Quasispecies Theory for Evolution of Modularity

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Abstract

Biological systems are modular, and this modularity evolves over time and in different environments. A number of observations have been made of increased modularity in biological systems under increased environmental pressure. We here develop a quasispecies theory for the dynamics of modularity in these systems. We find a principle of least action for the evolved modularity at steady state and a fluctuation dissipation relation for the rate of change of modularity. We also derive a relationship between rate of environmental changes and rate of growth of modularity, and show how the steady-state fitness in a randomly changing environment can be computed. Finally, we compare our predictions to simulations of protein evolution and find them to be consistent.

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I. INTRODUCTION

Biological systems have long been recognized to be modular. In 1942 Waddington presented his now classic description of a canalized landscape for development, in which minor perturbations do not disrupt the function of developmental modules [1]. In 1961 H. A. Simon described how biological systems are more efficiently evolved and are more stable if they are modular [2]. A seminal paper by Hartwell et al. firmly established the concept of modularity in cell biology [3]. Systems biology has since provided a wealth of examples of modular cellular circuits, including metabolic circuits [4, 5] and modules on different scales, i.e. modules of modules [6]. Protein-Protein interaction networks have been observed to be modular [7–9]. Ecological food webs have been found to be modular [10]. The gene regulatory network of the developmental pathway exhibits modules [11, 12], and the developmental pathway is modular [13]. Modules have even been found in physiology, specifically in spatial correlations of brain activity [14, 15].

The modularity of biological system changes over time. There are a number of demonstrations of the evolution of modularity in biological systems. For example, the modularity of the protein-protein interaction network significantly increases when yeast is exposed to heat shock [16], and the modularity of the protein-protein networks in both yeast and E. coli appears to have increased over evolutionary time [17]. Additionally, food webs in low-energy, stressful environments are more modular than those in plentiful environments [18], arid ecologies are more modular during droughts [19], and foraging of sea otters is more modular when food is limiting [20]. Other complex dynamical systems exhibit time-dependent modularity as well. The modularity of social networks changes over time: stock brokers instant messaging networks are more modular under stressful market conditions [21], and socio-economic community overlap decreases with increasing stress [22]. Modularity of financial networks changes over time: the modularity of the world trade network has decreased over the last 40 years, leading to increased susceptibility to recessionary shocks [23], and increased modularity has been suggested as a way to increase the robustness and adaptability of the banking system [24]. Much of the research on modularity has suggested that gene duplication, horizontal gene transfer, and changes in the total number of connections may all play a role in the evolution of modularity [25–27].

In an effort to proceed further with these observations, we here present a quasispecies
theory for the evolutionary dynamics of modularity. This analytical theory complements numerical models that have investigated the dynamics of modularity [27–30]. We assume that modularity can be quantified in the system under study. We further consider that modularity is a good order parameter to describe the state of the system. That is, we project the dynamics onto the slow mode of modularity, $M$. In section II we introduce the quasispecies description for the dynamics of modularity. The details of the sequence level evolutionary dynamics are what, when projected out, define the fitness function $f(m)$ introduced in this section. In the limit of long time, we find the evolved, steady-state value of modularity by a principle of least action. In section III we derive a fluctuation dissipation theory for the dynamics of modularity. In section IV we derive a relationship between rate of environmental change and rate of growth of modularity. In section V we show how the steady-state fitness in a randomly changing environment can be computed from the time-dependent average fitness starting from random initial conditions. In section VI we compare some of the predictions to simulations of protein evolution. We conclude in section VII.

II. THE QUASISPECIES THEORY FOR DYNAMICS OF MODULARITY

Quasispecies theory captures the basic aspects of mutation and evolutionary selection in large, evolving populations [31, 32]. These models have been widely used in the physics literature to describe evolutionary biology [33]. A series of papers showed how these models could be solved in the steady-state limit, first by a mapping to an inhomogeneous Ising model [34–38] and later by solution with functional integral techniques [39–41]. A Hamilton-Jacobi approach has been used to derive dynamical predictions in these models [42]. Quasispecies theory has been extended to larger alphabets [43] and to describe the effects of horizontal gene transfer [44–46] and finite populations [47, 48].

We here develop quasispecies theory for the dynamics of modularity. In this section we write the master equation that describes the dynamics of modularity in the quasispecies limit. We rewrite the dynamical equations in the language of field theory. We solve the field theory in the limit of large system sizes to determine the steady-state modularity that emerges at long time. The theory is distinct from traditional quasispecies theory because the replication rate depends on the modularity rather than the Hamming distance from a wild-type strain. Nonetheless, we will show that the theory can still be solved exactly in the
limit of a large system size.

