Metanetworks of artificially evolved regulatory networks

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Abstract. We study metanetworks arising in genotype and phenotype spaces, in the context of a model population of Boolean graphs evolved under selection for short dynamical attractors. We define the adjacency matrix of a graph as its genotype, which gets mutated in the course of evolution, while its phenotype is its set of dynamical attractors. Metanetworks in the genotype and phenotype spaces are formed, respectively, by genetic proximity and by phenotypic similarity, the latter weighted by the sizes of the basins of attraction of the shared attractors. We find that evolved populations of Boolean graphs form tree-like giant clusters in genotype space, while random populations of Boolean graphs are typically so far removed from each other genetically that they cannot form a metanetwork. In phenotype space, the metanetworks of evolved populations are super robust both under the elimination of weak connections and random removal of nodes.

Keywords: models for evolution (theory), computational biology, percolation problems (theory), random graphs, networks

Online supplementary data available from stacks.iop.org/JSTAT/2016/043501/mmedia
1. Introduction

Biological networks, such as gene regulatory networks (GRNs) or protein–protein interaction networks have drawn a lot of attention over the last 15 years [1–4]. More recently
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In a metanetwork, which literally means ‘a network of networks’, the nodes themselves consist of individual networks, or equivalently, ‘graphs’. Links between the nodes of a metanetwork can be defined with reference to the properties of the networks which constitute the nodes, and may be assigned different weights depending on, say, the similarity or the proximity of the nodes which they connect.

A metanetwork of special relevance to evolution and evolvability is the so-called ‘neutral network’, which has been defined as the network of individuals which differ genetically due to point mutations, but which nevertheless exhibit the same fitness or the same phenotype [7–9].

Ciliberti et al [5, 6] have studied the robustness and the capacity for innovation of a population of GRNs (modeled by Boolean graphs [10, 11]), by studying the ‘neutral network’ [8] formed by individuals within one mutational distance from each other and displaying the same same phenotype, namely the same expression pattern. The individual’s genotype corresponds to the wiring of its GRN, and a mutation is a simple alteration thereof. Capacity for innovation arises when the neutral network spans a large portion of the genotype space, and many of its nodes are one mutation away from genotypes which possess novel phenotypes. In their model, the authors define as ‘viable’ those GRNs which, starting from a unique (but arbitrary) initial state eventually reach a single (again arbitrarily chosen) stationary state or ‘attractor’, which represents the phenotype. However, Boolean graphs (discrete cellular automata) may, in general, have many attractors reached from different initial conditions. These different attractors may be shared by different sets of graphs.

This paper has been partially motivated by the fact that computational studies are bound to depend to a lesser or a greater extent on the model, and that testing the ideas of the Ciliberti et al papers on a more complex model would yield new results, as it indeed has. While previous papers have substituted the evolutionary process by a random walk on a neutral network (see, e.g. Nimwegen et al [8]), or a Monte Carlo sampling of a large number of Boolean graphs generated at random [5, 6], our paper specifically addresses evolution under artificial natural selection with respect to a simple but biologically relevant criterion [12]. We can thus show how a collection of disconnected genotypes actually evolves into a connected neutral network on which individuals have the same fitness. Allowing for more complex phenotypes, each corresponding to the set of all attractors of a Boolean graph, gives rise to a complex weighted metanetwork in phenotype space. The metanetwork of artificially evolved graphs within one mutational distance from each other, spans the metanetwork formed in phenotype space by graphs with shared phenotypical features. This metanetwork in phenotype space is super-robust under random removal of bonds as well as under the elimination of weak edges.

The model GRNs, which constitute the nodes of the metanetwork, are small Boolean graphs with a fixed number \( N = 7 \) of nodes (Ciliberti et al use \( N = 8 \) [5] and \( N = 20 \) [6]). The ‘on’ or ‘off’ states of the nodes are denoted by ‘1’s or ‘0’s, hence the appellation ‘Boolean’. They are evolved under selection for short dynamical attractors, with the assumption that only GRN with a predominance of relatively short attractors are viable. The motivation of this choice is as follows: in the context of differentiation into different cell types, where GRNs play a supreme role, it is necessary for the pattern
of gene expression to be maintained stably once the cell differentiates. In the case of genetic switches, which may be components of more complex networks, the GRN may have a few stable states and must be able to cleanly switch between them with some input from its environment [13]. The ‘motif statistics’ [14] of the Boolean graphs evolved under this selection rule bear a close resemblance to those of gene regulatory networks of E. coli, S. cerevisiae and B. subtilis [12]. These statistics have been empirically found to be universal [14] for many different organisms. Our selection rule therefore has a strong biological justification.

In section 2 we present our model, where each Boolean graph displays a collection of attractors, with basins of attraction of different sizes and therefore gives rise to multivalent metanetworks in both genotype and phenotype space; this enables us to study the weighted metanetwork of phenotypes, as well as the metanetwork of genotypes connected via single mutations.

In section 3, we investigate topological properties of the metanetworks in the genotype and phenotype spaces, such as the degree and weight distributions and the extent to which a distinctive structure (which goes beyond random wiring) can be identified by focusing on their \( \kappa \)-core distributions. All results are compared with the null results found for populations of randomly generated Boolean graphs.

For the evolved metanetworks in phenotype space we find an unusual, increasing probability distribution for the degree and strength of the nodes, rather than an exponential or power law decay. This shows that natural selection in its later stages may indeed be indistinguishable from a random walk on a neutral network [8], where the population gets concentrated in areas of high connectivity, i.e. where nodes with a large number of edges are the rule rather than the exception. This can be understood by our finding that the probability distribution for the frequency of occurrence of various attractors within the evolved population is much more sharply peaked than in a random population.

