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Accessibility
Universality of fixation probabilities in randomly structured populations

Ben Adlam & Martin A. Nowak

The stage of evolution is the population of reproducing individuals. The structure of the population is known to affect the dynamics and outcome of evolutionary processes, but analytical results for generic random structures have been lacking. The most general result so far, the isothermal theorem, assumes the propensity for change in each position is exactly the same, but realistic biological structures are always subject to variation and noise. We consider a finite population under constant selection whose structure is given by a variety of weighted, directed, random graphs; vertices represent individuals and edges interactions between individuals. By establishing a robustness result for the isothermal theorem and using large deviation estimates to understand the typical structure of random graphs, we prove that for a generalization of the Erdős-Rényi model, the fixation probability of an invading mutant is approximately the same as that of a mutant of equal fitness in a well-mixed population with high probability. Simulations of perturbed lattices, small-world networks, and scale-free networks behave similarly. We conjecture that the fixation probability in a well-mixed population, \( \frac{1 - r^{-1}}{1 - r^{-n}} \), is universal: for many random graph models, the fixation probability approaches the above function uniformly as the graphs become large.

In physics, a system exhibits universality when its macroscopic behavior is independent of the details of its microscopic interactions\(^1\). Many physical models are conjectured as universal and long programs have been carried out to establish this mathematically\(^2,3\). However such universality conjectures have been lacking in biological models.

It is well known that population structure can affect the behavior of evolutionary processes under both constant selection\(^4-10\), on which we focus here, and frequency dependent selection\(^11-23\). However, so far deterministic and highly organized population structures have received the most attention\(^24-28\); while some populations are accurately modeled in this way\(^29-33\), often a random structure is far more appropriate to describe the irregularity of the real world\(^34-37\). Random population structures have been considered numerically, but analytical results have been lacking\(^7,13,38\).

The Moran process considers a population of \( n \) individuals, each of which is either wild-type or mutant with constant fitness 1 or \( r \) respectively, undergoing reproduction and death\(^39\). At each discrete time step an individual is chosen randomly for reproduction proportional to its fitness; another individual is chosen uniformly at random for death and is replaced by a new individual of the same phenotype as the reproducing individual. In the long run, the process has only two possible outcomes: the mutant fixes and the wild-type dies out or the reverse. When a single mutant is introduced randomly into a homogenous, wild-type population, we call the probability of the first eventuality the fixation probability.

Fixation probabilities are of fundamental interest in evolutionary dynamics\(^40\). For a well-mixed population as described above, the fixation probability, denoted

\[
\rho_{M_n}(r) = \frac{1 - r^{-1}}{1 - r^{-n}},
\]

depends on \( r \) and \( n \)\(^{41,42}\). Fixation probabilities also depend on population structure\(^43,44\), which is modeled by running the process on a graph (a collection of \( n \) vertices with edges between them) where vertices represent individuals and edges competition between individuals. Population structure forces reproducing individuals to replace only individuals with whom they are in competition, as described by the graph, and thus death is no longer uniformly at random but among the reproducing individual’s neighbors. See the SI for details.

With this enrichment of the model, the effects of population structure can be understood. Simple one-rooted population structures are able to suppress selection and reduce evolution to a standstill, while intricate, star-like
structures can amplify the intensity of selection to all but guarantee the fixation of mutants with arbitrarily slight fitness advantages. The former has been proposed as a model for understanding the necessity of hierarchical lineages of cells to reduce the likelihood of cancer initiation. Some population structures have fixation probabilities which are given exactly by and a fundamental result, called the isothermal theorem (stated precisely in Theorem SI.1.1), gives conditions for this. As a special case of these conditions are all symmetric population structures or graphs with undirected edges. More generally, a graph is called isothermal if the sums of the outgoing and ingoing edge weights are the same for all subsets of the graph’s vertices (or equivalently if a graph’s weighted adjacency matrix is doubly stochastic). This is our first hint of universality but it was not the first time certain quantities were observed as independent of population structure. Maruyama introduced geographical population structure by separating reproduction, which occurs within sub-populations, and migration, which occurs between sub-populations, and found that the fixation probability was the same as that of a well-mixed population structure. In the framework of evolutionary graph theory, Maruyama’s model would correspond to a symmetric graph. In this sense his finding is a special case of the isothermal theorem.