A. The dynamical equations of modularity

We consider the equations of motion for the modularity of the system. In particular, we consider an ensemble of systems, each with different values of the modularity, and each evolving. The evolutionary dynamics of this system is fully specified by the rate at which systems reproduce, $f$, termed “fitness,” and the rate at which changes of modularity arise, $\mu$. Since the state of the system is specified by the slow variable $M$, the fitness is a function of the modularity, $f = f(M)$. The $f(M)$ function is from a detailed calculation, numerical simulation, or experimental observation. Thus, the rate at which systems with modularity $M$ replicate, $f(M)$, is an input to the theory. The theory predicts how modularity in an ensemble of systems will evolve, given the replication rates and mutation rates.

The fitness function $f(M)$ fundamentally characterizes an evolving network. With this $f(M)$, the dynamics of modularity can be calculated. For example, the $f(M)$ could be deduced for the evolution of the protein-protein interaction network in *E. coli*, showing the evolutionary advantage of modularity for this system [17]. One result will be that the $f(M)$ is the driving force for spontaneous emergence of modularity in a protein network [27]. The $f(M)$ will be used to show the benefit of modularity to the system and that this system evolves to a finite modularity at steady state.

Modularity is defined on a network of nodes and edges. Equivalently, we can consider a matrix, with the $ij$ element representing the value of edge $ij$. Thus, we define the “connection matrix” of the network. The connection matrix gives the links between the nodes of the network. For example, in the protein-protein interaction network, the nodes are the proteins and the links tell one whether protein $i$ interacts with protein $j$. The connection matrix $\Delta_{ij}$ is a binary matrix which denotes whether nodes $i$ and $j$ interact ($\Delta_{ij} = 1$) or not ($\Delta_{ij} = 0$). The detailed dynamics of the system may well have non-trivial couplings between nodes [27], and the connection matrix is the projection of the non-zero couplings. We allow each node to be connected to $C$ other nodes on average. The number of nodes is denoted by $L$. Rearrangement of the entries within this matrix changes the modularity of the matrix. For simplicity, we assume that the modules which form are of size $l$. There are two ways to view the fixed partitioning that we consider. First, this partitioning results
from modularity that is induced by horizontal gene transfer of segments with fixed length \( l \), as was previously shown \[17, 27\]. Second, biological modules are often of roughly fixed size, so it is not too much of a simplification to say the module size is constant for all modules. A fixed partitioning is a subset of all possibilities; in this work, we consider only this fixed partitioning. Thus a modular system will have excess of connections along the \( l \times l \) block diagonals of the connection matrix. In other words, the probability of a connection is \( C_0/L \) outside the block diagonals when \( \lfloor i/l \rfloor \neq \lfloor j/l \rfloor \) and \( C_1/L \) inside the block diagonals when \( \lfloor i/l \rfloor = \lfloor j/l \rfloor \), with \( C = C_0 + (C_1 - C_0)l/L \). Modularity is defined by the excess of connections in the block diagonals, over that observed outside the block diagonals: \( M = (C_1 - C_0)l/(LC) \).

We define \( \mu \) to be the rate at which any given 1 in the \( \Delta \) matrix hops to another random location. Modularity changes because the entries in the connection matrix change. There are several possible models for how the connection matrix may reorganize. We here consider the model in which connections may independently reorganize. This model is biologically appropriate when connections between nodes are governed by independent pieces of structure in each node. We are not specifically considering “hub” nodes that connect to a very large number of other nodes. A model of this effect would be hierarchical. We are here considering one level of this hierarchy in the present model. Thus, we here consider a simple model in which each of these connections has a rate \( \mu \) to rewire. In a typical biological system there are a finite number of connections per site, even for a large matrix, and so we consider the limit of \( C \) finite and \( L \) large, i.e. a dilute matrix of connections. Thus, the entries in the connection matrix each have rate \( \mu \) to independently move to a new position in the connection matrix, and collisions between connections do not significantly affect the dynamics in the dilute limit.

