



# The mutation–drift balance in spatially structured populations



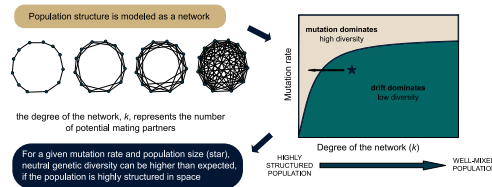
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## HIGHLIGHTS

- We model population structure using networks of constant degree  $k$ .
- Evolution follows a Moran process and is mapped into the voter model.
- If  $k$  is small, substantially smaller mutation rates are enough to overcome drift.
- The critical  $k$  for overcoming drift increases as a power law with population size.
- The stationary distribution becomes tri-modal at this mutation threshold.

## GRAPHICAL ABSTRACT



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## ABSTRACT

In finite populations the action of neutral mutations is balanced by genetic drift, leading to a stationary distribution of alleles that displays a transition between two different behaviors. For small mutation rates most individuals will carry the same allele at equilibrium, whereas for high mutation rates of the alleles will be randomly distributed with frequencies close to one half for a biallelic gene. For well-mixed haploid populations the mutation threshold is  $\mu_c = 1/2N$ , where  $N$  is the population size. In this paper we study how spatial structure affects this mutation threshold. Specifically, we study the stationary allele distribution for populations placed on regular networks where connected nodes represent potential mating partners. We show that the mutation threshold is sensitive to spatial structure only if the number of potential mates is very small. In this limit, the mutation threshold decreases substantially, increasing the diversity of the population at considerably low mutation rates. Defining  $k_c$  as the degree of the network for which the mutation threshold drops to half of its value in well-mixed populations we show that  $k_c$  grows slowly as a function of the population size, following a power law. Our calculations and simulations are based on the Moran model and on a mapping between the Moran model with mutations and the voter model with opinion makers.

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## 1. Introduction

Despite the ongoing debate over the relative importance of randomness and environmental selection in determining the properties of organisms during evolution, stochastic processes are certainly an inherent property of living populations. In particular, random variation in the outcome of different life-history events collectively result in what is often summarized in the concept of

“random genetic drift” (Lenormand et al., 2009). Although its influence in large populations may be weak when compared to selection, its role can be decisive in the process of fixation of rare alleles and cannot be neglected in small populations.

In population genetics, mutation and genetic drift are two inescapable sources of stochasticity with opposing effects regarding the maintenance of variation in the population. In the case of a single biallelic locus under reversible mutation, the dynamics of allele frequencies can be calculated in the limit of large and well-mixed (panmictic) populations. The equilibrium distribution converges to a Beta distribution that resembles a Gaussian for high

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mutation rates and a U-shaped curve for small mutation rates (Crow and Kimura, 1970; Gillespie, 2004). These two regimes reflect the relative importance of each evolutionary force in the dynamics. For a haploid population of size  $N$  and mutation rate  $\mu$ , drift dominates whenever  $2\mu N \ll 1$ . In this regime, one of the alleles becomes nearly fixed. For  $2\mu N \gg 1$ , on the other hand, mutation dominates over drift and both alleles evolve to nearly equal frequencies, maximizing genetic diversity. The transition occurs at a well defined threshold,  $\mu_c = 1/2N$ , where the equilibrium distribution of allelic frequencies becomes uniform. The dynamics can also be computed with the help of hypergeometric functions. The exact dynamics for populations of arbitrary size was only recently computed (Chinellato et al., 2015). When several loci and multiple alleles are taken into account the equilibrium condition gives the expected genetic diversity under neutrality, which may be taken as a null model for testing the effects of other evolutionary forces (Crow and Kimura, 1970).

The consequences of random genetic drift were first worked out by Wright and Fisher using a formulation currently known as the Wright–Fisher process (Gillespie, 2004). From these early results, it became apparent how drift could generate genetic differentiation between subdivided populations. Subsequently, the study of genetic drift and population structure became entwined. Contrary to early results that suggested that population structure could have little effect on evolutionary dynamics (reviewed in Ewens, 2004), it has been shown that the dynamics of allele frequencies is sensitive to the spatial distribution of individuals in a population. Specifically, the roles of mutation, selection and drift can be affected by the geographical structure, and quantities like fixation probability, time to fixation and allele distribution can differ significantly from those derived for panmictic populations (see for example Whitlock, 2003; Lieberman et al., 2005; Patwa and Wahl, 2008; Constable and McKane, 2014; Allen, 2015).