In section 4, we present simulation results regarding the robustness properties under random removal of nodes of the genotype and phenotype metanetworks, i.e. their percolation behavior. Although the genotype network displays correlations at relatively short range (i.e. high clustering coefficients), it essentially behaves like a random graph and is therefore tree-like at large distances, with a large Cheeger’s constant. This means that the evolved metanetwork is a very efficient instrument for sampling the genotype space. In fact the giant cluster of the phenotype metanetwork is completely spanned by the genotype metanetwork, if we require very high similarity between the phenotypes before we can link them. We moreover find that the phenotype networks are super-robust, tending linearly to zero only in the limit of unit probability of node removal. Phenotypic metanetworks prove super-robust under both uncorrelated (random) and under correlated removal of weak bonds.

Conclusions and a discussion are provided in section 5.

In appendix A, we provide the percolation behavior of random graphs for comparison. All terms which might be unfamiliar to non-physics readers have been defined in appendix B and Appendix C. A table of numerical results is provided in supplementary material I (stacks.iop.org/JSTAT/2016/043501/mmedia) and \( \kappa \)-core analyses of all the evolved sets are provided in supplementary material II (stacks.iop.org/JSTAT/2016/043501/mmedia).
2. The model

A gene regulatory network is a collection of genes, corresponding to the ‘nodes’ of this network. The genes interact with each other through the mediation of the proteins which they code. These interactions are represented as directed ‘links’, or equivalently ‘edges’ connecting the nodes. These proteins, which are called ‘transcription factors’, either activate or inhibit the transcription of the target gene whose transcription region they bind. The GRN (or a module thereof, see e.g. the cell cycle module studied by Li et al [15], Davidich and Bornholdt [16]) can be modeled as an automaton which, given a certain initial configuration of ‘on’ (1) and ‘off’ (0) genes, goes through a succession of states and finally arrives at a steady state. This steady state is termed an attractor in dynamical systems literature [17–19] (see appendices B and C for further definitions.). Such models of GRNs have been introduced by Kau mann and coworkers [10, 11] and are termed ‘Boolean graphs’. ‘Graph’ here is synonymous with ‘network’. We will keep to ‘graph’ to avoid confusion with ‘metanetwork’, which is going to be defined as a network connecting these graphs.

To describe how the nodes of a directed graph are connected, we number the nodes from 1 to $N$, and define the ‘adjacency matrix’ $A$, with elements $A_{ij}$. If $i$ and $j$ are connected by a directed edge in that order, $A_{ij} = 1$ and zero otherwise. The set of nodes $\{j\}$ for which $A_{ij} \neq 0$ are the ‘neighbors’ of $i$. The adjacency matrix is the ‘genotype’ of a Boolean graph.

Dynamics (see appendix C) on the Boolean graph is modeled by defining variables $\tau_i$, $i = 1 \ldots N$ which live on the nodes of the graph, and take on the values of 1 or 0, for an active or a passive state of the node, respectively. The ‘state’ of the system (GRN) is given by the vector $\tau = (\tau_1, \ldots, \tau_N)$. To specify the type of interaction (activating or suppressing) between each pair $(i, j)$ of nodes we have defined a matrix with elements $B_{ij}$ such that $B_{ij} = 1$, for a suppressing, or ‘0’ for an activating, interaction respectively.

The interaction matrix $B$ is randomly generated (with equal probabilities for zeros and ones) once and for all in the beginning of the simulations and is the same for all the graphs. In our artificial evolution scheme, mutations only affect the topology of the graphs, by changing elements $A_{ij}$ of the adjacency matrices.

The synchronous updating at each time step $t$ is given by a majority rule,

$$\tau_j(t + 1) = \begin{cases} 
1 & \text{if } \sum_{i} A_{ij}(\tau_i(t) \text{ XOR } B_{ij}) \geqslant N/2 \\
0 & \text{otherwise.}
\end{cases}$$

(1)

Clearly, the outcome at $j$ is only affected by its neighbors.

There are $2^N$ different possible states of the Boolean graph. Choosing each of these states in turn as initial states and following the dynamics, one arrives at a (smaller) set of ‘attractors’, or ‘steady states’. An attractor may consist of one state (a point attractor) or a periodic state (which cycles between a number of states). The set of all attractors of the Boolean graph will be denoted as its ‘phenotype’.

In our model, initial populations of random directed graphs are generated with a uniform edge density $p$. Each graph consists of $N = 7$ nodes. The populations are evolved using a genetic algorithm [20], a standard procedure for solving optimization...
problems with an extremely large number of possibly conflicting degrees of freedom. In the present case, the parameter that is optimized is $a$, the attractor length averaged over all initial states. We select for Boolean graphs that have dominant attractors that are either fixed points or oscillators between two states. These type of attractors we will define as ‘viable’.

The implementation of the genetic algorithm is as follows:

- At each step of the algorithm half of the graphs with the mean attractor length $a \leq 2$ are chosen at random to be cloned.
- The chosen graphs are mutated by the standard edge-swapping approach. We randomly pick two independent pairs of connected nodes and switch either the in- or out-terminals of the edges. Four elements in the adjacency matrix of the graph change as a result. Note that simply deleting some bonds at random would just lead to a decrease of the density of the graph, which trivially leads to a shortening of the average attractor length $a$. Preserving the total number of edges avoids domination by sparse graphs which would trivially lead to a small attractor length. This method also preserves the in- and out-degrees of each node, and prevents graphs from breaking up into smaller graphs.
- An equal number of graphs randomly chosen from the whole population are then removed.

The genetic algorithm was iterated until the average attractor length $a$ stabilized. A steady state population was achieved after 150 iterations on the average (over 16 populations of $10^3$ individuals each). Measurements were taken over a window of 100 steps within the steady state regime ($300 < t < 400$) and at one given point in time ($t = 400$) and averaged over the different populations. We provide the average values and standard deviations of the attractor lengths and the degree of the nodes in table I, supplementary material I. Further details of the simulations are explained in [12]. The codes used in the simulations can be accessed at [23].