When the population of systems is large, the probability distribution to have a matrix with modularity \( m \) obeys (see Appendix A)

\[
\frac{dP_m(t')}{dt'} = L[f(m) - \langle f \rangle]P_m(t') + \mu Cl \left[(1 - m) \left(1 - \frac{l}{L}\right) + \frac{1}{LC}\right] P_{m-1/([L-l]C)}(t')
+ \mu C (L - l) \left[m + (1 - m) \frac{l}{L} + \frac{1}{LC}\right] P_{m+1/([L-l]C)}(t')
- \mu C (L - l) \left[m + 2(1 - m) \frac{l}{L}\right] P_m(t')
\]

(1)

where \( m \) takes values \(-l/(L-l), (-l+1/C)/(L-l), (-l+2/C)/(L-l), \ldots, 1\). The average
fitness is given by \( \langle f(t') \rangle = \sum_m f(m) P_m(t') \). The average modularity as a function of time is given by \( M(t') = \sum_m m P_m(t') \).

**B. Field Theory for the Dynamics of Modularity**

For large values of \( L \), for which the changes in \( M \) are nearly continuous, we here determine the average fitness implied by Eq. (1) at long time by techniques borrowed from quantum field theory \([39, 40]\). We write the dynamical equations in Eq. (1) in terms of raising and lowering operators. We then use coherent states to write this second quantization in terms of a Bosonic field theory, with fields \( z^*_{ij}(t), z_{ij}(t) \) representing density at \( \Delta_{ij}(t) \) at time \( t \).

The action of this field theory is

\[
S = \int_0^{t_f} \sum_{ij} z^*_{ij}(t) \partial_t z_{ij}(t) dt + \sum_{ij} \left[ z^*_{ij}(0) z_{ij}(0) - z_{ij}(t_f) \right] + LC 
- \frac{C_1}{L} \sum_{ij} z^*_{ij}(0) - \frac{C_0}{L} \sum_{ij} z^*_{ij}(0) 
- L \int_0^{t_f} f \left[ \frac{1}{LC} \left( \sum_{ij} z^*_{ij}(t) z_{ij}(t) - \frac{1}{L/l-1} \sum_{ij} z^*_{ij}(t) z_{ij}(t) \right) \right] dt 
- \frac{\mu}{L^2} \int_0^{t_f} \sum_{ij} \sum_{mn} \left[ z^*_{mn}(t) - z^*_{ij}(t) \right] z_{ij}(t) dt
\]  

(2)

Note that the fitness depends on the modularity of population of connection matrices at each point in time in Eq. (2), just as it did in Eq. (1). Also note that Eqs. (1) and (2) are exact for arbitrary, non-linear fitness functions \( f(m) \). Here “\( \text{in} \)” means in the \( l \times l \) block diagonals and “\( \text{out} \)” means outside these block diagonals. The quadratic terms can be integrated out (see Appendix B) \([40]\), and we are left with an action expressed in terms of a modularity field, \( \xi \), and its conjugate, \( \bar{\xi} \):

\[
S = L \int_0^{t_f} [C \bar{\xi}(t) \xi(t) - f(\xi(t))] dt - LC \ln Q 
\]  

(3)

where the determinant is \( Q = |lC_1(t_f) + (L-l)C_0(t_f)|/LC) \), where the vector \( C(t) = (C_1(t), C_0(t)) \) satisfies

\[
dC/dt = A(t)C(t) 
\]  

(4)

where

\[
A(t) = \begin{pmatrix}
-\mu(L-l)/L + \bar{\xi}(t) & \mu(L-l)/L \\
\mu l/L & -\mu l/L - \bar{\xi}(t) l/(L-l)
\end{pmatrix}
\]  

(5)
and \( C(0) = (C_1, C_0) \).

**C. The Steady-State, Average Value of Modularity**

The average modularity follows a dynamical trajectory away from an initial state to a final steady state value. For large \( L \), this action becomes large, and a saddle point calculation can be used (see Appendix C). The remarkable result from this derivation is that the modularity which emerges at long time obeys a principle of least action:

\[
 f_{\text{pop}} = \max_\xi \left\{ f(\xi) - \mu C[(L - l)l/L^2][2 + (L/l - 2)\xi - 2\sqrt{(1 - \xi)(1 + (L/l - 1)\xi)}] \right\}
\]

with modularity determined by the solution of the implicit equation

\[
 f(M) = f_{\text{pop}}
\]

Here \( f_{\text{pop}} \) is the mean population fitness divided by \( L \). Thus, a principle of least action gives the evolved modularity at steady state.

