Title: Self-organization can guide natural selection

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**Abstract:**

Developmental dynamics in Boolean models of gene networks self-organize, either into point attractors (stable repeating patterns of gene expression) or limit cycles (stable repeating sequences of patterns), depending on the network interactions specified by a ‘genome’ of evolvable bits. Genome specifications for dynamics that can map specific gene expression patterns in early development onto specific point attractor patterns in later development are essentially impossible to discover by chance mutation alone, even for small networks. We show that selection for approximate mappings, dynamically maintained in the states comprising limit cycles, can accelerate evolution by at least an order of magnitude. These results suggest that self-organizing dynamics that occur within lifetimes can in principle guide natural selection between lifetimes.

**One Sentence Summary:**

Intrinsic properties of network self-organization can accelerate natural selection by smoothing fitness landscapes.

**Main Text:**

Self-organization and natural selection are fundamental forces that shape all biological systems. Self-organization occurs when global order in the dynamics of a network cannot be predicted by inspection of the local network interactions in isolation. Self-organization therefore describes dynamics that occur across all spatial and temporal scales throughout the lifetimes of all organisms. Natural selection is instead a description of dynamics that occur primarily between lifetimes, via the communication of genetic information from organisms to their offspring. It is clear how natural selection can operate on the self-organizing processes by which organisms develop and compete, because information communicated via the exchange of DNA sequences specifies the interactions within and between those processes. But the extent to which self-organization can operate on natural selection is not yet understood. Here we show that fitness landscapes can indeed be modified by the intrinsic properties of dynamical network self-organization, via a simple, biologically plausible mechanism that is compatible with conventional descriptions of evolution by natural selection.

Consider a network of interacting genes and assume for simplicity that their expression levels may be either high or low only. A network of interactions can be specified by assigning to each gene a truth table that determines its expression level in response to each of the possible patterns of expression. The network can thus be completely specified by a ‘genome’ comprising binary digits, for which there are possible configurations. See Fig. 1A.

The dynamics in these networks self-organize to reveal attractors (*1,2*). From a given initial state (a state is a pattern of binary expression levels), the network activity will eventually settle, either into an endless repetition of a single state, known as a point attractor, or into a limit cycle, where a specific sequence of states repeats endlessly. In the broadest terms, different initial states represent different environmental contexts in which the network dynamics may develop, as determined by factors extrinsic to the network, such as the transient influence of another gene or gene network, differences between cell or tissue types, or different chemical or temperature conditions. Thus we might consider a mapping from a given initial state to a point attractor to constitute a robust response of the network to that environmental context. The problem is then for natural selection to configure an -dimensional genome such that the resulting network interactions will map a given set of initial states to a given set of point attractor states.

An instructive example was considered by Giacomantonio & Goodhill (*3*), concerning the interactions between genes Fgf8 (*4,5*), Emx2 (*6-8*), Pax6 (*8,9*), Coup-tf1 (*10,11*), and Sp8 (*11,12*), which specify position information in the embryonic neocortex and ultimately guide the growth of thalamocortical axons by chemoattraction (e.g., (*13,14*); see (*15,16*) for reviews). At embryonic day 9.5 (E9.5), before the other transcription factors are known to be expressed, the telencephalic morphogen Fgf817 is secreted only at the anterior neural ridge of the developing forebrain (*5*) (see (*15*) for a review). Together with other signalling molecules and patterning centers, the secretion of Fgf8 at E9.5 induces the graded expression of Emx2, Pax6, Coup-tf1, and Sp8 in the progenitor cells in the ventricular zone. Interactions between these genes yield posterior to anterior gradients in Emx2 and Coup-tf1 expression and anterior to posterior gradients in Pax6 and Sp8 expression. Hence, in two environment contexts, defined by the differential expression of Fgf8, genes map initial state [00000] to the target point attractor [01010] in the posterior, and map initial state [10000] to the target point attractor [10101] in the anterior (bits ordered as the names of the genes are listed above). See Fig. 1B.

By chance mutation alone, the problem of finding a genome configuration to facilitate such developmental dynamics is very difficult. Even for genes, the genome is of length , and there are possible configurations. An exhaustive search reveals that 11384 of these (0.068%) map differential expression of one gene to differential expression of genes, e.g., mapping initial states [000] and [100] to point attractors [010] and [101]. Current computing power does not allow for an equivalent figure to be determined by exhaustive search of the genome spaces for more than three genes.

However, the problem becomes tractable for larger networks if we assume that self-organization and natural selection are able to interact, as follows. Starting with a random genome, a network of genes () might from some initial state, e.g., [00000], settle into a particular limit cycle, e.g., [11000] then [00011] then [01011], before repeating [11000] and continuing indefinitely. Thereafter the five genes will be expressed in the following proportions: 1/3, 2/3, 0/3, 2/3, 2/3. These values correspond to the relative production rates of five proteins. If the target point attractor state is e.g., [01010], then the protein production levels are ‘correct’ in the following proportions: 2/3, 2/3, 3/3, 2/3, 1/3. The product of these values thus represents the extent to which downstream processes will be orchestrated by the correct distribution of proteins, and as such it can be used as a measure of the fitness of the genome,

where indexes states comprising the attractor for initial state , and is the target level of gene expression.

