Hierarchical Network Structure Promotes Dynamical Robustness

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The analysis of dynamical systems that attempts to model chemical reaction, gene-regulatory, population, and ecosystem networks all rely on models having interacting components [1–7]. When the details of these interactions are unknown for biological systems of interest, one effective approach is to study the dynamical properties of an ensemble of models determined by evolutionary constraints that may apply to all such systems [8–12]. One such constraint is that of dynamical robustness, the probability of a stable system to remain stable under perturbations to the strength of interactions among its components [13–22]. Despite previous investigations, the relationship between dynamical robustness—an important functional characteristic of many biological systems—and network structure is poorly understood. Here we analyze the stability and robustness of a large class of dynamical systems and demonstrate that the most hierarchical network structures, those equivalent to the total ordering, are the most robust. In particular, we determine the probability distribution of robustness over system connectivity and show that robustness is maximized by maximizing the number of links between strongly connected components of the graph representing the underlying system connectivity. We demonstrate that this can be understood in terms of the fact that permutation of strongly connected components is a fundamental symmetry of dynamical robustness, which applies to networks of any number of components and is independent of the distribution from which the strengths of interconnection among components are sampled. The classification of dynamical robustness based upon a purely topological property provides a fundamental organizing principle that can be used in the context of experimental validation to select among models that break or preserve network hierarchy. This result contributes to an explanation for the observation of hierarchical modularity in biological networks at all scales [23–27].

INTRODUCTION

The traditional approach taken in the study of chemical reaction, gene-regulatory, population, and ecosystem networks is to derive a system of differential equations to model a particular biological network, attempt to fit that model to data and adjust the modeling assumptions along with parameter values until a good fit is achieved [28]. All of these models utilize essentially equivalent mathematical structures Fig. 1 [1–7]. Developing unified mathematical descriptions of all of these is one of the paramount goals of systems biology.

Recent work has demonstrated that as a result of the existence of largely insensitive directions within the parameter space for such models, the approach outlined above often allows for a large variety of models to fit equivalent data [29–35]. In addition, there is often uncertainty about the very structure of such networks. In this context, it is crucial to gain insight into what dynamical phenomena are possible to observe within a given class of dynamical systems, which is necessary to understand in order to determine whether or not a particular dynamical phenomenon should be regarded as unique or generic in the development and investigation of models applied to particular systems [36, 37]. This can be achieved using a method common in statistical physics involving the consideration of an ensemble of systems that, in comparison to one another, appear to have components that are randomly interlinked.

Indeed, investigating generic properties of a large class of dynamical systems was the approach taken by May in models of ecosystem dynamics [8, 9]. The class of dynamical systems studied by May is, however, not restricted to ecosystem dynamics and encompasses, among others, the dynamics of all of the networks represented in Fig. 1. May conjectured on the basis of results from random matrix theory what eventually came to be referred to as the May-Wigner stability theorem [10–12, 38], which implies a relationship between a topological property, system connectivity, and a dynamical property, stability.

Some conclusions derived from this approach may be sensitive to the probability distribution from which the strengths of interconnection are sampled, whereas others are independent of the specific form of this distribution. In the former case, discovering the constraints that contribute to determining the functional form of the distribution can be a matter for empirical investigation and results that are themselves functions of this distribution can be reinterpreted in light of ongoing updates from relevant empirical observations. On the other hand, results that are independent of the specific form of this distribution can be expected to hold in any case and a specific distribution may simply be chosen for the purposes of exemplifying the result.
Here we determine the relationship between network hierarchy, a topological property, and the probability of robustness, a dynamical property. Robustness is of interest in biological systems at all scales, and has been previously studied in the context of gene-regulatory networks [13, 16, 17, 19, 20, 22]. Intuitively, robustness is the probability of stability to potentially large perturbations of the parameters for systems which have already been determined to be stable in the sense of linear stability analysis [42]. The maximally hierarchical network is considered to be the graph associated to the total ordering, which is the complete directed acyclic graph for a given system size [43]. Here, hierarchy is then defined as the edit distance from this maximally hierarchical network [44]. We demonstrate that systems with the most hierarchical network topology according to this definition exhibit maximal robustness and explain why this results from an invariance of robustness to particular kinds of transformations of the network topology. Moreover these results hold for networks of arbitrary size and independent of the probability distribution from which the strengths of interaction are sampled.

RESULTS

Overview

The dynamical model given in terms of a system of differential equations for any network can be represented in terms of an interaction graph (Fig. 1 top row). These interaction graphs can be viewed as deriving from the combination of system modules that accept a given pattern of inputs and produce a given pattern of outputs (Fig. 2A). Symmetries are characterized by the ability to interchange these modules or their connectivity without changing some property of the system.

The network architecture can be represented in terms of an adjacency matrix and further abstracted by mapping the interaction graph to the network of strongly connected components (SCCs, see Supplementary Information) (Fig. 2B). This map from the interaction graph of a network, referred to as Hier, has a collection of symmetries shown in Fig. 2C. These three symmetries represent transformations that can be performed on the interaction graph that do not change the network of SCCs to which it is associated Fig. 2B. Two of these three are also symmetries with respect to dynamical robustness. Fig. S1 shows an example of these symmetries applied to a specific interaction graph.

We have derived an analytical expression for dynamical robustness, $R_{tot}$, of a network in terms of its interaction graph as a weighted average of the robustness of the SCCs, $R_i$, the corresponding number of links within each SCC, $d_i$, and the number of links between the SCCs, $l$. This expression is fully developed in Eq. 6, but can be schematized as in Eq. 1 (see Fig. 2B for examples demonstrating this expression)

$$R_{tot} = \frac{l + d_1 R_1 + d_2 R_2 + \cdots}{l + d_1 + d_2 + \cdots}. \quad (1)$$

Examining this expression noting that $R_i$ are all strictly less than one proves that networks maximizing $l$, will also maximize $R_{tot}$. This implies that the interaction graphs for systems that are the most robust will maximize the number of links between SCCs as well as the overall num-
ber of SCCs with respect to a particular system size. This analytical result predicts that any network whose associated dynamical system has the interaction graph Fig. 2B top will be more robust than those associated to any of the other interaction graphs in Fig. 2B. Because this result is purely topological in nature, it does not depend at all upon any particular details such as the probability distribution from which the component interaction strengths are sampled or the size of the system. The result that dynamical robustness is correlated with network hierarchy therefore applies to an even broader class of dynamical systems than the particular random ensembles we have studied directly.