**D. Phase Diagrams for The Emergence of Modularity**

While Eq. (6) is a general result, we can proceed further in the limit that evolved modularities are small. Expanding for small \( M \), we find

\[
 \xi_{\text{max}} \sim \frac{2l [df/dM]|_{M=0}}{\mu C(L - l) - 2l [d^2f/dM^2]|_{M=0}}
\]

\[
 f_{\text{pop}} \sim \frac{l [df/dM]|_{M=0}}{\mu C(L - l) - 2l [d^2f/dM^2]|_{M=0}} + f(0)
\]

\[
 M \sim \frac{l [df/dM]|_{M=0}}{\mu C(L - l) - 2l [d^2f/dM^2]|_{M=0}}
\]

Thus, as long as a modular system has a higher fitness, \( df/dM > 0 \), modularity will spontaneously emerge, \( M > 0 \), for large enough system sizes, \( L \). For fitness functions for which \( df/dM|_{M=0} = 0 \), more analysis is required. For example, if \( f(M) = kM^2/2 \), there is a phase transition at \( \mu^* \): For \( \mu < \mu^* \) modularity emerges, whereas for \( \mu > \mu^* \) the system remains in the non-modular phase. This phase transition is analogous to the error catastrophe found in traditional quasispecies theory. Phase diagrams for a number of fitness functions are shown in Fig. [1].
FIG. 1: The phase diagram for emergence of modularity. Below a critical mutation rate, modularity spontaneously emerges. Results are shown for $f(M) = kM^2/2$ (solid), $f(M) = kM^3/2$ (long-dashed), $f(M) = kM^4/2$ (short-dashed), $f(M) = kM^{10}/2$ (dotted), and $f(M) = e^{kM} - kM - 1$ (dot-dashed). Results here are shown for $l = 10, L = 120$.

III. A FLUCTUATION DISSIPATION THEOREM

There is a fluctuation dissipation relation for the rate of change of modularity. Multiplying Eq. (1) by $m$ and summing, we find that the rate of change of modularity satisfies

$$\frac{dM}{dt} = L \langle mf(m) \rangle - LM \langle f \rangle - \mu M$$

This equation is a type of continuous-time Price equation [49]. This equation implies a type of useful fluctuation-dissipation theorem. Expanding $f(m)$, we can alternatively write this fluctuation dissipation relation describing the evolution of modularity as

$$\frac{dM}{dt} \approx L \left. \frac{df}{dm} \right|_{M} \langle (\delta m)^2 \rangle - \mu M$$

Here $M$ is the average modularity of the population, and $m$ is the modularity for any particular member in the population, i.e. $M = \langle m \rangle$.

IV. ENVIRONMENTAL CHANGE SELCTS FOR MODULARITY

We here consider how to describe the effect of environmental change on the evolution of modularity. We characterize the environmental changes by their magnitude and frequency. We denote the magnitude of environmental change by $p$. If $p = 0$, the environment does
not change at all, and if $p = 1$, the environment is completely different before and after the change. Although the environmental change is random, on average a fraction $p$ of the environment’s effect on the fitness of the system is modified by the change. This model is used to describe evolution of influenza viruses, where $p$ is defined as above \[50, 51\]. In application to data on influenza vaccines, $p$ is termed $p_{\text{epitope}}$ and serves as an accurate order parameter to characterize how effective a vaccine against one strain will be in protecting against another strain that is distance $p_{\text{epitope}}$ away \[52–54\]. Here we consider these environmental changes to occur with a frequency, which we denote by $1/T$. In particular, we consider that the environmental changes occur every $T$ timesteps. This characterization of environmental change by magnitude and frequency, $p$ and $1/T$, has been used extensively in the past \[17, 18, 23, 27, 55\].