It should be stressed that we do not have any intention or claims of modeling the process of evolution of GRNs per se; we employ the genetic algorithm as a generic tool for obtaining a steady state population with optimized values of a chosen parameter. Nevertheless, our definition of a mutation can be interpreted as a ‘speeded up’ shorthand for the process whereby mutations severe certain regulatory interactions while possibly establishing new ones [24, 25].

2.1. The metanetwork in genotype space

The metanetwork in genotype space consists of all the Boolean graphs in a given population (the nodes) and edges between those graphs which have a mutational distance less than or equal to unity.

We define mutational distance $d_{IJ}$ between two Boolean graphs $I$, $J$ as the number of edges that differ from one graph to the other, in terms of the elements of their adjacency matrices, $A^I$ and $A^J$. 

\[ d_{IJ} = \sum_{ij} |A^I_{ij} - A^J_{ij}| \]
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\[ d_{I,J} \equiv \frac{\sum_{k,l} |A_{I,k}^l - A_{J,k}^l|}{4}. \]  

The adjacency matrix $\tilde{A}$ of the metanetwork in genotype space is then given by,

\[ \tilde{A}_{I,J} = \begin{cases} 1, & \text{if } d_{I,J} \leq 1 \\ 0, & \text{otherwise} \end{cases}. \]  

### 2.2. The metanetwork in phenotype space

The metanetwork in phenotype space consists of the set of all Boolean graphs (the nodes) and the set of edges connecting pairs of graphs that have at least one viable attractor in common (see figure 1).

Clearly, if the graphs share more than one viable attractor their phenotypes will be more similar to each other. Moreover, if their common attractors have large basins of attraction (i.e. large numbers of initial states which converge to the attractors they have in common), their overall behavior will be yet more similar. We define the extent of their similarity to be the ‘weight’ of an edge connecting two Boolean graphs,

\[ w_{I,J} = \frac{\sum_{\alpha \in S} |\Omega^{I}_{\alpha}| |\Omega^{J}_{\alpha}|}{(2^N)^2}, \]  

where $|\Omega^{I}_{\alpha}|$ and $|\Omega^{J}_{\alpha}|$ are the sizes of the basin of attraction of a given attractor $\alpha$ in the respective phase spaces of the graphs $I$ and $J$; the summation is over all such common $\alpha$; $S$ is the intersection of their sets of viable attractors. The weights are normalized by the total phase space of the two Boolean graphs.

Figure 1. Illustration of a metanetwork in phenotype space. Each node (Boolean graph) is pictured as a cluster of balls. Balls of the same color correspond to attractors that are shared between graphs associated with the nodes. Their radii represent the size of the basin of attraction of the attractor, for the dynamics at that node. The colored lines represent links in the phenotype space and black lines (where present), links in the genotype space. The thicknesses of the colored edges are proportional to their weights (see equation (4)).
The ‘strength’ of a node is defined [26] as the total weight of edges impinging on the node,

\[ W_i = \sum_j w_{ij}. \]  

(5)

3. Simulations and results

3.1. General considerations

We have performed measurements on 16 independent populations (of size \(N = 10^3\)) of randomly generated connected graphs with \(N = 7\) nodes each and an initial mean edge density \(p = 0.5\). The populations were evolved according to the genetic algorithm described in section 2.

3.1.1. Variability We have taken a large number of independently generated populations so that we are able to monitor the inter-population variability. We found in [12] that independently evolving populations find different solutions to optimizing the average attractor length and end up with different mean degrees (see [12], figure 5). Other features, such as degree distributions, may also vary quite a bit from one population to another, since different populations explore different regions both in the genotype (adjacency matrix) and in the phenotype (attractor) space. The diverse solutions to the same optimization process starting from different initial conditions, as well as the slow, power-law relaxation to the evolutionary steady state, indicates that the fitness landscape is a rugged one [12, 27, 28]. This is a feature encountered in spin glasses [29, 30], a physical system which has a very large number of conflicting constraints. Another source of variability is our finite sample size (10^3).

3.1.2. Size of the population, graph sizes and graph density The exponential growth of the size of the phase space (and therefore the possible number of attractors) with the graph size makes it prohibitively expensive to increase the graph size arbitrarily. Moreover, the topological features, i.e. significance profiles of the evolved graphs are found to be similar to those of the core graphs (the innermost \(\kappa\)-core, see appendix B) of biological networks with varying graph sizes [12]. This suggests that the main topological properties of the biological regulatory networks do not depend strongly on the graph size.

The modular structure of gene regulatory networks [31] with relatively small and denser modules strung together into larger units [32, 33] has further encouraged us to keep the graph size small. The cell cycle module of yeast studied by Li et al [15], Davidich and Bornholdt [16] with \(N = 13\) and \(N = 9\) respectively, is a case in point. The average degree is \(\langle k \rangle = 4.8\) and 4.9, yielding the densities \(p = \langle k \rangle / N = 0.37\) and 0.54. For comparison note that the densities for the whole (known) gene regulatory networks of E. coli, S. cerevisiae and B. subtilis are 0.0016, 0.00065, and 0.0016 respectively [32] while the densities in the innermost \(\kappa\)-core are 0.28, 0.072, 0.089 respectively [12].

We have taken an initial edge density of \(p = 0.5\) (giving an initial mean degree \(\langle k \rangle = 3.5\)), in order to allow for the selection of graphs with shorter attractors out of a
population which potentially has much longer ones. In creating the initial population of random graphs, we independently query whether each pair of nodes are to be connected or not with the initial probability $p$. This results in an initial population of graphs with a binomially distributed number of edges and the average degree can drop (see table I, supplementary material I) in the course of the iterations of the genetic algorithm [12]. Larger graph densities, are known to lead to more chaotic behavior, i.e. longer periods, in the case of finite graphs, with a critical density for the onset of chaoticity growing with the graph size [11, 21, 22, 34–36].