To test this prediction, we computed the probability distribution of stability and dynamical robustness relative to network architecture for ensembles of systems having two or three interacting components (see Table S1 and Table S2). For all of these, we found that robustness is correlated with connectivity, but that the most robust systems have intermediate connectivity for a given network size (Fig. 3A). Accounting for the number of cycles in a network architecture reveals a strong correlation between robustness and connectivity that was hidden when networks with any number of cycles were considered together (Fig. 3C). While the most hierarchical network architecture will always lack cycles altogether, cycle number alone is clearly insufficient to account for robustness as the members of each class span nearly the entire range of possible robustness values. Consistent with our analysis of the symmetries of robustness, we found that the most hierarchical network architecture is the most robust (Fig. 3B). Moreover, if we consider hierarchy partitioned by connectivity, we find that there is a monotonic increase in robustness following any line of increasing hierarchy in Fig. 3D.

Dynamical systems on biological networks

In the construction of a class of potential models for biological systems at any level of the biological hierarchy from metabolic to ecosystem-level networks, it is common to first attempt to define a collection of observable phenomena of interest and determine a domain (such as binary numbers, integers, or real numbers) in which each observable can be quantified. Next, it is necessary to establish the interdependencies among system components. The specific manner in which the components depend upon one another must be clarified, which is often done by determining a particular system of mathematical functions that represents a hypothesis about how the quantified observables evolve in time. To the degree to which there is uncertainty about the interactions among system components, parameters are introduced to broaden the class of models under consideration. Finally, whatever model class remains may be compared to empirical observations to determine how capable the model is of representing the phenomena of interest.

For the case of continuous deterministic observables, the above process can be made more precise by associating a manifold $M_1$ to each observable, a directed graph, $G$, to the interdependencies, and a vector field $V$ over the space determined by taking the product of the manifolds associated to the collection of observables, satisfying these interdependencies for each observable [45]. For example, if we have two observables $\{x_1, x_2\}$ where the domains in which they are quantified are given by manifolds $\{M_1, M_2\}$ such that $x_1 \in M_1 \equiv \mathbb{R}^1$ and $x_2 \in M_2 \equiv \mathbb{R}^1$, a directed graph $G_X$ describing the dependencies between these observables and vector field $V$ with components $\{F_1, F_2\}$ defined on $M_1 \otimes M_2 \equiv \mathbb{R}^2$ satisfying the dependencies determined by $G_X$. If the system under consideration has the graph given in Fig. 2A with adjacency matrix

$$
\text{adj}(G_X) = \begin{pmatrix} 0 & 1 \\ 1 & 1 \end{pmatrix}
$$

having connectivity $d$ equal to the number of edges of the graph, in this case $d = 3$. For a general system the directed graph $G_X$ that describes the manner in which each of the variables depends upon one another is given by the adjacency matrix $\text{adj}(G_X)$ where

$$
\text{adj}(G_X)_{ij} = \begin{cases} 1, & F_i \text{ depends on } x_j \\ 0, & F_i \text{ does not depend on } x_j \end{cases}.
$$

For the system $X = \{G_X, M_X, F_X\}$, where $M_X \equiv \{M_1, M_2\}$ and $F_X \equiv \{F_1, F_2\}$ such that $F_1$ is a function of $x_2$ alone and $F_2$ is a function of both $x_1$ and $x_2$ yielding the flow equations

$$
\frac{dx_1}{dt} = F_1(x_2), \\
\frac{dx_2}{dt} = F_2(x_1, x_2).
$$

In the more general case of a system with $n$ components we would have an $n$-dimensional vector of observables

$$
x(t) = (x_1(t), \ldots x_n(t)) = \vec{x}(t)
$$

whose components are solutions to the arbitrary first order system

$$
\frac{dx_i(t)}{dt} = F_i(\vec{x}(t)), \quad (i = 1, \ldots, n)
$$

where $F_i$ represent, potentially nonlinear, functions of the given vector of state variables.

In order to accommodate the possibility of uncertainty in our modeling, we will generalize our notion of a system on a network to that of a system with random parameters. Again, this will involve three steps. First, we provide a measure space $S$ which represents the values over which our parameters can vary. Next, instead of a single vector field, we consider a family of vector fields param-
eterized by this space. As before, for each point \( p \in S \), the vector field \( V(p) \) must be consistent with the system graph. Finally, we select a probability measure \( \mu \) which represents our understanding of which values of the parameters are likely. In accord with Bayesian statistics, we might revise this distribution as data comes in or use it to estimate parameters and error bars from experimental results.

Having done this, we are now in a position to do a probabilistic analysis of our system and its properties. Given some quantity \( q \) characterizing our system, this quantity becomes a random variable which may be discrete or continuous depending on the quantity under consideration. For example, if the quantity is the time it takes for a particle to travel between two points, we have a real-valued random variable; if the quantity is the number of fixed points, we have an integer-valued random variable; and if the quantity is whether or not the system possesses a limit cycle, we have a binary random variable.