We now derive an approximate relationship between the rate of growth of modularity and the environmental pressure. Immediately after a complete environmental change ($p = 1$), let us say that the average fitness of the system as a function of time for small values of modularity can be expressed as $\langle f(m) \rangle(t) = f_0(t) + m\Delta f(t)$. Equation (9) becomes $M' = L\sigma^2_M \Delta f - \mu M$, where $\sigma^2_M = \langle m^2 \rangle - M^2$. For small $L/l$, this equation combined with Eq. (8) implies that at steady state $\sigma^2_{M_\infty} = l/[L(L - l)C]$. The $\langle f(m) \rangle(t)$ function is the response function of the system to a $p = 1$ environmental change at time $t = 0$. As noted previously, details of the evolutionary dynamics at the sequence level such as gene duplication, horizontal gene transfer, and changes in the total number of connections all affect this function $\langle f(m) \rangle(t)$ \[25–27\]. Here, we investigate the dynamics for small modularity, and we consider a Taylor series expansion of this function for small $m$. We investigate the growth of modularity from an initially non-modular state. Now we consider how the response function depends on $p$, i.e. how the value of $\Delta f$ depends on $p$. If $p = 0$, the environment is not changing, and the system will stay in the $M = 0$ state with $\Delta f = 0$. If $p = 1$ then $\Delta f = f_1 - f_0 \approx f_1(\infty)$ because only the modular system can evolve significantly during the time $T$ on the completely randomized, new landscape. Making a linear interpolation on $f$, we find $\Delta f \approx pf_1(\infty)$. We thus find $M' \approx L\sigma^2_M pf_1(\infty)$, leaving out the small term proportional to $M$ in Eq. (9). This expression for $M'$ is measuring rate of change on the timescale of each environmental change. Considering, instead, the rate of change on a unit
timescale, i.e. \( dM/dt = M'/T \), we find

\[
p_E \approx \frac{1}{R} \frac{dM}{dt}
\]

where \( p_E = p/T \) is the environmental pressure, and \( R = L \sigma^2 \langle \delta m \rangle \). In this equation, \( R \propto \langle (\delta m)^2 \rangle \), which as experimentalists have anticipated is related to replicate variability in experiments \[56\].

This Eq. (11) follows from the principle of least action \[6\], the fluctuation dissipation relation in Eq. (9), and the response function of the modular system being greater than that of the non-modular system at short time. Equation (11) may be interpreted as a Taylor series expansion of \( dM/dt \) in allowed combinations of \( p \) and \( 1/T \). Alternatively, Eq. (11) may be interpreted as the linear response of the modularity to the environmental pressure. The coefficient \( R \) is a measure of ruggedness, since \( R \) is proportional to the variance of the modularity, which is expected to be related to the ruggedness of the landscape.

Equation (11) is a description of how the evolvability of the system depends on the environmental change. That is, \( dM/dt \) is a measure of the evolvability of the system, with larger values indicating a greater rate of change of the measurable order parameter \( M \). This measure of evolvability is greater for greater environmental pressures, \( p_E \). The drive for spontaneous emergence of modularity, large \( dM/dt \), is also greater for landscapes that are more rugged, i.e. larger \( R \), which can be estimated from variability of replicate experiments.

Equation (11) says that an increase of environmental pressure should lead to the evolution of systems with increased modularity. A study of 117 species of bacteria showed that the modularity of the bacteria’s metabolic networks increased monotonically with variability of the environment in which the bacteria lived \[57\]. Metabolic networks of pathogens alternating between hosts were found to be more modular than those of single-host pathogens \[58\].

V. THE STEADY-STATE FITNESS IN A RANDOMLY FLUCTUATING ENVIRONMENT

A changing environment will put pressure on the population to have an efficient response function. As the environment changes, the favorable niches for the system change, and the system must adapt to the changing landscape. The more rapidly the environment changes
or the more dramatically the environment changes, the more pressure there is on the system to be adaptable. As noted above, it has been widely observed that systems under pressure tend to become more modular. If we denote the rate of change of environment as $1/T$ and the magnitude of the change as $p$, the mean fitness of the population of systems at time $t = T$ after an environmental change will depend on these parameters, as well as the modularity: $\langle f \rangle (T) = f_{p,T}(M)$. We can derive this function $f_{p,T}(M)$ from the $p = 1$ response function considered in the previous section, $\langle f(M) \rangle (t)$. The change of environment decreases the fitness by $1 - p$ on average [55], and the time of evolution in each environment is $T$. These two conditions imply $f_{p,T}(M) = \langle f(M) \rangle (t^*)$ where $t^*$ is defined by $\langle f(M) \rangle (t^* - T) = (1 - p) \langle f(M) \rangle (t^*)$. The function $f_{p,T}(M)$ tells us the average, evolved fitness of the system at the end of each environmental change. This function can be considered to be the fitness when the environmental change is integrated out. This is the fitness function that goes into Eq. (1).