For comparison we provide the results found for null sets consisting of an equal number of random Boolean graphs with the same edge density and with the same Boolean functions assigned to their nodes as the evolved populations (see table I, supplementary material I). The random graphs sample the genotype space in a statistically uniform manner.

### 3.2. Metanetworks in genotype space

In this section we first consider the inter-graph distances in genotype space within the random and evolved populations and establish that only the evolved populations form a sparsely connected metanetwork. The degree distribution of this metanetwork turns out to be Poissonian, as for random networks. We go on to examine further topological properties of these metanetworks and compare them with those of random networks generated \textit{ab initio}. We find that the former indeed exhibit a more complex organization than a random network and to have a larger clustering coefficient, indicating higher short range correlations.

#### 3.2.1. Inter-graph distances in genotype space

The distribution of the pairwise mutational distance $d_{IJ}$ (equation (2)) for populations of the evolved and randomly generated graphs is given in figure 2. The distance takes its maximum value when all the elements of the adjacency matrices of the two networks are different from each other $d_{\text{max}} \equiv N^2/4 = 12.25$ for $N = 7$. For the evolved populations (figure 2(a)), there is a small but finite probability for $d_{IJ} = 1$, so that the graphs can get connected in genotype space. Of the evolved metanetworks 13 out of the 16 populations exhibit a giant component of size $\geq 594$, i.e. spanning 60% or more of the whole population. For the randomly generated populations, $d_{\text{min}} = 2$, so that the metanetwork in genotype space consists only of isolated nodes. (figure 2(b)).

The insets of figure 2 concentrate on one particular population. We consider clusters formed by Boolean graphs sharing a given attractor and plot pairwise distance distributions within the 10 largest such clusters. For the evolved population (figure 2(a)), the distributions corresponding to different attractors are not the same, however they all have a peak at $d_{IJ} = 4$. Some of the distributions exhibit yet another peak at $d_{IJ} = 6$, which coincides with the mean inter-graph distance, $\langle d_{IJ} \rangle$, of the random graphs (figure 2(b)). We conjecture that the two peaks of the evolved set correspond to the inter-cluster and intra-cluster distance distributions.

#### 3.2.2. Degree distribution and other topological properties of the metanetworks in genotype space of evolved populations

The degree distributions (see appendix B) are shown in figure 3. Most of the distributions are approximately Poissonian, which suggests that
these metanetworks might essentially be random [38, 39]. However, comparing the κ-core decompositions (see appendix B) of the metanetwork of an evolved set with that of a random network with the same edge density, we find that they can be quite different (figure 4) and that the evolved metanetwork in genotype space displays a lot more structure. See supplementary material II (stacks.iop.org/JSTAT/2016/043501/mmedia) for the κ-core decomposition of all the other evolved sets.

To compare with random networks, we have also calculated the clustering coefficient. For a random network, the clustering coefficient is equal to the edge density (connection probability) $p$. (see appendix B) For the evolved metanetworks we find the clustering coefficient ranges in $\langle C \rangle \in (0.096, 0.38)$, while the edge density ranges in
$p \in (0.002, 0.044)$, so the clustering coefficient is appreciably higher than expected for a random graph with the same edge density.

In figure 5, we display the distribution of the nodes over the different $\kappa$-shells, for the 16 different evolved populations. Since populations of randomly generated graphs with the same edge density do not form metanetworks in genotype space in general, 16 surrogate random networks of the same size ($N = 10^3$) and with the same steady state edge density have been generated for comparison, and their distributions are also presented in figure 5 as red lines. Distributions for the random networks are narrow and approximately symmetric around the mean shell number. Distributions of the metanetworks formed by the evolved populations are broader, not symmetric around the mean shell number and differ widely from each other due to the ruggedness of the fitness landscape as already discussed above. The mean shell numbers and their standard deviations are given in table I in supplementary material I.

### 3.3. Metanetworks in phenotype space

In phenotype space we find that both the evolved and random graphs form connected metanetworks, with striking differences with respect to the $\kappa$-core organization (evolved metanetworks are much more hierarchically organized). The degree distribution, the extent of similarity between graphs, defined in equation (4) as the ‘weights’ of the edges, the summed weights at each node (the ‘strength’ of each node, equation (5)) all show peaks at high values. The average strength distribution over all the different evolved populations exhibits increasing power law (‘scale free’) behavior. The high frequency of edges (nodes) with higher weights (strengths) for the evolved populations is a mark of the increasing connectivity in the course of evolution, since the metanetwork of random graphs displays exponentially decaying distributions for all these quantities.
3.3.1. Topological properties: $\kappa$-core decomposition and weight distributions  In figure 6, we display the visualization of the $\kappa$-core decomposition of an evolved metanetwork in phenotype space. The corresponding ‘random’ metanetwork is formed using the same rule, equation (4), but on the population of random Boolean graphs with the same edge density as the evolved networks. In carrying out the $\kappa$-core decomposition, we have treated all non-zero weights to be unity. In figure 7, we display the superposed distribution of the nodes over the different $\kappa$-shells. Note that the superposed distribution of the evolved metanetworks shows a linearly increasing trend, i.e. the number of nodes is larger for higher connectivities.