A quality of interest to us is robustness, which is related to the concept of structural stability [46], whose evaluation requires the determination of whether or not a given dynamical system that is determined to be stable remains stable under a perturbation to one or more of its defining parameters. We mean to refer to perturbations to the structure of the system itself as determined by the strengths of the couplings between the components as determined by the parameters and not only to perturbations of the state vector at a given point in time. For example, when the network of components and interactions corresponds to a gene-regulatory network, then mutation is one mechanism by which such perturbations may arise. We will quantify this as the probability that, if some property holds for a set of parameters, it will continue to hold if we make a random perturbation about those parameter values. To do so, we will introduce, in addition to the probability distribution \( \mu \) described above, a family of probability distributions \( \mu' \) such that \( \mu'(x, y) \) encodes the conditional probability that a system with a parameter value \( x \) will have its parameter values changed to \( y \) under a perturbation. For our biological models, we will be interested in large perturbations rather than the small or infinitesimal perturbations usually considered in the theory of dynamical systems. Then, given a binary random variable \( q \), we define its robustness as the following conditional probability where \( \mathbf{1}_q(x) \) is the standard indicator function equal to 1 when \( x \) satisfies \( q \) and 0 otherwise:

\[
R(q, \mu') = \frac{\int_S d\mu(x) \int_S d\mu'(x, y) \mathbf{1}_q(x) \mathbf{1}_q(y)}{\int_S d\mu(x) \mathbf{1}_q(x)} \tag{2}
\]

**Stability analysis of biological networks**

The class of dynamical quantities on which we shall focus in this investigation involve stability of equilibria. Suppose that \( \bar{x} \) is a point on our phase space which depends upon the parameters. Then we may take \( q \) to be a binary random variable which describes whether or not \( \bar{x} \) is a fixed point of the system (i.e. \( q \) is true if and only if \( F_i(\bar{x}) = 0 \) for all \( i \)) and perform a probabilistic analysis of the sort discussed above.

Furthermore, if it turns out that \( \bar{x} \) is indeed a fixed point, we may proceed to ask whether it is a dynamically stable fixed point. Intuitively, dynamic stability means that, if one chooses the initial conditions sufficiently close to the fixed point, the solution will stay close to the fixed point. Physically, this is important because, if a fixed point \( \bar{x}^0 \) is unstable, we have zero probability of observing the solution \( \bar{x}(t) = \bar{x}^0 \).

To determine stability, we linearize the equations of motion about the fixed point \( \bar{x}^0 \):

\[
\frac{d\bar{y}(t)}{dt} = A\bar{y}(t), \tag{3}
\]

where \( \bar{y} = \bar{x} - \bar{x}^0 \) and the \( n \times n \)-matrix \( A \) has components

\[
A_{ij} = \left\{ \begin{array}{ll} 1, & a_{ij} \neq 0 \\ 0, & a_{ij} = 0 \end{array} \right. 
\]

To each dynamical system having Jacobian matrix \( A \) at some fixed point \( \bar{x}^0 \) we can associate a linearized interdependency graph \( G_A \) given by an adjacency matrix \( \text{adj}(G_A) \) where

\[
\text{adj}(G_A)_{ij} = \left\{ \begin{array}{ll} 1, & a_{ij} \neq 0 \\ 0, & a_{ij} = 0 \end{array} \right. 
\]

In general, the graph \( G_A \) is a subgraph of \( G_X \) because the condition \( F_i \) independent of \( x_j \) definitive of \( \text{adj}(G_X) \) corresponds precisely to \( \frac{\partial F_i}{\partial x_j} = 0 \), while for some \( F_i, x_j, \) and \( \bar{x}^0, \frac{\partial F_i}{\partial x_j} \big|_{\bar{x}^0} = 0 \) despite the fact that \( F_i \) depends upon \( x_j \). However, for nearly all systems, \( G_A \) is equivalent to \( G_X \) since, in general, the condition \( \frac{\partial F_i}{\partial x_j} \big|_{\bar{x}^0} = 0 \) is independent of \( F_i(\bar{x}^0) = 0 \). For those cases where a distinction exists at all, we refer to the linearized interdependency graph \( G_A \).

The spectral abscissa of the matrix \( A \) is defined as

\[
\eta(A) = \max_i \{ \Re(\lambda_i) \}
\]

where \( \lambda_i \) are the eigenvalues of \( A \). The system defined by \( F_i \) and \( \bar{x}^0 \) is dynamically stable if the spectral abscissa of \( A \) is less than zero, equivalently, \( \eta(A) < 0 \). This is because the general solution to Eq. 3 is

\[
y_i(t) = \sum_j b_{ij} e^{\lambda_j t}, \quad (i = 1, \ldots, n)
\]

for some matrix \( B = (b_{ij}) \) and thus all \( \bar{y} = \bar{x} - \bar{x}^0 \) decay to zero when all \( \lambda_i < 0 \). This criterion can be checked equivalently in terms of conditions on the coefficients of the characteristic polynomials \( \chi(A) \) associated to the sys-
tems described by matrices $A$ [47].

Even though the determination of stability only requires examining linearized equations of motion, it is worth noting that knowing the stability of a fixed point can yield information about the non-linear dynamics of a system. For instance, in two dimensions, Poincare-Bendixson theory implies that every limit cycle must encircle at least one fixed point [42]. Furthermore, in the case where the cycle contains a single fixed point (such as in the Lotka-Volterra model of conflicting populations), the stability of the fixed point will determine whether the limit cycle is attractive or repulsive.

Suppose that our Jacobian $A$ is an $n \times n$ matrix with real coefficients, connectivity $d$, and denote the proposition “$A$ is stable” as $\text{stab}(A)$. Then we may compute the robustness of this proposition using Eq. 2 once we have specified the probability densities $\mu$ and $\mu'$. In general, these will depend upon the parameters of the non-linear system. For the purpose of the current investigation, we shall make the ansatz that these are such that the distribution of entries of $A$ is (at least approximately) the uniform distribution $U(-1,1)$ on the $d$-dimensional hypercube, $H^d$, of edge length $r = 2$, centered about the origin. Note that our conclusion relating network hierarchy to robustness is independent of the form of this distribution. There is therefore no loss of generality in using such a distribution for the purpose of elaborating examples. To model the perturbations, we resample the elements $k_1, k_2, \ldots, k_m$ of this matrix from the same uniform distribution yielding

$$
\mu_{k_1, \ldots, k_m}(x, y) = \prod_{j \notin \{k_1, \ldots, k_m\}} \delta(x_j - y_j) \prod_{j \in \{k_1, \ldots, k_m\}} 1_{[-1,1]}(y_j) 1_{[-1,1]}(x_j)
$$