Evolution of modularity depends on how the response function $f_{p,T}(M)$ of the system varies with the parameters of environmental change, $p$ and $T$. Since systems under stress tend to become more modular, an interpretation is that the population average fitness for a modular system is greater than that for a non-modular system, at least for small $T$ or large $p$ where stress is large. This behavior has been observed in a model system evolving in a changing environment, when horizontal gene transfer is included [27]. We have recently proven this canonical behavior for a Moran model of population evolution in a glassy, modular fitness landscape [59]. Glassy evolutionary dynamics has been noted a number of times [60, 61]. Conversely, at long time, the non-modular system should have a higher fitness, because modularity is a constraint on the optima that can be achieved.

In Eq. (1), we here take this function $f(M) = f_{p,T}(M)$ as input. We assume only that this function for large $M$ and small $M$ looks like the dashed and solid curves in Fig. 2a. Putting these points together, the quasispecies theory presented here quantitatively describes the emergence of modularity at small $p$ or large $T$, as shown in Figs. 1 and 2b. Note also when $M$ is small, that the steady state modularity calculated exactly from Eq. 8 in agreement with the small $M$ result in Eq. 8 as shown in Fig. 2b.
FIG. 2: Shown is the fitness of an evolving system. a) The fitness of the non-modular ($f_0$, solid) and block-diagonal ($f_1$, dashed) systems are shown, starting from a random initial configuration. These $f_0$ and $f_1$ are inputs to the theory. The modular system is taken to be more fit at short time and less fit at long time. b) The evolved, steady-state fitness of a system predicted by the theory in a changing environment (dot dashed), shown for varying $T$ and $p = 1$. The fitness follows the high-modularity curve at rapid environmental changes, small $T$, and the low-modularity curve at slow environmental changes, large $T$. Since $p = 1$, the function $f_{p, T}(M) = \langle f(M) \rangle(t = T)$. The function $f(t, M)$ is here taken for simplicity to be $(1 - M)f_0(t) + Mf_1(t)$. Note the modularity tends to 1 and the fitness to $f_1$ for rapid environmental change (small $T$), and the modularity tends to 0 and the fitness to $f_0$ for slow environmental change (large $T$). The modularity calculated from theory, Eq. 6 is shown (dotted). Also shown is the theoretical result for small $M$, Eq. 8 to first order in $l/L$ (short dashed). In this example $L = 120$, $l = 10$, $\mu = 0.01$, and $C = 12$. For more than two particular $f_0$ and $f_1$, the modularity emerges only for environmental changes that occur on a timescale $T < t_c \approx 285$.

VI. USING QUASISPECIES THEORY TO EXTRAPOLATE SIMULATION DATA ON SPONTANEOUS EMERGENCE OF MODULARITY

We use Eq. 1 to analyze $M(t)$ data on spontaneous emergence of modularity in a simulation of an evolving protein network [27] to deduce $df/dm$ and to derive $f(M)$ by integration. For this system, we know the mutation rate, as two of the connections change per time step in the upper half of the connection matrix, and so we can use Eq. 1 at short
FIG. 3: Shown is modularity versus time for a system that exhibits spontaneous emergence of modularity. The curves are from theory, Eq. (1), and the data (circles) are from [27]. Two different initial conditions are shown, \( M(0) = 0 \) and \( M(0) = 0.38 \). In this example the derived underlying fitness function is \( f(M) = 1.4M - 1.31M^2 \) and the mutation rate is \( \mu = 2/(346) \).

time to determine \( df/dm \). Alternatively we can determine \( df/dm \) if we know the variance of the modularity and \( M(t) \), c.f. Eq. (10). We assume \( f(M) \) is quadratic, and integrate the \( df/dm \) to determine the \( f(M) \). There are \( N_D = 346 \) total connections in the upper half of the connection matrix and \( N_0 = 22 \) connections in the upper half of the connection matrix when \( M = 0 \) for the parameters of [27]. When \( M = 0 \), the system was prepared by four discrete time iterations of the mutation step, from a single initial configuration [27]. We find \( f(M) \sim 1.4M \) reproduces the data at small \( M \). For the initial condition of \( M = 0.38 \), the configurations were taken from an ensemble [27], which we take to satisfy Eq. (1). We find \( f(M) = 1.4M - 1.31M^2 \) approximately reproduces the data, as shown in Fig. 3. Equation (6) predicts a steady-state value of \( M = 0.45 \), toward which the computationally costly simulations appear to be heading.

