analyzed [14–16]. Here phenotypes are regarded as spin configurations that are updated by a Hamiltonian with spin-spin interactions under thermal noise, whereas genotypes specify such spin-spin interactions. Individuals are subjected to selection pressure, where fitness, the number of selected offspring, is given by a function of configuration of a subset of spins, termed target spins. It is then important to identify possible phases
for genotype-phenotype mapping by using the set of order
parameters, a concept rooted in statistical physics.

In the present paper, to address these problems in a sys-
tematic way, we formulate double replica methods both for
spins (phenotypes) and couplings (genotypes), as well as both
for target and nontarget parts. Even though we adopted spin-
coupling representation here our formulation can generally be
applied to other problems, in which the interactions among
many degrees of freedom are also dynamical variables with
their own dynamics. For the sake of demonstration, however,
we here explain this approach by using specifically a spin-
glass Hamiltonian model developed in [14–16]. These works
uncovered that, within an intermediate range of phenotypic
noise and under sufficiently strong selection pressure, the
evolved spin-systems could attain high fitness and robustness
to noise and mutation. A systematic way to elucidate the
condition to achieve such robust fitted states with regards
to the noise strength, selection pressure, and relative size of
target spins, and to understand possible relationship between
robustness to mutation and to noise, however, has not been
developed yet.

One might expect an application of mean-field methods
for disordered systems [17] in this model since a spin-glass
Hamiltonian formulation was adopted by replacing random
couplings among spins (phenotypes) by genotypes that are
evolving [14–16]. Gradual change in the couplings might fit
with partial annealing approach based on a finite number of
replicas $n$. However, such study is restricted to the case
in which the coupling dynamics are affected by a spin-spin
correlation term [18–22], and is not directly applicable for our
purpose, in which the coupling dynamics depend on the fitness
determined by the spin configurations. Another theoretical
method assumes the quench limit ($n \to 0$) for a replicated
spin system [23], in which the couplings are treated effect-
ively as “static” and hence is not suitable to investigate the
evolution of both genotypes (couplings) and phenotypes (spin
configurations).

In this paper we develop a mean-field approach that we
term double replica theory. It describes the evolution of both
genotypes and phenotypes by considering spins and links as
two different replica species. With this formulation, we obtain
fitness and replica overlaps for spins and couplings, which
work as the order parameters. Using these order parameters
we identify five regions in the temperature vs selection pres-
sure phase diagram: two nonfitted paramagnetic phases, fitted
and nonfitted spin glass phases, and a robust fitted phase.
The last phase is the most biologically important, and can
only be achieved under intermediate noise level (temperature)
and sufficient selection pressure, whereas robustness can only
arrive at the cost of lowering the fitness from its maximal
value. Dependence of the robust fitted phase on the ratio of
functional to nonfunctional parts has been analyzed in depth.
As the former ratio is increased, the selection pressure to
achieve this phase is drastically increased, whereas, if the
phase is achieved, it can persist for slightly higher noise.
This suggests the relevance of having sufficient nonfunctional
parts in biological systems. In addition, correlation between
robustnesses to noise and to mutation is formulated as a pro-
portionality between susceptibilities to external field and to
coupling change.

II. DOUBLE REPLICA THEORY

Following [15,16] we study the evolution of the relation-
ship between phenotype and genotype by representing phe-
notypes as spin configurations, and genotypes as interaction
matrix for spins. In a system of $N$ spins, each spin $i$ can take
values $s_i \in \{-1, 1\}$ and is linked to exactly $N - 1$ other spins,
thus forming a fully connected network. Here the evolution
progresses through the change in genotype, whereas the selec-
tion is based on the phenotype, resulting in an evolution of the
genotype-phenotype relation. Moreover, fitness is determined
by a subset of target spins denoted by $T$. Those spins that do
not contribute to the fitness are called nontarget. In general,
the fitness $\Psi$ is some field that acts on $J_{ij}$ but whose value
depends only on $s_i, s_j \in T$. How such dependence is explicitly
described is model specific and will not limit the use of our
approach. See Eq. (A1) in Appendix A for an example of $\Psi$
given by the target spin configurations at equilibrium [15,16].

Stochastic dynamics of phenotypes are considered as the
evolution of spin configurations at a temperature $T$, according
to a Hamiltonian

$$H_S = -\sum_{i<>j} J_{ij} s_i s_j$$

[24]. Here the couplings $J_{ij}$ are regarded as fixed over the course of the spin
evolution that follows a Glauber update because they are
assumed to evolve on much slower timescale than that of the
spins. Furthermore, the couplings are symmetric, i.e., $J_{ij} =
J_{ji}$, and, initially, are independently and identically distributed
by a Gaussian distribution with zero mean and the variance

$$J^2 := \text{var}(J_{ij}) = N^{-1}.$$  

The coupling matrix $J$ includes interactions between target spins $J_{ij}^{(t)}$ for $i \in T$ and $j \in T$, those
between target spin and nontarget spin $J_{ij}^{(nt)}$ for $i \in T$ and $j \in \bar{T}$, and those
between nontarget spins $J_{ij}^{(nn)}$ for $i \in \bar{T}$ and $j \in \bar{T}$, where $\bar{T}$ and $\bar{S}$ denote the subsystems of target spins
(with their interactions $J^{(t)}$) and the subsystem of nontarget spins (with the couplings $J^{(nn)}$ among them), respectively.
The Hamiltonian of the full system denoted by $S$ can be decomposed into

$$H_S = -\sum_{i<>j} J_{ij}^{(t)} s_i s_j - \sum_{i<>j} J_{ij}^{(nt)} s_i s_j - \sum_{i<>j} J_{ij}^{(nn)} s_i s_j,$$  

where $H_T$ and $H_{O}$ are the Hamiltonians of the subsystems
$S_T$ and $S_O$, respectively, while $H_{TO}$ describes the interactions
between these subsystems.