Under these assumptions, the expression for robustness becomes a special case of Eq. 2:

$$
R(\text{stab}, \mu'_1, \ldots, k_m) = \frac{\int_{H^d} dx_1 \cdots dx_d \int_{H^m} dx'_1 \cdots dx'_m \prod_{k_1, \ldots, k_m} 1_{\text{stab}} 1_{\text{stab}'} }{\int_{H^d} dx_1 \cdots dx_d 1_{\text{stab}}},
$$

where we use the abbreviations

$$
1_{\text{stab}} = 1_{\text{stab}}(x_1, \ldots, x_{k_1}, \ldots, x_{k_m}, \ldots, x_d),
$$

$$
1_{\text{stab}'} = 1_{\text{stab}'}(x_1, \ldots, x'_1, \ldots, x'_m, \ldots, x_d),
$$

i.e. $1_{\text{stab}'}$ corresponds to replacing $x_{k_1}, \ldots, x_{k_m}$ with their primed counterparts.

While one can resample a fixed subset of the links, more typically we will be randomly selecting which links to resample with a uniform distribution on the links. The result of this operation corresponds to averaging our quantity over subsets of links:

$$
\langle R(\text{stab}, \mu') \rangle_m = \frac{1}{\binom{d}{m}} \sum_{\{k_1, k_2, \ldots, k_m\} \subset \{1,2,\ldots,d\}} R(\text{stab}, \mu'_{k_1, \ldots, k_m})
$$

Network hierarchy and strongly connected components

Dynamical networks of the kind described above can be viewed at the level of their interdependency graphs as being composed of more fundamental interacting subsystems Fig. 2A. One such kind of system composition and decomposition is given by the notion of open systems, which are distinguished by having some of the variables specified as control variables whose values are given as autonomous functions of time rather than determined by the dynamics via intrinsic interactions [48]. Given several
such open systems, we may combine them to produce a larger system by setting the control variables of a subsystem equal to the dynamical variables of another system. Taking this notion to its logical extreme, one can dissect a system into a collection of one open system for each dynamical variable. However, this decomposition is trivial since it is equivalent to the underlying system graph and what we instead want is an intermediate decomposition into relatively self-contained modules. One method of accomplishing this based upon the topology of the system graph is the decomposition into strongly connected components.

A strongly connected component (SCC) of a graph is a maximal subset of vertices where each vertex within the subset can be reached from any other \[43\]. The strongly connected components of some examples of three variable systems are outlined in Fig. 2B along with their adjacency matrices and hierarchy diagrams (to be defined below). The decomposition of a digraph into strongly connected components corresponds to a block triangular decomposition of its adjacency matrix. Say that the graph \( G \) has strongly connected components \( C_1, C_2, \ldots, C_n \), which have been labelled in such a way that there are no links from vertices in component \( C_i \) to component \( C_j \) when \( i < j \). Label the vertices in such a way that \( v_1, \ldots, v_{n_1} \) belong to \( C_1 \), \( v_{n_1+1}, \ldots, v_{n_2} \) belong to \( C_2 \), etc. Then, if we choose basis vectors corresponding to this labelling of the vertices, we will have \( a_{ij} = 0 \) whenever \( i \) and \( j \) correspond to different components and \( i > j \). This condition is equivalent to stating that the matrix is block triangular with blocks of size \( n_1, n_2, \ldots \).

Corresponding to this decomposition we can construct a directed acyclic graph \( \text{Hier}(G) \) or the condensed graph [27]. Each node of \( \text{Hier}(G) \) corresponds to a strongly connected component of \( G \). There is an edge from the node corresponding to component \( C \) to the node corresponding to component \( C' \) if and only if there exists a link from some vertex in \( C \) to some vertex in \( C' \) in \( G \). Because of the maximality of strongly connected components, \( \text{Hier}(G) \) is acyclic.

One can also perform this construction in the opposite direction. Start with a directed acyclic graph \( A \). To each node \( n \) of \( A \) associate a strongly connected graph \( C_n \). To each link \((i, j)\) of \( A \) associate a non-empty subset of \( \text{Vertex}(C_i) \times \text{Vertex}(C_j) \). The result will be a graph \( G \) such that \( \text{Hier}(G) = A \) and furthermore, every graph \( G \) such that \( \text{Hier}(G) = A \) can be obtained in this manner.

This map \( \text{Hier} \) is many-to-one and so there is a large class of operations which leaves \( \text{Hier}(G) \) invariant for a given graph \( G \). For instance, we may interchange the positions of the strongly connected components relative to each other Fig. 2Ca. Leaving the components fixed, we may move links between nodes in a component Fig. 2Cb or between components, or even add or delete links Fig. 2Cc. As we shall see later, some of these operations leave invariant key dynamical quantities, in our case dynamical robustness, so we may regard them as a symmetry groupoid of our system with respect to the robustness property.

The relationship between \( G \) and \( \text{Hier}(G) \) for all \( G \) with a given number of vertices suggests a heuristic method of quantifying the degree of hierarchy of a given graph and thus of the system structure it represents. The most hierarchical system is considered to be the graph corresponding to the total ordering, which for three nodes is given in Fig. 2B(top panel). This graph maximizes the number of links between strongly connected components, which also implies maximizing the number of strongly connected components. The graph edit distance (ED) on a fixed number of vertices from one graph to another is defined as the minimum number of modifications of the first graph in order to transform it into the second [44]. This distance between any given graph and the total ordering thus quantitatively represents how far a graph is from being maximally hierarchical. In this work we take \( \max(ED) - ED \) to be the definition of hierarchy, where \( \max(ED) \) is the maximum edit distance for all graphs with a given number of nodes.