VII. CONCLUSION

The examples of environmental stress leading to modularity, ranging from metabolic networks of bacteria in different physical environment to simulations of emergence of protein secondary structure, can be quantified by quasispecies theory. The approximate relation \( R_{PE} = dM/dt \) relates rate of growth of modularity to the ruggedness of the fitness landscape,
R, and environmental pressure, \( p_E \), for small values of modularity. The present theory should allow the analysis of complex, evolving systems to go beyond a demonstration of the existence of modularity to a quantitative analysis of the dynamics of modularity. That is, the theory presented here should allow the determination of the \( f(M) \) function for these evolving systems, by using the predictions to determine the \( f(M) \) that best matches observation. Knowing the \( f(M) \) and \( \mu \) that fundamentally characterize a system would then allow for out-of-sample predictions of dynamical modularity.

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VIII. APPENDIX A

We here derive Eq. (1). The rate to increase modularity for a matrix with modularity \( m \) is \( r_{\text{up}} = \mu n_{\text{out}}(L/l)^2/L^2 \). Recall we are in the dilute limit: \( C \) is finite, and \( L \) is large. Thus, collisions between entries in the connection matrix can be ignored. The rate to decrease modularity for a matrix with modularity \( m \) is \( r_{\text{down}} = \mu n_{\text{in}}L(L-l)/L^2 \). Here the number of connections inside the \( l \times l \) blocks is given by \( n_{\text{in}} \) and the number of connections outside the \( l \times l \) blocks is given by \( n_{\text{out}} \). We have the constraint \( n_{\text{in}} + n_{\text{out}} = CL \). We also have by the definition of modularity \( m = [n_{\text{in}}/l - n_{\text{out}}/(L-l)]l/(CL) \), which shows modularity changes by discrete increments of \( \pm 1/[C(L-l)] \). Thus, we find \( r_{\text{up}}(m) = \mu Cl(L-l)(1-m)/L \) and \( r_{\text{down}}(m) = \mu C(L-l)(Lm-lm+l)/L \). The rate of change of \( P_m(t) \) due to replication is \( L[f(m) - \langle f \rangle]P_m(t) \), where the second term ensures conservation of probability, \( \sum_m P_m(t) = 1 \ \forall \ t \). This is the first term on the right hand side in Eq. (1). The rate of increasing \( P_m(t) \) due to an increase of modularity from \( m-1/[C(L-l)] \) to \( m \) is \( r_{\text{up}}[m-1/(C(L-l))]P_{m-1/[C(L-l)]}(t) \), which is the first \( \mu \)-dependent term in Eq. (1). The rate of increasing \( P_m(t) \) due to a decrease of modularity from \( m + 1/[C(L-l)] \) to \( m \) is \( r_{\text{down}}[m + 1/(C(L-l))]P_{m+1/[C(L-l)]}(t) \), which is the second \( \mu \)-dependent term in Eq. (1). The rate of decreasing \( P_m(t) \) due to modularity changing from \( m \) to \( m \pm 1/[C(L-l)] \) is \( [r_{\text{up}}(m) + r_{\text{down}}(m)]P_m(t) \), which is the third \( \mu \)-
We use a trotter factorization and define $\epsilon$ as a constraint that there are LC per row is $C$. We define conjugate field $\bar{\xi}$ as a projection operator that leads to twisted boundary conditions. A modularity field is defined, with $\xi$ inside the blocks and $C$ outside the blocks. The overall average number of connections per row is $C = C_0 + (C_1 - C_0)L$. We here project the number of connections onto the constraint that there are LC total connections. As in [40], this constraint is enforced with a projection operator that leads to twisted boundary conditions. A modularity field $\xi$ and conjugate field $\bar{\xi}$ are defined, with $\xi(t)$ as the argument of the fitness function in Eq. (2). We use a trotter factorization and define $\epsilon = t_f/M$ and will take the limit $M \to \infty$. We define $\delta = 1$ if $[i/l] = [j/l]$ and zero otherwise. The partition function becomes

$$Z = \int [D\bar{\xi}D\xi] e^{-\epsilon L C \sum_{k=1}^{M} \bar{\xi}(k) \xi(k) + \epsilon L \sum_{k=1}^{M} f[\xi(k)]}$$

$$\times \int_{0}^{2\pi} \frac{d\eta}{2\pi} e^{-i\eta - L C [Dz^{\ast}Dz]} e^{-\sum_{k=1}^{M} \sum_{ij} z_{ij}^{\ast}(k)z_{ij}(k) + \sum_{ij} z_{ij}(M)$$