Now we introduce the effective potential to obtain the
distribution of $J$ [25]. For it, we consider a continuous
Langevin-type dynamics for the couplings,

$$\frac{dJ_{ij}}{d\tau} = -\frac{1}{N} \frac{\partial V}{\partial J_{ij}} + \frac{1}{\sqrt{N}} \xi_{ij}(\tau),$$  

where $V = V(J)$ is the potential of all the couplings and $\xi_{ij}$ is
the white noise whose intensity equal to the potential $T_j$.
The factors $1/N$ and $1/\sqrt{N}$ in front of the potential and the
noise term, respectively, ensure a correct relationship between
the drift and diffusive parts of the Langevin equation. If the
couplings were independent of each other, the potential would
simply take the form of the potential of a free Brownian
particle,
\[ V_0 = \frac{N}{2} \sum_{i<j} J_{ij}^2. \]

However, in the presence of fitness we need an additional term. Here we assume that the fitness would be maximized if a global alignment is established among target spins, so that we introduce
\[ \Psi = \frac{1}{N_T} \left| \sum_{i \in T} s_i \right|, \]
where \(N_T\) is the size of \(T\). Under this fitness that favors the alignment of target spins, the couplings are necessarily subjected to a fitness field \(K\) [26]:
\[ K = \frac{1}{\beta_j} \frac{\partial}{\partial J_{ij}} \ln \left( \sum_{|s_i|} \exp \left\{ \frac{\beta_j}{N_T} \sum_{i<j \in T} J_{ij} \left| \sum_{i \in T} s_i \right| \right\} \right), \]
or equivalently, \(V\) needs to be modified from \(V_0\) into
\[ V = V_0 - \frac{1}{\beta_j} \ln \left( \sum_{|s_i|} \exp \left\{ \frac{\beta_j}{N_T} \sum_{i<j \in T} J_{ij} \left| \sum_{i \in T} s_i \right| \right\} \right). \]

Without the evolution of genotypes, the Hamiltonians \(H_T\), \(H_O\), and \(H_{T O}\) dictate the spins to adapt to a set of fixed couplings \(J\) in order to minimize each term of Eq. (1) through the spin dynamics. Such adaptation results in an equilibriumlike stationary distribution \(P\), i.e.,
\[ P(J^{(oo)}) = \lim_{t \to \infty} P(J^{(tr)}, \tau), \]
where \(P(J^{(tr)}, \tau)\) and \(P(O(J^{(oo)}, \tau)\) are the time-dependent solutions of the corresponding Fokker-Planck equations with the effective potentials \(V_t\) for \(J^{(tr)}\) and \(V_o\) for \(J^{(oo)}\), respectively [28]. To obtain the distribution only of \(J^{(tr)}\) and \(J^{(oo)}\), we first replace \(J^{(tr)}\) as the given matrix by that obtained self-consistently from the equilibrium distribution. For it we need to modify \(V_t\) in such a way that the influence of \(J^{(oo)}\) on \(J^{(tr)}\) (\(J^{(oo)}\) can be taken into account in the effective potential \(V_{t o}\). The joint effect of \(H_{T O}\) and \(H_T\) on the dynamics of target spins suggests that the dependence of \(J^{(tr)}\) and \(J^{(oo)}\) on each other arises from any triad formed between \(i, j \in T\) and \(k \not\in T\), i.e., via \(J^{(tr)}_{ij}, J^{(oo)}_{ik}, J^{(oo)}_{jk}\). This influence is represented by the frustration [17], which implies that an optimal spin configuration \((s^*_i, s^*_j, s^*_k)\) can only be established if the relation \(J^{(tr)}_{ij}, J^{(oo)}_{ik}, J^{(oo)}_{jk} > 0\) holds [optimality in this context means that \(H_{T O}\) and \(H_T\) can be lowered simultaneously by \((s^*_i, s^*_j, s^*_k)\)]. Since for any given pair of \((i, j \in T\) there are \(N - N_t\) triads \(\Delta_k\) formed between it and a nontarget spin \(k \not\in T\), the total effect of frustration is given by
\[ F^{(oo-oo)}_{ij} = (N - N_t)^{-1} \sum_{k=1}^{N-N_t} J^{(oo)}_{ik} J^{(oo)}_{jk}. \]

Likewise, frustration among all \(N_t\) triads \(\Delta_k\) formed between a given pair of nontarget spins \(i \not\in T\) and \(j \not\in T\) with \(k \in T\) induces a force \(F^{(oo-oo)}_{ij}\) on the state of \(J^{(oo)}\):
\[ F^{(oo-oo)}_{ij} = N_t^{-1} \sum_{k=1}^{N_t} J^{(oo)}_{ik} J^{(oo)}_{jk}. \]

The proposed scheme just allows us to define the effective potential \(V_t\) for \(J^{(tr)}\) and \(V_o\) for \(J^{(oo)}\) as
\[ V_t = V_a - \frac{1}{\beta_j} \ln \left( \sum_{|s_i|} \exp \left\{ \beta_j \sum_{i<j \in T} J^{(tr)}_{ij} F^{(oo-oo)}_{ij} \right\} \right), \]
\[ V_o = V_a - \frac{1}{\beta_j} \ln \left( \sum_{|s_i|} \exp \left\{ \beta_j \sum_{i<j \in T} J^{(oo)}_{ij} F^{(oo-oo)}_{ij} \right\} \right). \]

The stationary distributions induced by the diffusion process in Eq. (2) with these effective potentials have a Boltzmann form, \(P_T(J^{(tr)}) = e^{-\beta V_t} / Z_T\) and \(P_O(J^{(oo)}) = e^{-\beta V_o} / Z_O\), where \(Z_T\) and \(Z_O\) are the partition function of the genotypes \(J^{(tr)}\) and that of the genotypes \(J^{(oo)}\), respectively [29]. Here we replace \(J^{(oo)}\) by the replica matrix \(\alpha^2_j : = J_{ij}^{(oo)}\), to be obtained. (This stepwise scheme is valid, as we are concerned with the equilibrium property). Denoting \(n := T_i / T_j\), we can compute \(Z_T\) and \(Z_O\) as
\[ Z_T = \int \prod_{i<j \in T} dJ_{ij}^{(t)} \sum_{\{ s_i, \sigma_i^k \}_{i \in T}} \exp \left\{ \beta_T \sum_{i<j} \left[ -\frac{N_t}{2} (J_{ij}^{(t)})^2 + J_{ij}^{(t)} \left( \frac{1}{N_t} \sum_{i \in T} s_i + \frac{1}{n} \sum_{a=1}^{N_t} \sigma_i^a \sigma_i^a \right) + \frac{1}{N_t} \sum_{k=1}^{N_t} \sigma_i^k \sigma_i^k \right] \right\}, \]

\[ Z_O = \int \prod_{i<j \in T} dJ_{ij}^{(o)} \sum_{\{ s_i, \sigma_i^k \}_{i \in T}} \exp \left\{ \beta_O \sum_{i<j} \left[ -\frac{N_t}{2} (J_{ij}^{(o)})^2 + J_{ij}^{(o)} \left( \tilde{\beta}_T + \frac{1}{n} \sum_{a=1}^{N_t} \sigma_i^a \sigma_i^a + \frac{1}{N_t} \sum_{k=1}^{N_t} \sigma_i^k \sigma_i^k \right) \right] \right\}. \]

In writing these equations, we assume that the fitness acts only on \( J_{ij}^{(t)} \) [30] and hence in \( Z_O \) we replace the fitness field \( K \) by a constant \( \tilde{K} \), which eventually will be set to 0 by virtue of calculations of the observables for nontarget spins. Although neglecting the fitness’s effect on \( J_{ij}^{(o)} \) does not follow exactly the above-mentioned implementation of the model, we expect that this holds true in the long-time limit because otherwise both target and nontarget configurations at equilibrium would determine the fitness. This restriction hence corresponds to a first-order approximation of the fitness’s effect, while a term that affects the dynamics of \( J_{ij}^{(o)} \) and \( J_{ij}^{(t)} \) is considered to be of higher order.