In simulation, states can be identified simply by iterating the network dynamics times (to guarantee that an attractor is reached) and then iterating a further times until a repetition is detected. Natural selection can then be represented in its simplest terms by flipping each of the genome bits with probability , accepting the modified genome if , and repeating the process for each simulated generation. Note that only if all initial states map to the target states as point attractors, that if any gene is not expressed correctly in any of the states into which any of the initial states are attracted, and that setting defines a control condition equivalent to sampling genomes at random.

Evolving for a total of simulated generations at each mutation rate, from to at increments of 0.05, revealed dynamics similar to ‘punctuated equilibria’ (*18,19*), whereby long periods of stasis () were punctuated by increments in fitness (see Fig. 1C). At each mutation rate, the distribution of the number of generations required to discover a maximally fit genome () was long-tailed, conforming increasingly to a log-normal distribution for smaller values of , i.e., for an increasingly local search of the genome space (see Fig. 1D). At , the number of genomes discovered was 70 times greater than by random sampling (), with discovery taking 853 generations on average. Reducing the mutation rate further (i.e., flipping an average of 6 or less bits per generation) reduced the evolutionary speed-up. Overall, the average number of generations, , required to discover networks was well approximated by .

These results show that self-organization can accelerate selection under the assumption that dynamically stable protein production levels that are more similar to ideal levels yield better fitness. Under this assumption, approximate network solutions that emerge within a lifetime as limit cycle attractors can provide a scaffold of graded fitness around otherwise isolated peaks in the fitness landscape, for natural selection to climb. We thus refer to this mechanism as *attractor scaffolding*. Self-organization can only assist selection via attractor scaffolding if the embedding of attractor landscapes in the -dimensional genome space is locally structured, as is evidenced here by further accelerations in the discovery of genomes at lower mutation rates, i.e., as the search through genome space is more local.

The effect of self-organization by attractor scaffolding resembles that presented by Hinton & Nowlan (*20*). In their seminal model, some genome bits are adaptable within the lifetime of each member of a population, and their genomes are recombined with a probability that decreases with the number of flips of these adaptable bits before a target genome is discovered. The state of adaptable bits is not inherited, but inheritance of the ability to flip state nevertheless increases the discovery rate. Faster discovery of target states within lifetimes therefore directs selection pressure in favour of genetic conditions from which targets can be more rapidly acquired. Attractor scaffolding confers a similar advantage; in both cases an approximation to the target is maintained within the lifetime and communicated only indirectly between lifetimes. An important distinction is that by attractor scaffolding the benefit of distributing approximate solutions across limit cycle states, rather than across members of a population, is conferred by developmental dynamics intrinsic to individual organisms.

Attractor scaffolding offers a potential mechanism for genetic assimilation, i.e., by the gradual evolution of limit cycle dynamics towards point attractor dynamics, and thus it might support a range of epigenetic phenomena, such as the Baldwin effect(s) (*21-24*). More specifically, scaffolding may play a role in determining the ‘molecular logic’ (*3,15,25,26*) by which genes responsible for the embryonic development of neocortical circuits interact. And similar principles may help to explain how intrinsic properties of network self-organisation constrain the postnatal development of functional neuronal networks to be highly conserved amongst lineages separated by millennia (*27-30*). Practical applications may involve new methods for programming large circuits of logic operations; for example, we found that an circuit, for which the space of configurations comprises possibilities, can be configured to robustly map three initial states to three distinct target states in a few million computationally inexpensive steps.

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**List of Supplementary Materials:**

Auxiliary Supplementary Materials.

**Supplementary Materials:**

*Auxillary Supplementary Materials.*A standalone c++ implementation of the model and a python script for recreating Figure 1D from the main text. Download the files and from the command compile using e.g., ‘g++ -O3 evolve.cpp -o evolve’, run the model using ‘./evolve’, then plot using ‘python plot.py’. This standalone program is part of the full code and analysis available in the repository: https://github.com/ABRG-Models/AttractorScaffolding

Figure1.pdf

**Figure 1.** *Self-organization accelerates natural selection*. **A** A network of interacting genes are shown labelled a–e, each with inputs labelled i–v. The (partial) truth table determines the expression level of each gene in response to each pattern of gene expression, and the coloured elements thus constitute the ‘genome’, here specifying a maximally fit network (). **B** The dynamics of this network reveal five attractors (one with a limit cycle of length two). Every possible gene expression pattern is represented by one dot, and the transitions between them are represented by arrows. Initial states [10000] and [00000] map to target states [10101] and [01010] as point attractors. **C** Evolution of ten genomes by attractor scaffolding (mutation rate ), with the generations at which aligned to zero; evolution yields long periods of stasis punctuated by sharp fitness increments. The bold trace shows the evolution that gave rise to the network in the preceding panels. **D** Distribution of generations required to discover networks at a range of mutation rates ( corresponds to random search). Lower mutation rates search more locally, and increasingly accelerate evolution.