\textbf{Figure 4.} (a) $\kappa$-core decompositions of metanetwork formed by an evolved population in genotype space and (b) random network generated with the same edge density. The plots are obtained using the Large Networks Visualization tool [37]. The color code with the numbers on the side marks the $\kappa$th shell within the network, the sizes of the balls (given on the left) grow with the degree of the node. The evolved population exhibits a more complex organization with seven shells, or levels of connectivity, versus only five for the random version. The $\kappa$-core decompositions for all 16 evolved populations are provided in supplementary material II (stacks.iop.org/JSTAT/2016/043501/mmedia).
In figure 8, we present the weight distributions exhibited by the metanetworks in phenotype space for evolved and random populations. The average weight distribution of the evolved sets (figure 8(a)) is very flat with the prominent peaks at 1 and 0.5 carrying the imprint of the size distribution of the basins of attraction (figure 3.9 in [40]), where, for both the evolved and random sets, approximately 30% of the graphs have a dominant basin of attraction occupying the whole phase space, and another 10% have basins of attraction at half this size. Those graphs with identical attractors occupying the whole of their phase space are joined by edges having $w = 1$, and this gives rise to extremely dominant hubs at the innermost $\kappa$-core of the evolved metanetwork (figure 6(a)). In figure 8(b), the average weight distribution of the random sets shows an exponentially decaying trend with some trace of the peaks in panel (a) still surviving. The less pronounced peaks lead to a loose conglomeration in the $\kappa$-core structure of the random metanetwork (figure 6(b)).

3.3.2. The degree distribution

The degree distributions of the evolved metanetworks are are displayed in figure 9. They are both quantitatively and qualitatively different from the random case, and also from the degree distribution of the evolved metanetworks in genotype space, which are Poissonian. In order to filter out the weakest bonds for better resolution, we have omitted bonds with $w_{ij} < 0.2$ in computing the degree distributions. The degree distributions of the metanetworks in phenotype space vary strongly from set to set. The majority of the individual distributions exhibit two different components, the first being an exponential distribution confined to small $k$, and the second a series of outlier peaks whose height increases with $k$. The degree distribution of the random sets, however, decays exponentially.

3.3.3. The strength distribution and strength-degree correlations

The strength distribution $p_w$ (figure 10) is qualitatively very similar to the distribution of the nodes over the $\kappa$-shells as depicted in figure 7, as well as the degree distribution [26], see figure 9. In fact, it follows from equation (5) that,
If the weight distribution $p_w$ is independent of the degree $k$, as suggested by figure 8(a), then equation (6) simplifies to $W_i = \langle w \rangle k_i$. We have checked that the correlation between the degree and the average weight,

$$c = \frac{\langle w \rangle k_i^2 - \langle w \rangle k_i}{\langle w \rangle k_i},$$



Figure 6. The $\kappa$-core decomposition [37] of the phenotype metanetwork of an evolved (a) and randomly generated population (b). The hierarchical organization of the metanetwork of the evolved graphs, going up to 252 shells, and degrees going up to $\sim 600$ is in stark contrast to the metanetwork of the randomly generated graphs with only 29 shells and largest degree $\sim 120$. (see figure 4 for further explanation of symbols). The $\kappa$-core decompositions for all 16 evolved and random populations are provided in supplementary material II (stacks.iop.org/JSTAT/2016/043501/mmedia).
is indeed small. Here the overbar signifies an average over the nodes $I$, as well as over the independent populations. We find $\langle c \rangle = -0.003$ and standard deviation $\sigma_c = 0.1$ over the sixteen sets.

3.3.4. Degree distribution for different weight thresholds

It is of interest to see how the degree distribution of the metanetwork in phenotype space changes when we require that the weights $w_{I,J}$ exceed certain threshold $\theta$ before we consider the graphs $I$ and $J$ to be connected. We can use this variable, $\theta$, as a ‘filter’ for probing the structure of the metanetworks in phenotype space.

In figure 11(a), we present the combined, log-binned degree distributions of all the 16 evolved metanetworks in phenotype space for different values of $\theta$. The degree distribution of the combined metanetwork has an incipient power law form, $p_k \sim k^{-\gamma}$, albeit...
over a relatively small interval. The novelty here is that for $\theta < 0.8$, one finds $\gamma < 0$, i.e. the distribution increases as a function of the degree. Superposing the 16 random populations and performing a linear binning (bin size = 0.1), the degree distribution is found to be exponential (figure 11(b)).

Examples of networks with increasing rather than decaying power law degree distribution have been observed by Barrat et al [26] for transport networks, with $\gamma = -1$. We observe the same phenomenon for the combined $\kappa$-shell distribution, figure 7(a), and the combined strength distribution, figure 10(a), where, for $\theta = 0$, we have effectively found a linear increase in the shell population with the shell number and the same linearly increasing trend in the probability $p_W$ to encounter nodes with strength $W$.

3.3.5. Convergence to regions of high connectivity in phenotype space The relatively greater probability to find nodes with high connectivity is precisely what one means by a population to concentrate in regions with a high density of edges [8] in genotype

Figure 8. The average weight distributions of the metanetworks formed in phenotype space of the evolved (a) and random (b) populations.
space; in our model, we see that this phenomenon holds also in phenotype space. What is more, we see that as $\theta$ grows, $\gamma$ becomes smaller in absolute value and the degree distribution flattens out. Thus, for sufficiently stringent conditions for edges to form in phenotype space, one ends up with an almost uniform degree distribution. For $\theta \geq 0.8$ we see that $\gamma$ becomes very slightly positive.