We here propose to interpret \( \sigma_i^k \) as the \( k \)th replica of another variable \( \sigma_i \in \{-1, 1\} \) that is also located at the site \( i \) of the graph (generally \( \sigma_i \neq s_i \)). To distinguish these different types of replicas from each other, we call \( s_i^* \) spin replicas and \( \sigma_i^k \) coupling replicas. Following this interpretation, apart from \( n \) that appears as the number of spin replicas \( s_i^a \), \( a = \{1, \ldots, n\} \), in \( Z_T \) and \( Z_O \) [31], we thus have \( N - N_t \) coupling replicas, \( \sigma_i^k \), for \( i \in T \) and \( k = \{1, \ldots, N - N_t\} \), and \( N_t \) coupling-replicas, \( \sigma_i^k \), for \( i \notin T \) and \( k = \{1, \ldots, N_t\} \) respectively. As, in general, none of these numbers are zero, our double-replica approach does not correspond to the conventional quenched limit in spin-glass models [17]. Once setting \( K = 0 \) and neglecting the terms corresponding to \( F^{(t-o-o)} \) and \( F^{(o-t-o)} \), we recover the model of Coolen et al. for neural systems with dynamic synapses [19]. In contrast to the use of a Hamiltonian for the couplings adopted in [23], here we have introduced the effective potential for couplings that, by using the timescale separation between the dynamics of genotypes and that of phenotypes, allows for the integration of the spin dynamics specified by the Hamiltonian (1) into the Langevin dynamics of the couplings through the second term in Eq. (6).

Here we characterize the equilibrium behavior of the model by the average fitness \( m \), the overlap between different spin replicas \( a \) and \( b \), \( q_{ab} \), and the correlation between adjacent links \( \theta \). Additionally, we want to quantify the mean value of the couplings among the target spins only \( \Phi \). Let \( \mathbb{E}[\cdot] \) and \( \mathbb{E}[\cdot]_T \) denote ensemble averages over \( \mathbb{P}_T(J^{(t)}) \) and \( \mathbb{P}_O(J^{(o)}) \), respectively. These order parameters are given by

\[ m_a = \mathbb{E}[s_i^a]_{i \in T}, \]

\[ q_{ab} = \mathbb{E}[s_i^a s_i^b]_{i \in T}, \]

\[ Q_{kk'} = \mathbb{E}[J_{ik}^{(o)} J_{ik'}^{(o)}]_{i \in T k, k' \notin T}, \]

\[ \Phi = \mathbb{E}[J_{ij}^{(t)}]_{i,j \in T}. \]

Similarly, for the nontarget spins we have

\[ m_a = \mathbb{E}[s_i^a]_{i \notin T}, \]

\[ q_{ab} = \mathbb{E}[s_i^a s_i^b]_{i \notin T}, \]

\[ Q_{kk'} = \mathbb{E}[J_{ik}^{(o)} J_{ik'}^{(o)}]_{i \notin T k, k' \notin T}, \]

\[ \Phi = \mathbb{E}[J_{ij}^{(o)}]_{i,j \notin T}. \]

In the thermodynamic limit, \( N \to \infty \) and \( N_t \to \infty \), while keeping \( p = N_t/N \) fixed, using a replica symmetric ansatz for the variables \( m_a \), \( q_{ab} \) and \( Q_{kk'} \), as well as \( M_{dk} = M \) and \( Q_{kk'} = Q \), where \( M_{dk} = \mathbb{E}[s_i^a s_i^b]_{i \notin T k, k' \notin T} \) and \( M_{dk} = \mathbb{E}[s_i^a s_i^b]_{i \notin T k, k' \notin T} \), we obtain the following free energy densities:

\[ f_R^T = \frac{1}{2} \left\{ \frac{q}{N} + \frac{Q}{N - N_t} + \frac{(n - 1)q^2}{2n} + \frac{Q^2}{2} + M^2 \right\} \]

\[ - \frac{1}{\beta_T} \ln \left[ \sum_{z=0}^{N_t} \left( \begin{array}{c} N_t \\ z \end{array} \right) \sum_{k=0}^{N-N_t} \left( \begin{array}{c} N - N_t \\ k \end{array} \right) I_k \right]. \]

\[ f_R^O = \frac{1}{2} \left\{ \frac{q}{N} + \frac{Q}{N_t} + \frac{(n - 1)q^2}{2n} + \frac{Q^2}{2} + M^2 \right\} \]

\[ - \frac{1}{\beta_O} \ln \left[ \sum_{k=0}^{N_t} \left( \begin{array}{c} N_t \\ k \end{array} \right) I_k \right]. \]

From the extremum condition of these free energies we can compute all the model order parameters via a set of self-consistency equations. These equations as well as the functions \( I_z \) and \( \mathcal{I}_k \) are given in Appendix B [32]. The use of the replica symmetry is justified in most of the \( (T_t, T_T) \) parameter space from the stability analysis [33]. At low \( T_t \) and \( T_T \) the replica symmetry is broken, which we will not explore fully. Nevertheless we will discuss later how robustness of phenotypes, postulated for biological systems that reproduce similar offspring, is lost in that scenario. The replica-symmetric free energy densities allow us to derive

\[ \Phi = \frac{1}{N_t} \left[ \psi + m^2 + r^2 \right], \]

\[ \Phi = \frac{m^2 + \tilde{r}^2}{N - N_t}, \]

where \( r \) and \( \tilde{r} \) are defined and computed in Appendix B.
phases that are typical for spin-glass systems, namely, ferro and t-ferro. Such difference arises from the nonzero correlations between a target and a nontarget spin that share a common nontarget spin $q$, which is similar to that of the Sherrington-Kirkpatrick (SK) model, the phenotype-genotype coupling and spin glass, which is in the second spin-glass phase with $m = \tilde{m} = \tilde{q} = 0$ and $q, \tilde{q} > 0$. Here $N_t = 10, N = 100$. Note the $y$ axis is on logarithmic scale.