Following Wright's (1931) classic island model, spatial structure has often been implemented by assuming that the population is divided into islands of arbitrary sizes, or demes, which are connected by migration. The connections can be seen as network links, which can connect all demes between each other to form a complete graph, or acquire more complex structures (see Constable and McKane, 2014 for a recent overview on island models). More recently, evolutionary graph theory has been introduced as a framework that could provide a more general account of any arbitrary population structure (Lieberman et al., 2005). In this case, the individuals themselves are placed in the nodes of a network and links represent interactions between pairs of individuals (Lieberman et al., 2005; Dick and Whigham, 2005; Gordo and Campos, 2006; Whigham and Dick, 2007; Tarnita et al., 2009; Voorhees, 2013; Monk et al., 2014; Allen, 2015). The main focus of these studies has been how population structure may affect the drift–selection balance (Lieberman et al., 2005; Gordo and Campos, 2006; Whigham and Dick, 2007; Tarnita et al., 2009; Voorhees, 2013; Monk et al., 2014) and/or the fate of a single mutation (Lieberman et al., 2005; Dick and Whigham, 2005; Whigham and Dick, 2007; Voorhees, 2013; Monk et al., 2014; Allen, 2015). Not much attention has been given to the balance between drift and mutation and the properties of the stationary allele distribution that arises in such process.

The aim of this paper is to quantify the effects of spatial structure on the genetic variability and allele distribution under the mutation–drift balance. We study a single biallelic gene in a population of haploid individuals within the framework of a Moran process on a network, for which exact results are known for panmictic populations. In this model, an individual chosen at random is substituted by a copy of another randomly chosen individual. Although the model has been proposed and studied in the context of population genetics (Watterson, 1961; Cannings,

1974; Gladstien, 1978; Ewens, 2004), the process has found applications in other areas, such as the spreading of cancer (Durrett and Moseley, 2015) and the evolution of altruism (Débarre et al., 2014). We also use results from the voter model, a closely related process developed in connection with the social sciences (Mobilia et al., 2007; Harmon et al., 2015; Liggett, 2012; Yildiz et al., 2013; Chinellato et al., 2015) with applications in physics (Mobilia, 2003; Mobilia et al., 2007). In this case, individuals have to choose between two candidates in an election and their opinions are influenced by other voters and external opinion makers. It has been recognized that the Moran model bears a close resemblance to the voter model. The connection was proven for well-mixed populations with mutations (de Aguiar and Bar-Yam, 2011) and for regular networks without mutations (Durrett and Moseley, 2015). In particular, the phase transition from disordered to ordered states exhibited by the voter model when the number of opinion makers for each candidate is exactly one is mapped into the critical mutation rate  $\mu_c = 1/2N$  of the Moran model.

Our main interest is to understand how the threshold changes for spatially structured populations. To that purpose, we place the  $N$  individuals on a regular network, where each successive node is connected to its  $k$  nearest neighbors, so that all nodes have the same degree  $k$ . We study the configurations ranging from  $k = N - 1$  to  $k = 2$ , which correspond to the extremes of panmictic to ring populations (in which individuals are in contact only with their two nearest neighbors). In the first place, we provide a connection between the Moran and voter models for networks of arbitrary topologies. We show that a direct equivalence exists for regular networks, where every node has the same degree  $k$ . Using approximate solutions that are available for the voter model we show that the equilibrium distributions of the Moran model should not be sensitive to  $k$ , i.e. that the genetic distribution should be independent of the population's spatial structure. However, analytical results for a small network and numerical simulations show that these approximations break down if  $k$  is small. For sufficiently low values of  $k$  the critical mutation, above which mutation dominates over drift, decreases substantially. As a consequence, populations that display marked spatial structure can have much higher diversity than expected for well-mixed ones. We define a critical value  $k_c$  as the degree for which the mutation threshold drops to half of its panmictic value and show that  $k_c$  grows slowly as a function of  $N$  following a power law.

## 2. The voter model with opinion makers on networks

The voter model consists of a set of individuals who must choose between two candidates (Liggett, 2012). Their opinion can be influenced by their friends and by opinion makers, such as journalists or politicians, whose power of persuasion toward one of the candidates extends over the entire population. The opinion makers are modeled by additional (external) nodes whose states are fixed and that reach all voters equally, acting as a perturbation to the intrinsic dynamics.

The population has  $N$  voters placed on the nodes of a network and connected according to a specified adjacency matrix  $A$ , defined by  $A_{ij} = 1$  if the nodes  $i$  and  $j$  are connected and  $A_{ij} = 0$  otherwise. Each node has an internal state which can take the values 0 or 1, indicating the intention of vote toward candidate 0 or candidate 1, respectively. The nodes are also connected to  $N_0$  nodes whose states are fixed at 0 and to  $N_1$  nodes whose states are fixed at 1, representing the opinion makers. In what follows we will refer as *free nodes* to those representing the set of voters and as *frozen nodes* to those referring to opinion makers. The free nodes can change their internal state by adopting the opinion of a connected friend or that of an opinion maker as specified below.

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