It is worthwhile to ask how the much stronger bonding between graphs in the evolved populations arise. The attractors shared by the Boolean graphs in the evolved

Figure 9. Superposed degree distributions of the metanetworks in phenotype space of 16 independent sets (a) of evolved graphs and (b) of randomly generated graphs, for the weight threshold $\theta = 0.2$. For better visibility, the degree distributions for evolved metanetworks in phenotype space have been superposed with an offset to the right on the $k$ axis by $\Delta_i = \langle k \rangle_i - \bar{k}$, where the $i$th set is ranked according to its mean degree $\langle k \rangle_i$ and $\bar{k} = 252$ is the overall average degree with a standard deviation of $\sigma_k = 144$. The offset with respect to the vertical axis is $0.003 \times \Delta_i$. (b) The degree distributions of the corresponding metanetworks for independent sets of randomly generated graphs all display exponential tails on a semi-logarithmic plot and fall right on top of each other, with $\bar{k} = 4.5$ and $\sigma_k = 1.3$.
populations have a narrower frequency distribution than those of the randomly generated populations. In figure 12(a), we display, for 16 independently evolved populations, the normalized incidence, or probability, of different attractors versus their rank. In figure 12(b), the same distribution for randomly generated graphs is displayed for comparison. The convergence to a small set of shared attractors (phenotypes) causes more and stronger bonds to form between the Boolean graphs in the evolved populations.
4. Robustness of the evolved and random metanetworks in genotype and phenotype space

Percolation (see appendix B) on networks [39, 41] has been a central issue since the seminal paper by Albert et al [42] where they showed that scale free networks were resilient to random failure of nodes (say on a power or communications grid) but vulnerable to malicious attack, whereas random graphs exhibited a percolation threshold.
at a finite fraction of removed nodes. A network which retains a finite connectivity until the fraction of removed nodes is taken to unity (while the size of the system is taken to infinity), is called robust.

In this section we first examine the evolved metanetworks in genotype space and both random and evolved metanetworks in phenotype space and their response to the random removal of nodes (note that the random Boolean graphs do not form a connected metanetwork in genotype space). Next we study how the metanetworks in phenotype space, which span essentially the whole population for zero threshold ($\theta = 0$), shrink as the value of $\theta$ is increased, leading to the removal of weak edges. We define the giant component of the evolved metanetwork in genotype space, to be the set of nodes found in the largest component.

Figure 12. The probabilities of occurrence of point and period two attractors in (a) the evolved populations and (b) the randomly generated populations, ranked in order of their incidence. The horizontal axes differ in their scales.
4.1. Random removal of nodes

We have examined the percolation behavior of the evolved metanetwork in genotype space under random removal of the nodes and compared it to those of the random networks generated with the same edge density. For random node removal, the generally accepted practice is that all remaining nodes at any stage are potential targets for removal, regardless of whether they belong to the largest cluster or not. For each successive value of the fraction $f$ of removed nodes, the largest cluster is identified anew.

We define $|G_f|$ to be the size of the largest connected component in the evolved genotype metanetwork, and plot it against the fraction of removed nodes, $f$ in figure 13. The ordinate is normalized by its value at $f=0$, namely $|G_f|^0$. The percolation behavior of the evolved genotype metanetwork is similar to that of a random network [41, 43], although it has a relatively high clustering coefficient compared to random graphs (see section 3.2.2). These short range correlations may be what modifies the percolation behavior from being perfectly linear, as they do for a finite random graph (see appendix A, figure A1). It is reasonable to deduce that, at larger scales, these stochastic networks have a tree-like structure as do the random graphs [39].

The dependence of the size of the giant component in the phenotype space, $|G_p|$, on the fraction of removed nodes, $f$, is shown in figure 14, for evolved and random populations. The normalization is again by the $f=0$ value, namely $|G_p|^0$. For the evolved populations at fixed $\theta = 0.2$, we see that $|G_p|^f/|G_p|^0$ decreases monotonically and essentially linearly with $f$ (figure 14(a)) and converges to zero when $f=1$. This is in contrast to the exponential approach (with a zero slope) to $|G_p|^f/|G_p|^0 = 0$ at $f=1$, found for scale-free networks [42]. The linear descent to zero at $f=1$ is what we have called super robustness.
The evolved phenotype metanetworks display, for most populations, a combination of Poisson-like behaviour at very small $k$ and then a small number of $\delta$-function peaks at some chosen $k$ values (see section 3.3.2 and figure 9(a)). The $\delta$-peaks in the degree distribution of the individual sets correspond to clique-like clusters. Under random removal of nodes, these tight clusters are super-resilient and do not fragment. Their size simply shrinks at the same rate as the total number of nodes being removed, giving rise to the linear dependence with unit negative slope that is observed in figure 14(a).

The corresponding metanetwork for a random population displays a percolation threshold at $f_c \approx 0.81$ (figure 14(b)). For comparison we have performed surrogate
simulations on random graphs of the same size, and with the same expected edge density. These are reported in appendix A. The random graph figure A1 shows classical percolation behavior at $f_c \approx 0.80$, in close similarity with figure 14(b).

It should be noted that the nodes of the metanetwork over the populations of random graphs are not featureless and entirely interchangeable with each other. Although consisting of random networks of seven nodes each, they have a dynamics of their own, with the same interaction matrix $B$ as provided to the evolved networks. After all, the set of attractors of the evolved and random sets are not completely disjoint, as can be seen from figure 12. Therefore we cannot totally eliminate the possibility of correlations between the edges of the metanetwork in phenotype space for random
populations, and this could lead to a slight departure from perfectly classical behavior, \( |G_0|/|G_0|_0 \sim (f_c - f) \), as was also observed for \( |G_1|/|G_1|_0 \), in figure 13.

4.2. Raising the edge weight threshold in phenotype space

The giant component of the metanetwork in phenotype space comprises 100\% of the nodes for \( \theta = 0 \). As the value of \( \theta \) is changed, the largest connected component shrinks and may even loose out to a smaller one; \( |G_\theta| \) is always measured on the largest surviving cluster. The dependence of \( |G_\theta| \) on the threshold \( \theta \) for the phenotype metanetworks for evolved and random populations are shown in figure 15, for \( 0 < \theta \leq 1 \). Many evolved metanetworks (figure 15(a)) persist all the way up to \( \theta = 1 \) and even hit the ordinate at a finite value for some sets, thanks to the prevalence of edges with \( w = 1 \) (figure 8(a)). Beyond \( \theta = 0.72 \) the giant component of the evolved metanetwork has shrunk in relative size to 50\% on the average. For larger \( \theta \) values, this giant component breaks up into relatively small, strongly connected clusters, each of which can be thought of as a small population with a distinct phenotype.