### III. PHASE DIAGRAM

In Fig. 1 we depict the order parameters as function of the temperature $T_j$ and $T_f$ for a particular choice of $N = 100$ and $N_t = 10$. Here for each point $(T_j, T_f)$ of the phase diagram, we solve numerically the set of mean-field equations for $m, q, Q$, while computing $\Phi$ from the knowledge of these quantities. In terms of only the magnetization $m$ and the overlap between spin-replicas $q$ for target spins, we observe three distinct phases that are typical for spin-glass systems, namely, $m = q = \tilde{q} = 0$ (paramagnet phase), $m = 0, q > 0$ (spin-glass phase), and $m > 0, q > 0$ with $\sqrt{\tilde{q}} > m$ (target-ferromagnet phase, “t-ferro” in short). The transitions between the phases are second order at small $T_j$, a robust fitted phase denoted by $R$ ($m, q > 0$) emerges in an intermediate range of $T_j$ (here $\tilde{m} = \tilde{q} = 0$). Adjacent to this phase on the side of high phenotypic noise is the second paramagnet phase $P2$ where the fitness value is low ($m = q = 0$) but there exists some structure in the genotypes such that $Q > 0$. On the other hand, for lower $T_j$, the system is in the second spin-glass phase $SP2$ with high fitness but nonrobust genotypes ($m \approx q \approx 1, Q = 0$). In particular, the transition from $R$ to $SP2$ is marked by a replica symmetry breaking (RSB) which indicates the loss of stability of the replica symmetric (RS) solutions [34]. The broad distribution of gene-gene correlations in the RSB phase implies that the genotype of offsprings is not preserved, in contrast to the RS phase. In the biological context, this means that replication is no longer stable so that genotypes are not conserved over generations.

Overall, the phase diagram agrees with what was observed numerically in [15,16]. However, thanks to the explicit account of the coupling replicas, so that $Q$ can be treated as an order parameter upon which the free energy density depends, we discover the existence of the second paramagnet phase $P2$ that was not reported before. This phase can be interpreted as a precursor region, in which genotypes are structured in such a way that supports ferromagnetic ordering among target spins, and hence have potentiality to acquire a high fitness, but due to the high fluctuation induced by $T_f$, this fitness cannot be maintained. Furthermore, by considering separately the effective dynamics of the target and nontarget sub-systems, $S_T$ and $S_C$, our approach can differentiate the phase $SP1$ from $SP2$. The previous approach [23] only stressed the distinct arrangement of target spins in the $SP2$ region,
where the subsystem of target spins becomes ferromagnetic whereas that of nontarget ones remains spin glass. Our present approach shows that this is no longer true for a high value of $T_f$. Upon increasing $T_f$, this ferromagnetic ordering is destroyed by genotypic fluctuations. The same structure of the phase diagrams is also observed for $N = 50$, $N_t = 5$ and $N = 200$, $N_t = 20$; see Appendix C for the phase diagram obtained in these cases, where $\beta_f$ is rescaled according to $N$ (and $N_t$). Accordingly, it is shown that the selection pressure needed to achieve robustness increases with the number of spins $N$ at a fixed fraction $N_t/N$. In addition, the present analysis allows one to obtain quantitative dependence of genotypic and phenotypic robustness on the fraction of targets. The phase diagram in Fig. 2 includes global information of the system including weak selection region without achieving nonzero fitness, $m$, of target, whereas there is biological interest if the fitted state is evolved robustly by the selection. To this end we focus on the low-$T_f$ region of the phase diagram to explore the dependence of the system behavior on the fraction $p = N_t/N$ of target spins. While overall the phase structure is similar for different $p$ in Fig. 3, in particular the robust fitted (yellow) region seems to change slightly with increasing $p$; the relative size and exact location of all the other phases vary with $p$. This suggests that a more quantitative analysis is needed to understand the genotype-phenotype relationship as a function of $p$. We carry on this analysis in the next section.

IV. STRUCTURE OF THE ROBUST FITTED PHASE

The most relevant region in the phase diagram is the robust fitted phase $R$, which is characterized by both the high fitness ($m > 0$) and robustness ($Q > 0$). For a sufficiently low given $T_f$ (i.e., high selection pressure), the phase is bounded by $T_s \in [T^{(1)}_c, T^{(2)}_c]$. Below $T^{(1)}_c$, $Q$ goes to zero, and above $T^{(2)}_c$, $m$ goes to zero, whereas these transition points depend on $T_f$. We first investigate the dependence on $p$ of the $R$ region by fixing $T_f$. In Figs. 4(a) and 4(b) we fixed $T_f = 0.005$. First, for a wide range of $p \in [0.04, 0.5]$, the temperature $T^{(1)}_c$ of the latter transition in (b) does not depend on $p$ (see Appendix D for the zoom-in of a small dip of $T_s$ at this point). On the other hand, $T^{(2)}_c$ slightly increases with increasing $p$ in (a), indicating that the fitness of the high $p$ case is relatively more robust to noise than the low $p$ case.

In Fig. 4(c) $1 - Q$ is almost constant against $T_f$ in the $R$ phase. This constant value was found to increase with the number of nontarget spins. Note that $Q \sim 1$ implies that the offspring of genotypes are preserved. The increase in $1 - Q$ thus means the increase in redundancy of genotypes, as is supported by a larger number of non-targets. Such a redundancy has another meaning in the context of spin-glass systems, where it is indeed equal to the local frustration [in the ($t$-$o$-$t$) triads with positive $J^{(t)}$].

In contrast, apart from the two critical points $T^{(1)}_c$ and $T^{(2)}_c$, the fitness $m$ does not depend on $p$. It follows a unique curve, independent of $p$. Even though the increase in genetic
heterogeneity $1 - Q$ for more nontargets may perturb

the target spin configuration, the fitness $m$ remains unchanged

even for smaller $p$.

Then, we estimate the critical value of $T_f$ below which

the $R$ phase can exist. While this critical value denoted by

$T_f^{(0)}$ can depend on $T_s$, as seen in Figs. 2 and 3, it can be

approximately identified with the upper part of the $P_2$ phase

from the phase diagram. In Fig. 4(d) $T_f^{(0)}$ is shown to decrease

with $p$. This result together with that in Fig. 4(a) mean that

the higher $p$ is, the higher the selection pressure that is needed
to achieve robustness, but once it is achieved, a system with

larger $p$ is more robust with respect to phenotypic noise than

one with smaller $p$.

Finally, we examine the fitness as function of $T_f$ at fixed

$T_s = 1.3$ for various $p$ in Fig. 4(e). While fitness decreases

with $T_f$, its behavior with the increase in $p$ is nonmonotonic.

This behavior is further shown in Fig. 4(f) where the critical

genotypic noise $T_f^{(m)}$ at which the fitness becomes nonzero

is plotted versus $p$. Similar behavior is observed for other

$T_s \in [T_s^{(1)}, T_s^{(2)}]$. The result supports $p = 0.5$ as the maximal

value of $T_f^{(m)}$, suggesting the existence of an optimal fraction

of target spins to acquire high fitness in this intermediate range

of $T_f$ [35].