### Stability and robustness analysis of particular system ensembles

For systems having two variables, we can analytically compute the probability of stability and robustness from Eq. 4. For those having three variables, we can estimate these same quantities using Monte Carlo simulations. Systems of larger size can be analyzed using the symmetry properties of robustness extracted from this analysis. We note again that while we use the uniform distribution for the purposes of illustration, the analysis could be performed for other distributions and our result relating network hierarchy to robustness is independent of the form of the distribution. For two-variable systems having \( 2 \times 2 \) Jacobian matrices, the aforementioned stability criteria result in the conditions \( T < 0 \) and \( D > 0 \) where \( T \) and \( D \) denote the trace and the determinant. Suppose we have a stable matrix

\[
\begin{bmatrix}
  a & b \\
  d & c 
\end{bmatrix}
\]

where \( a + c < 0 \) and \( ac > bd \). For the case in which \( x_1 = a, x_2 = b, x_3 = c, x_4 = d \) we need to compute what corresponds to \( R(\text{stab}, \mu'_1) \) where \( k = 1 \ldots 4 \). By symmetry, there are two cases to consider; resampling \( a \) is equivalent to resampling \( c \) and resampling \( b \) is equivalent to resampling \( d \) so we only need to explicitly compute \( R(\text{stab}, \mu'_1) \) and \( R(\text{stab}, \mu'_2) \). Suppose that we resample \( b \) to compute \( R(\text{stab}, \mu'_2) \). The denominator of Eq. 4 in this case is given by

\[
P\left(\text{stab} \left( \begin{bmatrix} a & b \\ d & c \end{bmatrix} \right) \right) = \frac{\int_{ac > bd} db \int_{a + c < 0} da \int_{-1}^{1} dd}{\int_{H^4} db \int_{ac > bd} da \int_{a + c < 0} dd}.
\]
FIG. 2. Open systems, strongly connected components and symmetries of robustness. (A) Example of the combination of open system modules to construct closed systems. (B) SCCs highlighted in gray for each of the four graphs representing the interdependencies relevant to four different three variable systems. The most hierarchical network, top panel, is the one that maximizes the number of SCCs and the number of links between them. We therefore define hierarchy as \( \text{max}(ED) - ED \) where \( ED \) is the edit distance representing the number of link addition/deletion operations necessary to transform a given graph into the most hierarchical one. The two panels in the middle represent examples of hierarchical modular systems that possess both modularity (i.e. SCCs with more than one variable) and hierarchy. (C) Symmetries of the \( \text{Hier} \) transformation between graphs and SCCs. The transformation \( a \) represents an interchange of SCCs, \( b \) moving a link between nodes in a component and \( c \) adding a link. All three transformations represent symmetries of the \( \text{Hier} \) transformation from graphs to SCCs while only \( a \) and \( b \) are symmetries of robustness.

Since the trace does not involve \( b \), the \( T < 0 \) condition will be satisfied automatically and we only need to examine the determinant. Thus, we have the inequalities \( ac > b'd \) and \(-1 < b' < 1\) in addition to the previous constraints leading to an expression for the numerator of Eq. 4

\[
P\left(\text{stab} \left( \begin{bmatrix} a & b \\ d & c \end{bmatrix} \right) \text{ and stab} \left( \begin{bmatrix} a & b' \\ d & c \end{bmatrix} \right) \right) = \frac{\int_{a'b'd}^{ac>bd} \int_{a+c<0}^{ac>bd} da \, db \, dc \, dd \, db' \, 1}{\int_{H^5} da' \, db \, dc \, dd' \, 1}.
\]

The analogous equation for resampling \( a \) is

\[
P\left(\text{stab} \left( \begin{bmatrix} a & b' \\ d & c \end{bmatrix} \right) \text{ and stab} \left( \begin{bmatrix} a' & b' \\ d & c \end{bmatrix} \right) \right) = \frac{\int_{a'b'd}^{ac>bd} \int_{a+c<0}^{ac>bd} da \, db \, dc \, dd \, db' \, 1}{\int_{H^5} da' \, db \, dc \, dd' \, 1}.
\]

Using this approach the probability of stability and of robustness for all two variable systems is given in Table S1. The analogous results for all three variable systems are computed using Monte Carlo integration and shown in...
Table S2 and Fig. 3A. This process is associated with some error relative to the exact integration described above. In all simulations we use $N = 10000$ so that the maximum error is 0.005 (see Methods).

It has been stated previously on the basis of simulation that system stability decreases with connectivity as the system size goes to infinity [9]. For small system sizes such as the two and three variable systems, the situation is not so clear cut. For two variable systems, system stability is constant across the entire range of connectivities. For three variable systems, the trend shows a minor decrease from connectivity 4 to 5 followed by small fluctuations as shown in Fig. S2.

The relationship between connectivity and robustness for two variable systems is shown in Table S1 and likewise for three variable systems in Table S2 and Fig. 3A. If we average over the different classes of matrices for a given connectivity we see there is a correlation between connectivity and robustness demonstrated by the red lines in Fig. 3A. Fig. S3 shows the robustness for all three variable systems as a function of the number of simple cycles (elementary circuits) of length greater than one in the corresponding directed graph [49]. There appears to be a weak negative correlation between robustness and the number of simple cycles.

The combination of connectivity and cycle number as shown in Fig. 3C provides a better classification of the dependence of robustness upon network topology. Here the robustness of three variable systems with a given number of cycles, increases monotonically with connectivity. The network with the highest robustness for three variable systems is that of Fig. 2B(top panel). This network is the most hierarchical of all three variable systems in the sense that it represents a total ordering of the components of the network and its adjacency matrix also shown in Fig. 2B(top panel) has a block triangular structure.

This observation suggested that graph edit distance from Fig. 2B(top panel), hierarchy, might provide a better characterization of dynamical robustness. Fig. 3B shows dynamical robustness as a function of hierarchy. There is a monotonic correlation between the upper bound of robustness and hierarchy. Fig. 3D shows dynamical robustness as a function of both hierarchy and connectivity. The monotonic correlation between hierarchy and robustness is refined by an underlying correlation between robustness and connectivity analogous to that of Fig. 3C.