However, the assumptions of the isothermal theorem sit on a knife edge—when any small perturbation is made to the graph, the assumptions no longer hold and the original isothermal theorem is silent. In particular, it cannot be applied to directed, random graphs. We address these shortcomings in Section SI.1, where we strengthen the forward direction of the isothermal theorem by proving a deterministic statement: we weaken the theorem’s assumptions to be only approximately true for a graph and show that the conclusion is still approximately true, that is, the fixation probability of a general graph is approximately equal to . We call this the robust isothermal theorem (RIT).

**Theorem** (Robust isothermal theorem). Fix . Let \( G_n = (V_n, W_n = \{w_{ij}\}) \) be a connected graph. If for all nonempty \( S \subseteq V_n \) we have

\[
\frac{w_O(S)}{w_I(S)} - 1 \leq \epsilon,
\]

where \( w_O(S) = \sum_{i \in S} \sum_{j \notin S} w_{ij} \) and \( w_I(S) = \sum_{i \notin S} \sum_{j \in S} w_{ij} \) are the sums of the outgoing and ingoing edges respectively, then

\[
\sup_{r > 0} |\rho_{M_n}(r) - \rho_{G_n}(r)| \leq \epsilon.
\]

The proof begins by ignoring spacial structure and considering only the number of mutants. Since \( \rho_{G_n}(r) \) depends only on the ratio of the probability of increasing to the probability of decreasing the number of mutants for each subset, a bound on these ratios and a coupling argument establish that \( \rho_{G_n}(r) \) is close to \( \rho_{M_n} \). Finally, the mean value theorem and smoothness properties of \( \rho_{M_n} \) simplify the bound and yield the result. We remark that assumption (2) is necessary in the sense that there are graphs whose fixation probability is far from \( \rho_{M_n}(r) \) but whose weighted adjacency matrix is arbitrarily close to being doubly stochastic (see SI.1.10) for an example.

![Figure 1](https://www.nature.com/scientificreports)
The proof verifies something essential for the process: as in physics, our laws should not depend on arbitrarily small quantities nor make disparate predictions for small perturbations of a system. The RIT generalizes the isothermal theorem in this sense; if an isothermal graph is perturbed with strength \( \varepsilon \) such that the assumption (2) holds, then its fixation probability is close to that of the original graph (Figure 1). There are many ways of rigorously perturbing a graph, so we do not make a precise definition of perturbation here. All we claim is that any perturbation which changes the assumptions of the RIT generalizes the isothermal theorem in this sense; if an isothermal graph is perturbed with strength \( \varepsilon \) such that the assumption (2) holds, then its fixation probability is close to that of the original graph (Figure 1). There are many ways of rigorously perturbing a graph, so we do not make a precise definition of perturbation here. All we claim is that any perturbation which changes the assumptions of the RIT continuously can be controlled. The RIT has many useful applications and is our first ingredient to universality.

Robustness is essential for the analysis of random graphs. We say a random graph model exhibits universal Moran-type behavior if its fixation probability behaves like \( \rho_{M_r}(r) \) as the graph becomes large. That is, as the graphs become large their macroscopic properties, fixation probabilities, are independent of their microscopic structures, the distributions of individual edges. Mathematically, we ask that the random variable \( \sup_{r \geq 0} |\rho_{G_r}(r) - \rho_{M_r}(r)| \) converges in probability to 0, as \( n \) goes to infinity. For finite values of \( n \), we can require finer control over this convergence such that

\[
P\left[ \sup_{r \geq 0} |\rho_{G_r}(r) - \rho_{M_r}(n,r)| \leq \delta(n) \right] = 1 - \varepsilon(n),
\]

where the functions \( \delta(n) = o(1) \) and \( \varepsilon(n) = o(1) \) can be specified. For the generalized Erdős-Rényi model where edges are produced independently with fixed probability \( p \) (see Definitions SI.2.4 and SI.4.1) we prove universality. In Sections SI.2 and SI.4 we analyze the typical behavior of random graphs and show that with very high probability they satisfy the assumptions of the RIT, giving us the paper’s main result:

**Theorem.** Let \( (G_n)_{n \geq 1} \) be a family of random graphs where the directed edge weights are chosen independently according to some suitable distribution (the outgoing edges may be normalized to sum to 1 or not). Then there is a constant \( C > 0 \), not dependent on \( n \), such that the fixation probability of a randomly placed mutant of fitness \( r > 0 \) satisfies

\[
|\rho_{G_r}(r) - \rho_{M_r}(r)| \leq \frac{C(\log n)^{C + C_\xi}}{\sqrt{n}}
\]

uniformly in \( r \) with probability greater than \( 1 - \exp(-v(\log n)^{C_\xi}) \), for some positive constants \( C_\xi \) and \( v \).

The proof applies the RIT to random graphs, showing that with high probability they satisfy assumption (2) with \( \varepsilon \) approximately order 1/\( \sqrt{n} \). This relies on two main results. Using large deviation estimates, we show that the sum of the ingoing edge weights to each vertex (its temperature) are within approximately order 1/\( \sqrt{n} \) of 1...
values of $b$ and them exactly, so that 1-rooted graphs were given fixation probability rather than estimating their fixation probabilities, we calculated Degenerate graphs were not excluded from the simulations but proportion of times that the mutant fixed in the simulation.

Figure 3 | Small-world networks also show universal behavior. Representative Watts-Strogatz random graphs display increasing disorder as the rewiring probability $\beta$ increases from 0 to 1, which may be viewed as an interpolation between an isothermal graph and an Erdős-Rényi random graph. For all values of $\beta$ the correspondence to $\rho_{M\hat{}}$ is striking but mathematical proof is lacking.

with high probability (Lemma sl.2.7) and that sum of the outgoing (and ingoing) edge weights of each subset are at least the same order as the size of the subset or its complement for some uniform constant with high probability (Lemma s1.2.8).

This theorem isolates the typical behavior of the Moran process on these random structures. It can be interpreted as stating that random processes generating population structures where vertices and edges are treated independently and interchangeably will almost always produce graphs with Moran-type behavior. While such processes can generate graphs which do not have Moran-type behavior (for example one-rooted or disconnected graphs), these graphs are generated with very low probability as the size of the graphs becomes large. Moreover, it improves upon diffusion approximation methods by explicitly controlling the error rates46.

The result holds with high probability but sometimes this probability becomes close to 1 only as the graphs become large. The necessary graph size depends on the distribution from which the random graph’s edge weights are drawn. In particular, it depends inversely on the parameter $p$ from the generalized Erdős-Rényi model, which is the probability that there is an edge of some weight between two directed vertices. The smaller this parameter the more disordered and sparse the random graphs and the less uniform their vertices’ temperatures, which all tend to decrease the control over the graph’s closeness to isothermality, (2). Regardless, our choice of the parameters $\xi$ and $\nu$ guarantees that the bound (sl.2.54) decays to 0 and that it holds with probability approaching 1 as $n$ becomes large.