V. MUTATIONAL SUSCEPTIBILITY AND PHENOTYPIC

SUSCEPTIBILITY IN THE ROBUST FITTED PHASE

Correlation between variances of phenotypes due to ge-

netic changes and to noise has been discussed in both

experiments and simulations, and relationships to robustness

have been discussed both theoretically [10,14,36–39] and

experimentally [40–43]. In statistical physics, this issue can

be analyzed in terms of susceptibility, as it is proportional

to environmental perturbations [46], does not exist in the RSB

phase, as the second term in Eq. (13) is no longer proportional
to $\chi_m$.

VI. DISCUSSION

In the paper we propose an approach towards biological
evolution due to the interrelationship between genotype and

phenotype where fitness is determined solely by the latter

but not by the former. Though the emergence of structured

genotypes from initially random couplings under this rela-
tion has been numerically reported, apart from a study which

imposed a specific condition on the couplings [23], this has

not been studied analytically yet. We here are able to tackle

this problem thanks to what we termed double-replica theory.

Within this framework we obtain the phase diagram, that is
classified not only by the fitness but also by the overlap in
dual replicas. The diagram is not only in good agreement with

previous studies (including paramagnet, t-ferro, and robust fit-
ted phases, all existing at sufficiently low $T_f$), but also contains

additional phases. These include the first spin-glass phase $SP_1$

and the second paramagnet phase $P_2$. The former corresponds
to a system with both target and nontarget spins residing in a

spin-glass phase (at low selection pressure), while the latter

corresponds to a paramagnetic phase for all spins but retains

genetic correlations encoding target and nontarget couplings

(at high selection pressure and high $T_s$). Here, even though the

genotypes favor a high value of fitness, due to large fluctua-
tions induced by $T_s$, such a value can not be maintained over
gen erations. The existence of the phase suggests that even

though the average fitness is zero due to large noise, there

exists a genetic precursor to generate individuals with nonzero

fitness. The relevance of this scenario to evolutionary biology

needs to be explored in future, though.

The system can only acquire high fitness at some $T_f \leq T_f^{(2)}$, where the fitness increases discontinuously. If $T_f$ is too low,
then RSB will happen, leading to a phase without genetic overlap, where biologically required robustness of genotypes is lost. Hence a lower bound of $T_s \geq T_{c(1)}$ is necessary to have RS and robustness, accordingly.

From this approach, the target-fraction dependence of genotypic and phenotypic robustness can also be understood quantitatively. Such dependence is quantified via the behavior of the fitness $m$ and genetic reducndancy $1 - Q$ in the robust region bounded by $T_{c(1)}$ and $T_{c(2)}$. Here we find that a genetically homogeneous population can only be robustly reproduced under a sufficiently high selection pressure and under a sufficient level of phenotypic noise (temperature). As the fraction of target spins is increased, the robust fitted phase is slightly expanded to a higher temperature, whereas higher selection pressure is needed to achieve it. The existence of an optimal fraction for attaining high fitness under intermediate phenotypic noise is suggested. This may explain why, in biological systems, such as in proteins, the fraction of units that are responsible for function is generally limited, and a sufficient fraction of nonfunctional units is needed, providing redundancy. While it is hard to obtain an accurate estimation of the functional sites in real proteins, rough estimates suggest they are of the order of 10–20% [47]. It hence will be interesting to discuss this range of functional regions, in relationship with evolvability and robustness as discussed here.

In the present theory, the proportionality between the standard thermodynamic susceptibility and mutational susceptibility is derived in the robust fitted phase. As the susceptibility measures the change of fitness due to varying conditions, a correlation between responses to environmental perturbations and that by genetic changes is suggested. Such correlation, or evolutionary fluctuation-response relationship [10,14,36–39] has been observed in experimental data from the evolution of protein dynamics and bacterial protein expressions, whereas we can derive it here under the replica symmetry assumption. As argued in [14], such correlation can only be achieved in the replica symmetric region where the original high-dimensional dynamics of the phenotypes are reduced to a low-dimensional manifold due to evolution towards robustness. The variations of fitness due to noise and that due to mutation then happen to occur along the same low-dimensional manifold, resulting in a correlation between them. If RSB occurs, such restriction of the phenotypic dynamics no longer exists, because in this case changes of fitness upon varying the environmental conditions will vary arbitrarily from realization to realization of the $J_{ij}$’s dynamics. As a result, the system will have random, uncorrelated responses to noise and to mutations.

In our formulation by assuming that the entire system reaches an equilibrium, we approximate the effect of the slowly evolving $J^{(oo)}$ that couple the subsystem $S_T$ to $S_D$ on these subsystems’ own dynamics by the equilibrium correlations $\langle J^{(oo)} J^{(oo)} \rangle$. Such correlations are then incorporated separately into each of the dynamics of the $J^{(oo)}$ and $J^{(oo)}$ couplings by modifying the effective potentials of these dynamics, thus making the dynamics of these two different sets of coupling independent of each other. In an equilibrium statistical physics formulation, this leads to the necessity of introducing another type of replica, so-called coupling replicas, into the partition functions, besides the first (standard) spin replicas that take care of the effect of the phenotypes on the evolution of genotypes. This scheme hence allows us to treat the model in a standard mean-field manner. On one hand, being of mean-field nature, our approach can not provide a formal argument to support the hypothesis of [14] about the emergent dimensional reduction from phenotype-genotype coevolution. On the other hand, the correlation between the mutational and environmental susceptibilities in the robust fitted phase suggests the existence of a funnel-like landscape [48,49] that reinforces the dynamics to reside in a low-dimensional manifold by a global attraction.

Despite of its abstraction, our model may have some other implications on the proteins that acquire function through evolution. First, the presented correlation between robustness to noise and to mutation has been discussed previously in RNA [9] and in proteins [39]. Further quantitative analysis will be needed to establish the mechanism of such a general phenomenon. Second, the observed consistency between a global attraction to the robust fitted state in the replica symmetric phase and the funnel picture in protein folding dynamics suggests the importance of replica analysis in studying the protein free-energy landscape.

The current choice of fitness for the sake of simplicity, however, limits the possibility of having different global maxima in the fitness landscape. One can enrich the model behavior by determining fitness either by a combination of $N_{\text{lin}}$ different target spin configurations or by a set of gauge-equivalent configurations.