The giant component of the genotype metanetwork for evolved populations continues to span 89\% of the total population on the average (except for the three populations out of 16 which do not have large connected components in their evolved genotype networks). Thus, even when the phenotype metanetwork has fragmented under very stringent conditions (large \( \theta \)) the giant component of the evolved genotype network connects essentially all of the different phenotypic clusters.

The giant components for the random populations shrink much faster and exhibit a phase transition in the size of the giant component around \( \theta \approx 0.5 \), see figure 15(b).

5. Conclusion

Nimwegen et al [8] have argued that under ‘neutral evolution’ [7] (see appendix B) modeled by a random walk on a metanetwork in genotype space, the population will tend to concentrate in regions of the metanetwork where the nodes have a large number of edges. In fact, this is true for any random walk on a network. The localization of a random walk on nodes with large degrees can be demonstrated by solving the discrete diffusion equation on a network.

An individual residing on a node with a large number of neighbors has a good chance to still stay on the ‘neutral network’ (i.e. will still be fit) in case it suffers a point mutation. Hence, the concept of ‘high mutational robustness’ is defined as the ‘average degree’ of nodes on the neutral network, where the average is weighted by the size of the number of individuals residing on the nodes (see [7, 9] and appendix B). This just means the average number of edges seen by individuals on the network. Therefore, a population undergoing ‘neutral evolution’ experiences an increase in the average degree, due to the localization of the population on nodes with large degrees, and by definition acquires high mutational robustness.

It should be noted, however, that the existence of an extended connected (meta)network in genotype space is not self-evident. We have shown that the metanetwork of random Boolean graphs consists of isolated nodes which do not form a connected
cluster spanning any appreciable portion of the genotype space; therefore one cannot explore the phenotype space effectively with single-mutation steps. In our model system, it is only evolution under the genetic algorithm that leads to populations of Boolean graphs where the giant connected cluster spans 60–100% of all the genotypes in the population, for almost all the populations.

Although the evolved metanetwork in genotype space has a higher than expected clustering coefficient for an essentially random-like graph, this is a relatively short-range effect, and at larger scales [39] the metanetwork has a tree-like structure. It is known that tree-like networks are the most efficient structures for spanning a given set of nodes, and are the basis of efficient search strategies on an unknown network. The efficiency goes up with the Cheeger constant [44], defined as the minimum ratio of the ‘surface’ nodes of a non-trivial subset of the network to the number of nodes contained within such subsets; it is thus a measure of the ‘expansion’ of the graph. Thus, an evolved metanetwork in genotype space is very efficient in probing the phenotype space. This is an example of the ‘evolution of evolvability’, [9].

Evolved metanetworks in phenotype space maintain a high degree of connectivity in the face of both correlated removal of weak edges and random removal of nodes. Both these processes have their analogues in evolutionary scenarios. The random removal of a large fraction of nodes is similar to a large scale catastrophe which indiscriminately destroys most of the population. The metanetworks in phenotype space are ‘super robust’ (they retain their integrity in the Albert et al [42] sense) under random elimination of nodes, with the relative size of the giant component tending linearly (rather than exponentially) to zero as the fraction of removed nodes approaches unity. Thus, in an evolved population, even for a death rate approaching unity, a finite fraction of the largest connected cluster in phenotype space will survive, besides isolated individuals. For a random population, all the survivors, if any, will be phenotypically disconnected. The former case means that, in a ‘great catastrophe’ scenario, a genetically related and phenotypically similar small community has a finite chance for survival.

The connectivity (degree and strength distributions) of the metanetworks in phenotype space depend upon the weight threshold $\theta$, which means the extent to which two phenotypes have to be similar to each other before they can be considered ‘connected’. In the ensemble of independently generated populations, for small values of $\theta$ (say $\theta = 0.2$), the averaged probability of having a degree $k$, increases with increasing $k$, having a putative power law scaling form $p_k \sim k^{-\gamma}$, with $\gamma < 0$, rather than an expected positive value as in many scale-free networks [39]. The weight and strength distributions, figures 8 and 10, also exhibit power laws with negative $\gamma$. This unusual behavior, also found for transport networks [26], leads to a clear dominance of hubs and to super-robust behavior in the face of random attack. For larger $\theta$, the exponent gradually crosses over to the usual power law decay, with $\gamma > 0$.

Filtering out phenotypic bonds weaker than a given threshold would correspond, e.g. to increased selection pressure sharpening the peaks in the fitness landscape. Tightening the minimum requirements (raising the minimum size of the basins of attraction of the shared attractors) for the identification of shared features, corresponds to stipulating that these features themselves should not vary due to variations in the ‘initial conditions’ or environmental inputs.
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Appendix A. Finite size effects

To estimate the finite size effects in the percolation behavior for random removal of vertices in metanetworks in phenotype space of random Boolean graphs, we have done independent simulations over 16 different sets of random graphs with the same number \(10^3\) of nodes and edge density \((\langle k \rangle)/N = 0.0046\) as in figure 13(b). In figure A1, the percolation threshold can be read off from extrapolating the linear part of the average curve in the inset, to be \(f_c = 0.80\). This matches the value which we obtain by following the steepest slopes of the individual curves and is also very close to the percolation threshold found in figure 14(b).