**Component decomposition, hierarchy, and the symmetries of robustness**

The fact that the most hierarchical of networks is the most robust in the case of three variable systems can be understood in general as resulting from the previously mentioned symmetry property of network robustness. By combining our decomposition of the graph with our analysis of the robustness of random ensembles of dynamical systems, we will deduce a general result which relates robustness to hierarchy.

Since the determinant of a triangular matrix equals the product of the determinants of its diagonal blocks, it follows that the characteristic polynomial factors as the product of the characteristic polynomials of its diagonal blocks. Hence, a block triangular matrix is stable if and only if its diagonal blocks are stable. Note that this condition does not depend upon the entries off the diagonal (which correspond to links between strongly connected components) and does not depend upon what order the components appear.

Using these observations, we may express the robustness of a graph in terms of the robustness of its strongly connected components. If each component $C_i$ of our graph $G$ has $v_i$ vertices, connectivity $d_i$, and there are $\ell_{ij}$ links between components $i$ and $j$, then there are a total of $\sum_{i,j \in \text{Hier}(G)} \ell_{ij} + \sum_{i=1}^{n} d_i$ links in $G$. If we resample a randomly chosen link in a component $C_i$, then the probability that the system will remain stable after resampling is $\langle R(\text{stab}(C_i), \mu') \rangle_1$. If we resample a link between components $C_i$ and $C_j$, the system will remain stable with probability 1. Hence, the probability that the system will remain stable upon resampling a random link is the weighted average of these probabilities:

$$
\langle R(\text{stab}(G), \mu') \rangle_1 = \frac{\sum_{(i,j) \in \text{Hier}(G)} \ell_{ij} + \sum_{i=1}^{n} d_i \langle R(\text{stab}(C_i), \mu') \rangle_1}{\sum_{(i,j) \in \text{Hier}(G)} \ell_{ij} + \sum_{i=1}^{n} d_i}.
$$

For instance, if our graph is the one in Fig. 2B(middle panels), then we have two connected components, one with two nodes, and one with one node. From Table S1, we know that the graph with two nodes has probability 0.25 of being stable and robustness 0.62. The graph with one node corresponds to a $1 \times 1$ matrix, so we have probability 0.5 of stability and robustness 0.5. Thus, the probability of our 3-node graph being stable is
0.5 × 0.25 = 0.125 and its robustness is
\[
\langle R(\text{stab}(G), \mu') \rangle_1 = \frac{2 + 0.5 + 4 \times 0.62}{2 + 1 + 4} = 0.714,
\]
which agrees with the value computed in Table S1 up to sampling error.

As can be seen from Eq. 6, all that is required to determine robustness is a set of SCC sizes and the number of links between them. This demonstrates that robustness is symmetric under the transformations shown in Fig. 2Ca and b. Since transformations of the type Fig. 2Cc change the number of links between connected components, this symmetry of \text{Hier} is broken by Eq. 6. Nevertheless, a considerable degree of symmetry remains. For example, Fig. S1 shows the symmetry groupoid of robustness for the case in which we fix connected component sizes \{2, 1, 1\} with a total of 3 links between them.

Next, we derive an upper bound on the robustness of any graph constructed from a given set of connected components. Since \( \langle R(\text{stab}(C_i), \mu') \rangle_1 \leq 1 \) for all \( i \), it follows that increasing \( \ell_{ij} \) will increase \( \langle R(\text{stab}(G), \mu') \rangle_1 \). Given two connected components \( C_i \) and \( C_j \) with \( v_i \) and \( v_j \) nodes respectively, we have a maximum of \( v_i v_j \) links going from \( C_i \) to \( C_j \). Hence, \( \ell_{ij} \leq v_i v_j \), so, we conclude that
\[
\langle R(\text{stab}(G), \mu') \rangle_1 \leq \frac{\sum_{(i,j) \in \text{Hier}(G)} v_i v_j + \sum_{i=1}^{n} d_i \langle R(C_i, \mu') \rangle_1}{\sum_{(i,j) \in \text{Hier}(G)} v_i v_j + \sum_{i=1}^{n} d_i},
\]
(7)

Since every acyclic digraph can be embedded into a totally ordered set, we may assume without loss of generality that our components have been ordered in a way such that, if \((i, j) \in \text{Hier}(G)\), then \( i < j \). Hence, after substituting into our expression and simplifying using the identity
\[
\sum_{i=1}^{n-1} \sum_{j=i+1}^{n} v_i v_j = \frac{1}{2} \left( \sum_{i=1}^{n} v_i \right)^2 - \frac{1}{2} \sum_{i=1}^{n} v_i^2,
\]
we arrive at the following upper bound on robustness in terms of the connected components:
Furthermore, this bound is attained. Suppose that $G_{\text{tot}}$ is the graph on $n$ nodes with a link from node $i$ to node $j$ whenever $i < j$. Then, by the construction described in the previous section on network hierarchy, we have a graph $G_{\max}$ such that the components of $G_{\max}$ are $C_1, \ldots, C_n$ and $\text{Hier}(G_{\max}) = G_{\text{tot}}$. By our formula, $\langle R(\text{stab}(G_{\max}), \mu') \rangle_m = R_{\max}(C_1, \ldots, C_n)$.