We investigated the issues of convergence for small values of $n$ numerically to illustrate our analytical result (Figure 2). For Erdős-Rényi random graphs (see Section s1.2 with the distribution chosen as Bernoulli), we generated 10 random graphs according to the procedure outlined in Definition sl.2.4 for fixed values of $0 < p < 1$. On each graph the Moran process was simulated $10^9$ times for various values of $0 \leq r \leq 10$ to give the empirical fixation probability, that is, the proportion of times that the mutant fixed in the simulation. Degenerate graphs were not excluded from the simulations but rather than estimating their fixation probabilities, we calculated them exactly, so that 1-rooted graphs were given fixation probability $1/n$ and many-rooted and disconnected graphs were given fixation probability 0. Trivially, such 1-rooted graphs are suppressors—that is, the fixation probability of a mutant of fitness $0 < r < 1$ (and a mutant of fitness $r > 1$) is greater than (and less than respectively) the mutant’s fixation probability in a well-mixed population—but suppressing graphs without these degenerate properties were also observed. As the graphs become larger their fixation probabilities match $\rho_{M\hat{}}$ closely and degeneracy becomes highly improbable as predicted by our result.

In addition to the generalized Erdős-Rényi random graphs, we also considered the Watts-Strogatz model and the Barabási-Albert model. The Watts-Strogatz model35 produces random graphs with small-world properties, that is, high clustering and short average path length. The model has three inputs: a parameter $0 \leq \beta \leq 1$, the graph size $n$, and the mean degree $2k$. Typically, the model produces random, undirected graphs, thus, to escape isothermality, it was modified slightly to produce weighted, directed graphs. We do this in the most natural way: we start with a directed 2k-regular graph where each node is connected to its 2k nearest neighbors if the graph is arranged on a cycle (Figure 3), and then we rewire each edge to a new vertex chosen uniformly at random with probability $\beta$ independently. Since the number of edges leaving each vertex is fixed at 2k, the weight of each edge is exactly $1/(2k)$. Potentially, there can be multiple edges for one vertex to another, which we account for by summing the edge weights. The model may be viewed as an interpolation between an isothermal, 2k-regular graph and an Erdős-Rényi graph by the parameter $\beta$.

Moran-type behavior was observed in the Watts-Strogatz model for all values of the input parameters we simulated (Figure 3). While mathematical proof of universality in the Watts-Strogatz model is still needed, there is hope that the techniques of this paper may be applied in this situation as the in-degrees of the vertices are concentrated around 1 for graphs with large degree $2k$.

Unlike the Erdős-Rényi and Watts-Strogatz models, scale-free networks are random graphs where the in-degrees of the vertices follow a power law. Normally, scale-free networks are undirected and unweighted. To produce weighted, directed scale-free networks, we modified the preferential attachment algorithm of Barabási-Albert45: we start with a connected cycle and then add directed edges
of equal weight in sequence to a randomly selected vertex where the
destination of each edge is selected proportional to the in-degree of
the current vertices.

Surprisingly, even though there is a sense in which vertices are not
treated interchangeably in the preferential attachment algorithm,
Moran-type behavior was observed in all simulations (Figure 4).
This is in contrast with the results in Lieberman et al. where they
observed some amplification in scale-free networks 7. The scale-free
property is emergent and only becomes apparent as the graph
becomes large, thus this increases the running time of the Monte
Carlo method for estimating the fixation probability. More simula-
tions are required here for conclusive findings, and again, there are
currently no mathematical results.

In summary, we have generalized the isothermal theorem to make
it biologically realistic and to increase its technical applicability. The
conclusion of the robust isothermal theorem now depends continu-
ously on its assumptions. With this new tool, we have proved ana-
tically that fixation probabilities in a generalized Erdős–Rényi
model converge uniformly to the fixation probability of a well-mixed
population. In our proof, we identify the reason for this convergence
and bound its rate. Thus, we confirm observations from many simu-
lations and give a method of approximation with a specified error.
Furthermore, we conjecture that many random graph models exhibit
this universal behavior. However, it is easy to construct simple exam-
pies of random graphs which do not, thus it still remains to deter-
mine the necessary assumptions on the random graph model for it to
exhibit universal behavior.

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B.A. and M.A.N. performed the research and wrote and reviewed the manuscript.

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