Appendix B. Definitions: networks

A network consists of nodes and edges (equivalently called ‘links’), which may be directed or undirected, connecting the nodes. A network can alternatively be called a graph. In this paper we study metanetworks, which are networks of networks. To avoid confusion we have used the term graphs for the small networks which constitute the nodes of the metanetwork.

A random graph is generated by randomly connecting each pair of nodes with a connection probability \(p\). The mean degree for a random graph is therefore \(\langle k \rangle = pN\). Clearly \(p\) is also equal to the edge density (expected number of edges divided by the total number of possible pairs, \(1/2N(N - 1)\) if self-connections are not allowed).

The number of edges connecting a node to other nodes (or to itself) is called its degree. The degree distribution, denoted by \(p_k(k)\) in this article, is the probability of encountering a node with the degree \(k\). The mean degree is \(\langle k \rangle = \sum_k kp_k(k)\). The clustering coefficient of nodes with \(k\) neighbors is defined as \(C_k = 2e_k[\langle k(k - 1) \rangle]; e_k\) is the expected number of edges interconnecting the \(k\) neighbors and it is normalized by the number of distinct pairs of neighbors. The average clustering coefficient of a network is defined as \(C = \sum_k p(k)C_k\). Since, for random graphs, \(e_k = \frac{1}{2}k(k - 1)p\), substituting in the above expression for \(C_k\) immediately gives \(C_k = p\), and therefore \(C = p\).

A network is a ‘tree’ if it does not have any loops. Random graphs are known to have a ‘tree’-like structure at large distances. [39]

It is possible to decompose a network into successive shells of lower to higher connectivity. This is termed \(k\)-core analysis [38, 45]. We have used the Greek letter \(\kappa\) in this article so that there is no confusion with the degree \(k\). The prescription is as follows. (i) Disconnect all nodes which have degree one. (ii) Repeat the process until no nodes of degree one remain. (iii) Label all these nodes as the first shell. (iv) Repeat this process for degree 2, 3, etc, labeling the severed nodes accordingly as belonging to the \(\kappa = 2, 3, \ldots\)-shell until no nodes remain. Those shells with \(\kappa\) greater than some given value, say \(\kappa’\), are called the \(\kappa’\)-core. The shell with the largest value of \(\kappa\) on that network will constitute the innermost \(\kappa\)-core.
Percolation is sometimes called a geometrical phase transition, in that it describes the quite sudden appearance of a far-reaching connected cluster at some point in the random addition of individual links between the members of a set. The largest cluster which interconnects a major portion of the nodes of a graph is called the giant component. The density of edges at which a giant component just appears is called the percolation threshold. One may also study the reverse process, of randomly removing links until no giant component remains.

In network theory, a network is termed robust under random removal or nodes (edges), if it retains a connected cluster containing most of the nodes, a giant component, even in very late stages of decimation. For a robust network, the proportion of removed nodes (edges) before total breakdown tends to unity as the number of nodes tends to infinity. This behavior has been demonstrated for scale free networks by Albert et al [42]. Random networks, in contrast, disintegrate into many nodes or very small clusters at intermediate stages of node (edge) removal.

Kimura [7] has introduced the concept of neutral evolution, a random walk on a 'neutral network', whose nodes are the connected set of relatively high fitness genotypes. Pairs of nodes are connected by an edge only in case they differ from each other by just a single mutation. In this context, the mutational robustness of a population subject to mutations is defined as the average probability that an individual continues to reside on the neutral network after suffering a random mutation [8]. The probability that an individual continues to reside on the high-fitness neutral network is equal to the probability $p_r$ that a random mutation takes it to a neighboring site. This probability is proportional to the number of links to neighboring sites (i.e. the degree) of the original site. For uncorrelated networks, the average probability $\langle p_r \rangle$ is clearly the number of links times the number of individuals at that site, summed over all the sites, normalized by the total population.
Appendix C. Definitions: dynamical systems

A finite dynamical system with discrete states is called an automaton. An automaton may be represented as a network consisting of nodes and edges. The nodes may take on different values. In this paper the nodes of the gene regulatory networks (GRNs) will be modeled by the discrete, Boolean values 0 or 1, corresponding to a gene being off or on. As explained in section 2, the state of an automaton is a list of the values of its nodes. The edges and some logic functions at the nodes, represent the interactions between the nodes of this Boolean graph.

In this paper we adopt a synchronous dynamics, which means that given any state of the automaton, an updating rule (see section 2) which updates the values of all the nodes simultaneously, determines the next state of the automaton, and then the next state and so on. The succession of states under this dynamics is called a trajectory. The number of possible states of an automaton is called its phase space. The phase space of a such a discrete, finite automaton has to be finite (in fact $s^N$ for a graph with $N$ nodes and $s$ possible states for each node). Therefore, any trajectory eventually has to repeat itself, i.e. is at most periodic.

In many cases, trajectories starting from many different states converge on one fixed point where all change ceases. This state is called a point attractor. There may also be collections of states whose trajectories eventually end up on an ordered set of states which keep cycling. This set of states is called a periodic attractor. We will call the cardinality of this ordered set the length of the periodic attractor. Clearly the length of a periodic attractor can at most be the size of the phase space, but in general it is much smaller. The collection of states which end up either in a point or a periodic attractor is called the basin of attraction of this attractor.

The phase space is partitioned into as many different basins of attraction as there are attractors. If the system is in a steady state (fixed point or periodic attractor) and an external intervention alters the state of the system and takes it to some other state within the basin of attraction of this attractor, then the system will return to its steady state. This means it is stable. It may be that the intervention takes the system to a state in a different basin of attraction. In this case it will flow to a new attractor. There may also exist isolated fixed points, to which no trajectory flows; such fixed points are unstable, i.e. once perturbed to any neighboring state, the system will eventually find itself in some other fixed point or periodic attractor.

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