In the present framework, since the couplings are symmetric, we constructed the effective potential of the coupling dynamics based partly on the existence of an energy landscape. For those models in other contexts [50,51] having such a landscape picture, we expect a straightforward application of our approach. Furthermore, the present double-replica theory can be extended to those stochastic dynamical systems that are not governed by Hamiltonian dynamics as well. In this case, instead of the effective potential and its associated partition function, one would need to characterize the ensemble of trajectories in the combined space of phenotypes and genotypes, using the moment generating function [52,53]. While we so far have solely used Hamiltonian dynamics as the main example of our approach, such an extension would allow for the applications to coevolution of gene-expression patterns and the gene-regulatory networks [10], that of species abundances and their ecological networks [54], and that of neuronal activities and network shaped by neural dynamics (learning) [55,56].

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**APPENDIX A: DETAILS OF THE SHK MODEL**

In the following we call the model originally introduced in [15,16] as the SHK model. In this model, phenotypes are spin configurations, and genotypes are the interaction matrix for spins. In a system of $N$ spins, each spin $i$ can take values $s_i \in \{-1, 1\}$ and is linked to exactly $N - 1$ other spins,
thus forming a fully-connected network. Moreover, fitness is determined by a subset of target spins denoted by $T$. Those spins that do not contribute to the fitness are called nontarget. The fitness $\Psi$ at a noise level $T_n$ is determined by the spin configurations at equilibrium as

$$\Psi(s) = \frac{1}{N_f} \left\langle \left| \sum_{i \in T} s_i \right|^2 \right\rangle,$$

(A1)

where $\langle \cdot \rangle_T$ is the thermal average according to an equilibrium distribution over spin configurations only. This distribution is computed from the partition function of a spin-glass Hamiltonian $H_S = -\sum_{i<j} J_{ij} s_i s_j$ in which the couplings $J_{ij}$ are regarded as fixed over the course of the spin dynamics because they are assumed to evolve on much slower timescale than that of the spins. Here the couplings are symmetric, i.e., $J_{ij} = J_{ji}$, and are independently and identically distributed by a Gaussian distribution with zero mean and the variance $J^2 := \text{var}(J_{ij}) = N^{-1}$. The model Hamiltonian of the full system is given by

$$H_S = -\sum_{i<j} J_{ij} s_i s_j.$$  

(A2)

Once the spins have relaxed to an equilibrium at a temperature $T_n$ via a Glauber update specified by $H_S$, the couplings are next updated with probability $\text{Pr}[\delta \rightarrow \delta'] = \min \{1, e^{\Delta \Psi} \}$, where $\Delta \Psi = \Psi(\delta') - \Psi(\delta)$ and $\beta_j = 1/T_j$ is the genotypic selection pressure. These two dynamics are implemented consecutively one after another until the entire system equilibrates. Implementing this way, the model captures the evolution of feedback process between the phenotype and genotype, where the phenotype dynamics are represented by the stochastic dynamics of spins $(s)$ according to the energy landscape $H_S$ for a given genotype $(\delta)$, whereas the evolution of genotype is given by the stochastic change of $(\delta)$ according to the fitness $\Psi(s)$ determined by the phenotype. In contrast to more common theories of evolution, this model hence explicitly considers the co-evolution of these coupled landscapes.

**APPENDIX B: REPLICA SYMMETRIC ANSATZ SOLUTION AND THE EXPRESSION OF $I_k$ AND $I_{k'}$**

The partition functions are given in terms of the target and the nontarget free energies, $f_T(\mathbf{m}; q, r, Q, M)$ and $f_O(\mathbf{m}; q, r, Q, M)$, respectively, by

$$Z_T = \int Dm \, Dq \, Dr \, DQ \, DM \, e^{-\beta T N p f_T(\mathbf{m}; q, r, Q, M)},$$

(B1a)

$$Z_O = \int D\mathbf{m} \, D\mathbf{q} \, D\mathbf{r} \, D\mathbf{Q} \, D\mathbf{M} \, e^{-\beta O N (1-p) f_O(\mathbf{m}; q, r, Q, M)},$$

(B1b)

**FIG. 5.** The phase diagrams obtained by combining the behavior of $m$ as function of $T_s$ and $T_j$ with that of $Q$ at $p = 0.1$ for $N = 50$ (a) and $N = 200$ (b). The yellow region in both (a) and (b) shows the robust fitted phase $(m > 0)$ and $Q \sim 1)$. The red dashed line depicts the critical line $\beta_j^{(0)} = 1/(N - N_t)$ that is obtained from Landau’s order-parameter-theory analysis of the free energy of target spins using the expression in Eq. (B4a).

**FIG. 6.** Magnetization for nontarget spins $\tilde{m}$ (a). Overlap between different replicas for nontarget spins $\tilde{q}$ (b). Averaged correlation of a pair of couplings between a target and a nontarget spin that share a common target spin $\tilde{Q}$ (c). Averaged value of the link $J^{(1)}$ among nontarget spins $\tilde{\Phi}$ (d). Here $N_t = 10$, $N = 100$. Note the $y$ axis is on logarithmic scale.

**FIG. 7.** The third-largest eigenvalue $\Lambda_3$ of the Hessian matrix for the target coupling replicas as function of the model parameter. Here we find the region with broken replica symmetry where $\Lambda_3 > 0$. The change in the sign of $\Lambda_3$ happens to coincide with the transition between $Q = 0$ and $Q > 0$. Here $N_t = 10$ and $N = 100$. Note the $y$ axis is on logarithmic scale.
where

$$f_T = \frac{1}{2} \left\{ \sum_{a,b} \frac{q_{ab}^2}{n^2} + \sum_{k < k'} \frac{Q_{ik,k'}^2}{(N - t)^2} + \frac{1}{n(N - t)} \sum_{a,k} M_{ak}^2 \right\} - \frac{1}{\beta_j} \ln \sum_{\{r,\sigma^k\}_{i \in T}} e^L, \quad \text{(B2a)}$$

$$f_o = \frac{1}{2} \left\{ \tilde{K} \sum_a \frac{\tilde{m}_a^2}{n} + \tilde{K} \sum_{k} \frac{\tilde{r}_k^2}{t^2} + \sum_{a,b} \frac{\tilde{q}_{ab}^2}{n^2} + \sum_{k < k'} \frac{\tilde{Q}_{ik,k'}^2}{t^2} + \frac{1}{n t} \sum_{a,k} M_{ak}^2 \right\} - \frac{1}{\beta_j} \ln \sum_{\{r,\sigma^k\}} e^L, \quad \text{(B2b)}$$