$$\times e^{\sum_{k=1}^{M} \sum_{ij} \left[ z_{ij}^{\ast}(k) + \epsilon(\mu/L^2) \sum_{mn}(z_{mn}^{\ast}(k)-z_{ij}^{\ast}(k)) + \epsilon\bar{\xi}(k)(L\delta - l)/(L-l)z_{ij}(k) \right] z_{ij}(k-1)$$

$$\times e^{(C_1(0)/L)e^{i\eta/(LC)} \sum_{ij} z_{ij}^{\ast}(0) + (C_0(0)/L)e^{i\eta/(LC)} \sum_{ij} z_{ij}(0)}$$

(12)

Integrating out $z_{ij}^{\ast}(0)$ and $z_{ij}(0)$, the action remains the same except the start on sums over $k$ are incremented by one, and the terms $C_1(0)z^{\ast}(0)$ and $C_0(0)z^{\ast}(0)$ become $C_1(1)z^{\ast}(1)$ and $C_0(1)z^{\ast}(1)$ with

$$C_1(1) = C_1(0) \left[ 1 - \epsilon(1) \left( 1 - \frac{l}{L} \right) + \epsilon\bar{\xi}(1) \right] + C_0(0)\epsilon(1) \left( 1 - \frac{l}{L} \right)$$

$$C_0(1) = C_0(0) \left[ 1 - \epsilon(1) \left( 1 - \frac{l}{L} \right) + \epsilon\bar{\xi}(1) \right] + C_1(0)\epsilon(1) \frac{l}{L}$$

(13)

Iterating the process of integrating out the $z^{\ast}(k)$ and $z(k)$, we find that the vector $C(t) = (C_1(t), C_0(t))$ renormalizes according to Eq. (4). Finally, integrating out $z^{\ast}(M)$ and $z(M)$, we find the final contribution to the partition function is

$$Z = \int [D\bar{\xi}D\xi] e^{-\epsilon L C \sum_{k=1}^{M} \bar{\xi}(k) \xi(k) + \epsilon L \sum_{k=1}^{M} f[\xi(k)]}$$

$$\times \int_{0}^{2\pi} \frac{d\eta}{2\pi} e^{-i\eta - L C e^{\left[ (C_1(M)/(L-1)C_0(M))e^{i\eta/(LC)} \right]}}$$

(14)
Performing the final integration over $\eta$, we find the final expression for the partition function to be

$$Z = \int [D\bar{\xi}D\xi]e^{-\epsilon LC\sum_{k=1}^{M} \bar{\xi}(k)\xi(k) + \epsilon L\sum_{k=1}^{M} f[\xi(k)\xi(k)]} \left[\frac{IC_1(M) + (L - l)C_0(M)}{LC}\right]^{LC}$$

(15)

Thus, the action in Eq. (3) is derived.

X. APPENDIX C

Here we calculate the saddle-point solution to the action (3) at large time. For large $L$, this saddle point solution is exact. For large $t_f$, Eq. (3) becomes

$$S = Lt_f[C\bar{\xi}\xi - f(\xi)] - LC\ln Q$$

(16)

where

$$Q = Tr \left[ e^{t_fA} \left( \begin{array}{c} C_1(0)/C \\ C_0(0)/C \end{array} \right) \left( \frac{l}{L}, \frac{L - l}{L} \right) \right]$$

(17)

The larger eigenvalue of $A$ is given by

$$\lambda_+ = -\frac{1}{2} \left( \mu - \frac{L - 2l}{L - l}\bar{\xi} \right) + \frac{1}{2} \left( \mu - \frac{L - 2l}{L - l}\bar{\xi} \right)^2 + \frac{4l\bar{\xi}^2}{L - l} \right]^{1/2}$$

(18)

Thus, the action tends to

$$- S \sim Lt_f[-\bar{C}\bar{\xi}\xi + f(\xi)] + LCt_f\lambda_+$$

(19)

Maximizing this over $\bar{\xi}$, we find

$$- S/(Lt_f) \sim f(\xi) - \mu C[(L - l)/L^2][2 + (L/l - 2)\xi - 2\sqrt{(1 - \xi)(1 + (L/l - 1)\xi)}]$$

(20)

Maximizing over $\xi$ gives Eq. (6). Using that the partition function $Z$ grows at long time as $\exp(Lf_{\text{pop}}t_f)$ [40], we find Eq. (7).

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