This argument also works when we resample more than one entry, although the notation becomes more complicated. Suppose that we resample $m$ nodes. Define

$$M = \left\{ (m_0, m_1, \ldots, m_n) \mid m = \sum_{i=0}^{n} m_i \quad \& \quad m_0 \leq \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} \ell_{ij} \quad \& \quad (\forall i \in \{1, \ldots, n\}) \; m_i < d_i \right\}.$$  

Then, given $(m_0, m_1, \ldots, m_n) \in M$, there are $\binom{m_0 + \sum_{i=1}^{n} m_i R(\text{stab}(C_i), \mu')} m$ ways of choosing $m_i$ links from $C_i$ and $m_0$ links between strongly connected components. Hence, our weighted average becomes

$$\langle R(\text{stab}(G), \mu') \rangle_m = \frac{\sum_{(m_0, m_1, \ldots, m_n) \in M} \binom{m_0 + \sum_{i=1}^{n} m_i R(\text{stab}(C_i), \mu')} m \sum_{(m_0, m_1, \ldots, m_n) \in M} \binom{m}{m_0, m_1, \ldots, m_n}}{\sum_{(m_0, m_1, \ldots, m_n) \in M} \binom{m}{m_0, m_1, \ldots, m_n}}.$$  

As before, since $\langle R(\text{stab}(C_i), \mu') \rangle_{m_i} \leq 1$, we may increase $\langle R(\text{stab}(G), \mu') \rangle_m$ by increasing the maximum possible value of $m_0$ while keeping the strongly connected components the same. Again, if we fix $\text{Hier}(G)$, the maximum possible value of $m_0$ is $\sum_{(i,j) \in \text{Hier}(G)} v_i v_j$ whereas, if we allow it to vary, the maximum is $\frac{1}{2\ell}(\sum_{i=1}^{n} v_i^2 - \sum_{i=1}^{n} v_i^2)$, which is attained when $\text{Hier}(G_{\max}) = G_{\text{tot}}$. Hence, we conclude that $\langle R(\text{stab}(G), \mu') \rangle_m \leq \langle R(\text{stab}(G_{\max}), \mu') \rangle_m$.

The preceding argument demonstrates that robustness is maximized by maximizing the number of edges between the strongly connected components of the graph underlying system interdependencies. And, the graph that has the latter property is that associated to the total ordering, $G_{\text{tot}}$, which is also considered to possess the highest degree of hierarchy. The fact that robustness is equivalent for any configuration of strongly connected components with an equivalent number of links between them demonstrates that it is invariant to permutations of strongly connected components. Because the argument presented here is purely topological in nature, it does not depend at all upon details such as the system size or the specific form of the probability distribution from which the component interaction strengths are sampled.

**Discussion**

Our theory predicts that, in general, an ensemble of systems where robustness has been the predominant object of selection and has been positively selected over a sufficiently long period of time should exhibit a bias toward more hierarchical network topologies. For example, at the ecological level, a system subjected to the environmental stress of overfishing, which may imply selection for robustness, has been observed to exhibit such a bias toward more hierarchical network architectures [50]. In the short term, this prediction may be further evaluated at the levels of both metabolic and transcription factor networks, which have already been shown to display hierarchical structure, but whose dynamics have not been sufficiently well characterized to ascertain their robustness [23, 25, 26]. In the long term, this prediction may be evaluated using experimental evolution by comparing the degree of hierarchy that emerges in the evolution of gene regulatory network topology in the context of both static and fluctuating environments that differentially select for robustness [51].

In order to further this work from a theoretical perspective, it will be necessary to deepen our understanding of the relationship between dynamical robustness and
the underlying network topology. It may be possible to prove a bound on the robustness of individual SCCs, which could provide more definite knowledge and circumvent the need for expensive simulations. The conservation of robustness with respect to nontrivial symmetries including the interchange of SCCs and permutation within SCCs suggests the existence of an evolutionary neutral space. A deeper mathematical characterization of the full symmetry groupoid of dynamical robustness may thus help to characterize this potential evolutionary constraint [52].

The relationship between structure and function is fundamental to networks at every level of the biological hierarchy. Equally fundamental is the ability of systems to persist over long periods of time, which is dependent upon their dynamical robustness. Here we have demonstrated a structure-function relationship wherein biological networks that are more hierarchical are more robust and thus more likely to persist when this feature is the dominant object of selection in the evolutionary process.

\[
\text{var}(\theta|D) = \frac{(a + N_{\text{stab}})(b + N_{\text{unstab}})}{(a + N_{\text{stab}} + b + N_{\text{unstab}})^2(a + N_{\text{stab}} + b + N_{\text{unstab}} + 1)}
\]

Since for the chosen prior \(a = b = 1 \ll N\) this simplifies to

\[
\text{var}(\theta|D) = \frac{\hat{\theta}(1 - \hat{\theta})}{N}
\]

yielding the error estimate given by the associated standard deviation. In all simulations we use \(N = 10000\) so that the maximum error for \(\hat{\theta} = 0.5\) is \(\sigma = \sqrt{\text{var}(\theta|D)} \approx 0.005\).

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FIG. S1. Example symmetries of robustness. In this example, the connected component sizes are fixed at \( \{2, 1, 1\} \) with a total of 3 links between them. Red arrows correspond to transformations like Fig. 2Ca where SCCs are swapped whereas purple arrows correspond to transformations like Fig. 2Cb where links are moved between nodes within a SCC. (A) shows all underlying graphs while (B) shows the number of nodes in each SCC and the number of links between the SCCs.
FIG. S2. **System stability as a function of connectivity.** The red points represent the average of system stability at each connectivity.
FIG. S3. Dynamical robustness as a function of number of cycles.
### TABLE S1. Probability of stability under resampling and *a priori* stability for two variable systems derived analytically. All matrices not listed have 0 probability of stability.