$$L = \frac{\beta_j}{4N_t} \left\{ \sum_{i \in T} s_i \right\}^2 + \frac{\beta_j}{2} \sum_{i \in T} \sum_{j \in T} \left[ \sum_{a = 1}^n \left( \frac{m_a}{n} + \sum_{k = 1}^{N_t - N_t} \tilde{r}_k \sigma^k \right) + \sum_{a,b} \frac{q_{ab} \sigma^a \sigma^b}{n^2} + \sum_{k < k'} \frac{Q_{kk'} \sigma^k \sigma^{k'}}{(N - N_t)^2} \right] + \frac{1}{n N_t \beta_j} \sum_{a,k} M_{ak}^2 \sigma^k \sigma^k \right\} \quad \text{(B3a)}$$

$$\tilde{L} = \beta_j \left( \sum_{a = 1}^n \tilde{m}_a \sigma^a + \frac{\tilde{K}}{N_t} \sum_{k} \tilde{r}_k \sigma^k + \frac{1}{n} \sum_{a,b} \tilde{q}_{ab} \sigma^a \sigma^b + \frac{\tilde{K}}{N_t} \sum_{k < k'} \tilde{Q}_{kk'} \sigma^k \sigma^{k'} + \frac{1}{n N_t} \sum_{a,k} \tilde{M}_{ak} \sigma^k \sigma^k \right) \quad \text{(B3b)}$$

Denoting $Dx \, Dy = \frac{e^{-Q} \beta_j}{2 \pi^2} \, dx \, dy$ and $A_m(r, m \beta) = \beta_j \left( \frac{(N - N_t)^2}{N_t} - \frac{\beta_j}{2} \frac{(N - N_t)^2}{N_t} \right)$, we have

$$I_{kz} = \iint Dx \, Dy \, \exp \left\{ A_z + \frac{N - N_t - 2k}{N - N_t} \left( y \sqrt{\beta_j} Q + \beta_j r \left[ \frac{1}{N_t} \right] \right) \right\} \cosh \left( \beta_j m \frac{|N_t - 2z|}{N_t} + x \sqrt{\beta_j q} \frac{m}{n} + \beta_j M \frac{N - N_t - 2k}{N - N_t} \right), \quad \text{(B4a)}$$

$$\tilde{I}_k = \iint Dx \, Dy \, \exp \left\{ \frac{N_t - 2k}{N_t} \left( y \sqrt{\beta_j} Q + \beta_j \tilde{K} \tilde{r} \right) \right\} \cosh \left( \beta_j \tilde{K} m + x \sqrt{\beta_j q} \frac{m}{n} + \beta_j \tilde{M} \frac{N - N_t - 2k}{N - N_t} \right). \quad \text{(B4b)}$$

The argument of the $\cosh(\cdot)$ function will be denoted by

$$\Omega = \beta_j m \frac{|N_t - 2z|}{N_t} + x \sqrt{\beta_j q} \frac{m}{n} + \beta_j M \frac{N - N_t - 2k}{N - N_t} \quad \tilde{\Omega} = \beta_j \tilde{K} m + x \sqrt{\beta_j q} \frac{m}{n} + \beta_j \tilde{M} \frac{N - N_t - 2k}{N - N_t} \quad \text{(B5)}$$

The replica symmetric free energy densities given in the main text yield the extremum condition after setting $\tilde{K} = 0$:

$$m = \sum_{z = 0}^{N_t} \sum_{k = 0}^{N_t - N_t} \int Dx \, Dy \, \exp \left\{ A_z + \frac{N - N_t - 2k}{N - N_t} \left( y \sqrt{\beta_j} Q + \beta_j r \theta \right) \right\} \cosh(\Omega) \frac{\delta}{\delta \theta} \tanh(\Omega) \right\} d\theta, \quad \text{(B6a)}$$

$$q = \sum_{z = 0}^{N_t} \sum_{k = 0}^{N_t - N_t} \int Dx \, Dy \, \exp \left\{ A_z + \frac{N - N_t - 2k}{N - N_t} \left( y \sqrt{\beta_j} Q + \beta_j r \theta \right) \right\} \cosh(\Omega) \frac{\delta}{\delta \theta} \tanh(\Omega) \right\} d\theta, \quad \text{(B6b)}$$

$$Q = - \frac{1}{N - N_t} + \sum_{z = 0}^{N_t} \sum_{k = 0}^{N_t - N_t} \left( (N - N_t)^2 \frac{N_t - N_t - 2k}{N - N_t} \right)^2 I_{kz}, \quad r = \sum_{z = 0}^{N_t} \sum_{k = 0}^{N_t - N_t} \left( (N - N_t)^2 \frac{N_t - N_t - 2k}{N - N_t} \right)^2 I_{kz}, \quad \text{(B7a)}$$

$$M = \sum_{z = 0}^{N_t} \sum_{k = 0}^{N_t - N_t} \int Dx \, Dy \, \exp \left\{ A_z + \frac{N - N_t - 2k}{N - N_t} \left( y \sqrt{\beta_j} Q + \beta_j r \theta \right) \right\} \cosh(\Omega) \frac{\delta}{\delta \theta} \tanh(\Omega) \right\} d\theta, \quad \text{(B7b)}$$

$$\tilde{m} = \sum_{z = 0}^{N_t} \sum_{k = 0}^{N_t - N_t} \left( (N - N_t)^2 \frac{N_t - N_t - 2k}{N - N_t} \right)^2 I_k, \quad \tilde{q} = \sum_{z = 0}^{N_t} \sum_{k = 0}^{N_t - N_t} \left( (N - N_t)^2 \frac{N_t - N_t - 2k}{N - N_t} \right)^2 I_k, \quad \text{(B8a)}$$

$$\tilde{Q} = - \frac{1}{N_t} + \sum_{z = 0}^{N_t} \sum_{k = 0}^{N_t - N_t} \left( (N - N_t)^2 \frac{N_t - N_t - 2k}{N - N_t} \right)^2 I_k, \quad \tilde{r} = \sum_{z = 0}^{N_t} \sum_{k = 0}^{N_t - N_t} \left( (N - N_t)^2 \frac{N_t - N_t - 2k}{N - N_t} \right)^2 I_k, \quad \text{(B8b)}$$

$$\tilde{M} = \sum_{z = 0}^{N_t} \sum_{k = 0}^{N_t - N_t} \left( (N - N_t)^2 \frac{N_t - N_t - 2k}{N - N_t} \right)^2 I_k, \quad \tilde{Q} = \sum_{z = 0}^{N_t} \sum_{k = 0}^{N_t - N_t} \left( (N - N_t)^2 \frac{N_t - N_t - 2k}{N - N_t} \right)^2 I_k. \quad \text{(B8c)}$$
of the fraction of nontarget spins. Here \( T^0 \) is the temperature above which \( \Delta m = 1 - m(T^0) \) is the drop of fitness at \( T^0 \). (c) Linear relationship between the frustration \( 1 - Q \) and \( \Delta m - \Delta m_{\text{min}} \) at \( T^0 \). (d) The drop \( m^* \) of fitness at \( T^0 \). Here \( N = 100 \).