| matrix | connectivity | robustness | probability of stability |
|--------|--------------|------------|--------------------------|
| \[
  \begin{pmatrix}
    a & b \\
    d & c
  \end{pmatrix}
\] | 4 | 0.62 | 0.25 |
| \[
  \begin{pmatrix}
    a & b \\
    d & 0
  \end{pmatrix}, \begin{pmatrix}
    0 & b \\
    d & c
  \end{pmatrix}
\] | 3 | 0.5 | 0.25 |
| \[
  \begin{pmatrix}
    a & 0 \\
    d & c
  \end{pmatrix}, \begin{pmatrix}
    a & b \\
    0 & c
  \end{pmatrix}
\] | 3 | 0.67 | 0.25 |
| \[
  \begin{pmatrix}
    a & 0 \\
    0 & c
  \end{pmatrix}
\] | 2 | 0.5 | 0.25 |
| matrix | orbit size | connectivity | edit distance | cycle number | robustness | probability of stability |
|--------|------------|--------------|---------------|--------------|------------|-------------------------|
| \( \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \) | 1 | 3 | 3 | 0 | 0.499 | 0.126 |
| \( \begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ 0 & 1 & 0 \end{pmatrix} \) | 6 | 4 | 4 | 1 | 0.505 | 0.121 |
| \( \begin{pmatrix} 0 & 0 & 1 \\ 0 & 1 & 1 \\ 0 & 0 & 1 \end{pmatrix} \) | 6 | 4 | 2 | 0 | 0.622 | 0.127 |
| \( \begin{pmatrix} 0 & 1 & 1 \\ 1 & 0 & 1 \\ 0 & 0 & 1 \end{pmatrix} \) | 12 | 5 | 3 | 1 | 0.595 | 0.121 |
| \( \begin{pmatrix} 0 & 1 & 1 \\ 1 & 1 & 0 \\ 0 & 1 & 1 \end{pmatrix} \) | 6 | 5 | 5 | 2 | 0.494 | 0.128 |
| \( \begin{pmatrix} 0 & 1 & 1 \\ 1 & 0 & 1 \\ 0 & 0 & 1 \end{pmatrix} \) | 12 | 5 | 3 | 2 | 0.41 | 0.061 |
| \( \begin{pmatrix} 0 & 1 & 1 \\ 1 & 1 & 0 \\ 0 & 1 & 1 \end{pmatrix} \) | 6 | 5 | 3 | 1 | 0.43 | 0.078 |
| \( \begin{pmatrix} 0 & 1 & 0 \\ 1 & 0 & 1 \\ 0 & 1 & 1 \end{pmatrix} \) | 6 | 5 | 1 | 0 | 0.707 | 0.127 |
| \( \begin{pmatrix} 0 & 0 & 1 \\ 1 & 0 & 0 \\ 1 & 0 & 1 \end{pmatrix} \) | 6 | 6 | 4 | 2 | 0.578 | 0.121 |
| \( \begin{pmatrix} 0 & 0 & 0 \\ 1 & 0 & 0 \\ 1 & 0 & 1 \end{pmatrix} \) | 3 | 5 | 3 | 1 | 0.587 | 0.128 |
| \( \begin{pmatrix} 0 & 0 & 1 \\ 1 & 1 & 1 \\ 0 & 1 & 1 \end{pmatrix} \) | 6 | 6 | 4 | 3 | 0.487 | 0.081 |
| \( \begin{pmatrix} 0 & 1 & 1 \\ 1 & 1 & 1 \\ 0 & 0 & 1 \end{pmatrix} \) | 12 | 6 | 2 | 2 | 0.543 | 0.098 |
| \( \begin{pmatrix} 0 & 1 & 1 \\ 1 & 1 & 1 \\ 0 & 0 & 1 \end{pmatrix} \) | 12 | 6 | 2 | 2 | 0.501 | 0.088 |
| \( \begin{pmatrix} 0 & 1 & 0 \\ 1 & 1 & 1 \\ 0 & 1 & 1 \end{pmatrix} \) | 12 | 6 | 2 | 1 | 0.662 | 0.123 |
| \( \begin{pmatrix} 0 & 1 & 1 \\ 1 & 1 & 1 \\ 0 & 1 & 1 \end{pmatrix} \) | 12 | 6 | 4 | 3 | 0.467 | 0.079 |
| \( \begin{pmatrix} 1 & 1 & 0 \\ 1 & 1 & 0 \\ 1 & 0 & 1 \end{pmatrix} \) | 3 | 6 | 4 | 2 | 0.583 | 0.13 |
| A          | B | C | D | E | F |
|------------|---|---|---|---|---|
| 1 0 1      | 12| 6 | 2 | 1 | 0.659 | 0.124 |
| 0 1 1      |   |   |   |   |    |    |
| 0 1 1      |   |   |   |   |    |    |
| 0 0 1      |   |   |   |   |    |    |
| 1 1 0      |   | 2 | 6 | 2 | 1  | 0.604 | 0.097 |
| 0 1 1      |   |   |   |   |    |    |
| 1 0 1      |   |   |   |   |    |    |
| 0 1 1      | 12| 7 | 3 | 3 | 0.564 | 0.103 |
| 1 1 1      |   |   |   |   |    |    |
| 0 1 1      |   |   |   |   |    |    |
| 1 0 1      |   | 3 | 7 | 5 | 5  | 0.475 | 0.068 |
| 1 1 1      |   |   |   |   |    |    |
| 0 1 1      |   |   |   |   |    |    |
| 1 0 1      | 6 | 7 | 3 | 3 | 0.591 | 0.108 |
| 1 1 1      |   |   |   |   |    |    |
| 0 1 1      |   |   |   |   |    |    |
| 1 0 1      | 6 | 7 | 1 | 1 | 0.717 | 0.119 |
| 1 1 1      | 3 | 7 | 3 | 2 | 0.648 | 0.122 |
| 1 1 1      |   |   |   |   |    |    |
| 0 1 1      | 6 | 7 | 1 | 2 | 0.627 | 0.105 |
| 1 0 1      |   |   |   |   |    |    |
| 0 1 1      | 3 | 8 | 4 | 5 | 0.577 | 0.093 |
| 1 1 1      |   |   |   |   |    |    |
| 1 1 1      | 6 | 8 | 2 | 3 | 0.639 | 0.109 |
| 1 1 1      |   |   |   |   |    |    |
| 1 1 1      | 1 | 9 | 3 | 5 | 0.638 | 0.106 |

**TABLE S2:** Robustness and stability for three variable systems estimated via Monte Carlo sampling. All matrices not listed have 0 probability of stability.