APPENDIX C: \( N \) DEPENDENCE OF THE PHASE DIAGRAM

Using an expansion of the free energy density of the target spins, based on Eq. (B4a), we can estimate the highest value of \( T^0 \) above which \( Q \) drops from a high value to zero: \( \beta_0^{c(0)} = 1/(N - N_t) \). Therefore, the robust fitted phase necessarily exists for all values of \( N \), though, at a given fraction \( p = N_t/N \), a higher selection pressure, i.e., a lower \( T^0 \) is needed to achieve it for larger \( N \). We show this kind of \( N \) dependence of the phase diagram for \( N = 50 \) and \( N = 200 \) in Fig. 5. Overall, the structure of the phase diagram remains the same as that obtained for \( N = 100 \) in Fig. 3(a) of the main text. The difference in the exact location of the highest value of \( T^0 \) above which \( Q \) drops from a high value to zero is well explained by our estimation shown as a dashed horizontal line.


We present the phase diagram for the order parameters of the non-target spins in Fig. 6 and that for the third-largest eigenvalue of the Hessian \( \Lambda_3 \) in Fig. 7. Without any effect of fitness acting on them, nontarget spins have only zero magnetization [Fig. 6(a)] and the averaged value \( \Phi \) of the coupling among them \( J^{(00)} \) is equal to zero [Fig. 6(d)]. Nevertheless, due to the effect of random couplings, \( J^{(oo)} \), a spin-glass ordering can appear at low \( T^0 \) and \( T^0 \) as seen in Fig. 6(c). As we expect a dependence of the drop in fitness at \( T^0 \), which is denoted by \( \Delta m_{\text{min}} \), on the fraction of target spins, we first show a zoom-in of the behavior of \( m \) at \( T^0 \) close to \( T^0 \) in Fig. 8(a). Then we find that at the critical number of target spins \( N_t^{(c)} \), this change has a minimal value \( \Delta m_{\text{min}} \) so that \( \Delta m - \Delta m_{\text{min}} \) can be depicted as function of \( 1 - p \) in Fig. 8(b). Once subtracted \( \Delta m \) from \( \Delta m_{\text{min}} \), we find a linear relationship exists between \( \Delta m - \Delta m_{\text{min}} \) and \( 1 - Q \). Such relationship is demonstrated Fig. 8(c). We finally measure how much fitness changes under a transition from robust to paramagnet phase at \( T^0 \). We denote this kind of drop by \( m^* \) in Fig. 8(d), where we find a decrease of \( m^* \) with increasing \( p \), implying that fitness is more robust at higher \( p \).


[25] Note the difference from the model implementation of [15] where couplings are updated at discrete time steps.

[26] Technically speaking, the field \( J \) is introduced to break the gauge-symmetry between different local Mattis states that have no frustration among target spins (i.e., triples \( J_{ij}^{(m)} J_{il}^{(n)} J_{lj}^{(0)} > 0 \), \( \forall i < j < k \in T \)). As this symmetry is broken, the ferromagnetic state (with all links between target spins being positive) is distinguished from all other unfrustrated states and, as a consequence, alignment among target spins can be achieved at low \( T_c \). One might want to consider a different form of \( K \) that explicitly takes into account the Boltzmann weights corresponding to the Hamiltonian \( H_k \) [i.e., \( e^{-\beta H_k} \), as defined in Eq. (4)]. Such a term, however, may not guarantee the evolution towards a subgraph of only ferromagnetic interactions among target spins.

[27] Here we used the identities \( \langle s \rangle_{T_c} = \frac{1}{\beta} \frac{\partial^2}{\partial \beta^2} \ln Z_1 \) and \( \langle s \rangle_{T_c} = \frac{1}{\beta} \frac{\partial^2}{\partial \beta^2} \ln Z_1 \), where the partition function of the target spins’ subsystem and that of the non-target spins’ subsystem are \( Z_1 := \sum_{\langle s \rangle_{T_c} = \langle 1 \rangle} e^{-\beta H_T(J^{(0)})} \) and \( Z_1 := \sum_{\langle s \rangle_{T_c} = \langle 0 \rangle} e^{-\beta H_C(J^{(0)})} \), respectively.

[28] Requiring that the couplings should remain bounded as \( T \to \infty \), we need to introduce a decay term \(-\lambda_{ij} J_{ij}\) to the couplings dynamics. In order to keep the genotypic selection pressure the same for all the couplings regardless of their types, we choose \(-\lambda_{ij} J_{ij}^{(0)} = -\sqrt{\beta J_{ij}^{(0)} \lambda_{ij}}\) and \(-\lambda_{ij} J_{ij}^{(0)} = -\sqrt{1 - \beta J_{ij}^{(0)} J_{ij}^{(0)} \lambda_{ij}}\), where \( p = N_t/|T| \) is the fraction of target spins.

[29] Note that \( Z_T \) and \( Z_0 \) are different from the partition functions of the target spins’ subsystem \( Z_1(J^{(0)}) \) and that of the non-target spins’ subsystem \( Z_1(J^{(0)}) \) given in [27].

[30] This can already be seen directly from Eq. (5) as the expression inside the curly braces does not depend on \( J_{ij}^{(0)} \) and \( J_{ij}^{(0)} \).

[31] Though \( n \) appears as an integer number here, we will analytically continue to real positive \( n \) in subsequent steps of calculations.

[32] Here \( I_k = I_k(m, q, Q, r, R) \) and \( I_k = I_k(n, q, Q, r, R) \) with \( r, M, R \) are other variables that the free energy densities depend on. Since these observables for target and non-target spins have their behavior correlated to that of \( (m, q, Q) \) and \( (n, q, Q) \), respectively, they do not provide additional information about the structure of the model phase diagram.


[34] The eigenvalue of the Hessian changes its sign on the border between these phases; see Appendix D. Note that though we do not calculate the full hierarchy of replica symmetry breaking (RSB) à la Parisi, but as long as RSB happens this nonrobustness is true for the full RSB solution.

[35] This optimality, however, does not happen in the spinglass phase SP2 with low temperature \( T_c \), since the selection pressure needed to achieve nonzero fitness crucially depends on \( p \). In fact as \( p \) is increased, higher pressure (i.e., lower \( T_c \)) is needed to achieve nonzero \( m \) of targets, i.e., to transition from SP1 to SP2.


[44] More precisely, in [14] \( \Psi_i = (\text{sign}(m)) s_i/\tau_c \).

[45] From the replica-symmetric free energy density \( f_{RS}^* \) we get \( \chi_{RS}^* = \beta [1 + (n - 1)p] \), while \( M \) can not be obtained directly within this ansatz.


