



# Stability of underdominant genetic polymorphisms in population networks

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## HIGHLIGHTS

- The role of underdominance in population connectivity is discussed.
- A simple model incorporating migration and underdominance in a meta-population with varying network topologies is presented.
- Simulations of underdominance with migration suggest the network topology of a meta-population is important to long term genetic stability.

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## ABSTRACT

Heterozygote disadvantage is potentially a potent driver of population genetic divergence. Also referred to as underdominance, this phenomena describes a situation where a genetic heterozygote has a lower overall fitness than either homozygote. Attention so far has mostly been given to underdominance within a single population and the maintenance of genetic differences between two populations exchanging migrants. Here we explore the dynamics of an underdominant system in a network of multiple discrete, yet interconnected, populations. Stability of genetic differences in response to increases in migration in various topological networks is assessed. The network topology can have a dominant and occasionally non-intuitive influence on the genetic stability of the system.

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## 1. Introduction

Variation in the fitness of genotypes resulting from combinations of two alleles (e.g., A- and B-type alleles combined into AA-, AB-, or BB-genotypes resulting in  $w_{AA}$ ,  $w_{AB}$ , and  $w_{BB}$  fitnesses respectively) result in different evolutionary dynamics. The case in which a heterozygote has a lower fitness than either homozygote,  $w_{AB} < w_{AA}$  and  $w_{AB} < w_{BB}$ , is termed underdominance or heterozygote disadvantage. In this case there is an internal unstable equilibrium so that the fixation or loss of an allele depends on its starting frequency. In a single population, stable polymorphism is not possible. However, when certain conditions are met, populations that are coupled by migration (the exchange of some fraction of alleles each generation) can result in a stable selection-migration equilibrium. This selection-migration equilibrium is associated with a critical migration rate ( $m^*$ ); above this point the mixing between populations is sufficiently high for the system to

behave as a single population and all internal stability is lost (Altrock et al., 2010).

Underdominance can be thought of as an evolutionary bistable switch. From the perspective of game-theory dynamics it can be interpreted as a coordination game (Traulsen and Reed, 2012). The properties of underdominance in single and multiple populations have led to proposals of a role of underdominance in producing barriers to gene flow during speciation (Faria and Navarro, 2010; Harewood et al., 2010) as well as proposals to utilize underdominance both to transform the properties of wild populations in genetic pest management applications (Curtis, 1968; Davis et al., 2001; Sinkins and Gould, 2006; Reeves et al., 2014) and to engineer barriers to gene flow (transgene mitigation) from genetically modified crops to unmodified relatives (Soboleva et al., 2003; Reeves and Reed, 2014).

The properties of underdominance in a single population are well understood (Fisher, 1922; Haldane, 1927; Wright, 1931) and the two-population case has been studied in some detail (Karlin and McGregor, 1972a, 1972b; Lande, 1985; Wilson and Turelli, 1986; Spirito et al., 1991; Altrock et al., 2010, 2011), with fewer analytic treatments of three or more populations (Karlin and McGregor, 1972a, 1972b). Simulation-based studies have been

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conducted for populations connected in a symmetrical one- and two-dimensional lattice (Schierup and Christiansen, 1996; Payne et al., 2007; Eppstein et al., 2009; Landguth et al., 2015) (see also Kondrashov, 2003; Hoelzer et al., 2008; Barton and De Cara, 2009 for extensions to multiple loci) and “wave” approximations have been used to study the flow of underdominant alleles under conditions of isolation by distance (Fisher, 1937; May et al., 1975; Barton and Rouhani, 1991; Piálék and Barton, 1997; Soboleva et al., 2003; Barton and Turelli, 2011). However, despite this body of literature, underdominance remains relatively neglected in population genetic research (Bengtsson and Bodmer, 1976). Models in which allele frequencies are distributed in continuous populations are easier to analyse, and are appropriate approximations when selection is weak and the number of discrete demes is large (Barton, 1979). However, here we are interested in the cases where the number of demes is small or selection is strong (as is the case in potential applications of underdominance) or demes are connected in more complex topologies (e.g., asymmetrical arrays). This is where the continuous approximation breaks down and many of the effects we see in the context of small network topology have been previously overlooked. Furthermore, a large focus of earlier theoretical work with underdominance was on how new rare mutations resulting in underdominance might become established in a population (Wright, 1941; Bengtsson and Bodmer, 1976; Hedrick, 1981; Walsh, 1982; Hedrick and Levin, 1984; Lande, 1984, 1985; Barton and Rouhani, 1991; Spirito, 1992). However, here we are addressing the properties of how underdominant polymorphisms may *persist* once established within a set of populations rather than how they were *established* in the first place.

We explicitly focus on discrete populations that are connected by migration in a population network. We have found that the topology of the network has a profound influence on the stability of underdominant polymorphisms aspects of which have been otherwise overlooked. This influence is not always intuitive *a priori*. These results have implications for the effects of network topology on a dynamic system (see for review Strogatz, 2001), particularly for interactions related to the coordination game (such as the stag hunt, Skyrms, 2001), theories of speciation, the maintenance of biological diversity, and applications of underdominance to both protect wild populations from genetic modification or to genetically engineer the properties of wild populations—depending on the goals of the application.

## 2. Methods and results

We are considering simple graphs in the sense of graph theory to represent the population network: each pair of nodes can be connected by at most a single undirected edge. A graph  $G = (\mathcal{N}, \mathcal{E})$ , is constructed from a set of nodes,  $\mathcal{N}$  (also referred to a vetexes), and a set of edges,  $\mathcal{E}$ , that connect pairs of nodes. For convenience  $V = |\mathcal{N}|$  and  $E = |\mathcal{E}|$ , we chose  $V$  (for vertex) to represent the number of nodes to avoid future conflict with  $N$  symbolizing finite population size in population genetics. A node corresponds to a population made up of a large number of random-mating (well mixed) individuals (a Wright–Fisher population, (Fisher, 1922; Wright, 1931) with independent Hardy–Weinberg allelic associations, (Hardy, 1908) and the edges represent corridors of restricted migration between the populations. We are also only considering undirected graphs: in the present context this represents equal bidirectional migration between the population nodes. Furthermore, we are only considering connected graphs (each node can ultimately be visited from every other node) and unlabeled graphs so that isomorphic graphs are considered equivalent.

The network graph  $G$  is represented by a symmetric  $V \times V$  adjacency matrix  $\mathcal{A}$ .

$$\mathcal{A} = \begin{bmatrix} a_{1,1} & a_{1,2} & a_{1,3} & \cdots & a_{1,V} \\ a_{2,1} & a_{2,2} & a_{2,3} & \cdots & a_{2,V} \\ a_{3,1} & a_{3,2} & a_{3,3} & \cdots & a_{3,V} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ a_{V,1} & a_{V,2} & a_{V,3} & \cdots & a_{V,V} \end{bmatrix}$$

The presence of an edge between two nodes is represented by a one and the absence of an edge is a zero. The connectivity of a node is

$$c_i = \sum_{j \in \mathcal{N}} a_{ij}$$

Each generation,  $g$ , the allele frequency,  $p$  of each population node,  $i$ , is updated with the fraction of immigrants from  $n$  adjacent populations,  $j$ , at a migration rate of  $m$ .

$$p_{i,g} = (1 - c_i m) p_{i,g-1} + \sum_{j=1}^N m a_{ij} p_{j,g-1}$$

Note that this equation will not be appropriate if the fraction of alleles introduced into a population exceeded unity. See the discussion of the star topologies illustrated in Fig. 1 and the Supplemental Methods for discussion of an alternative approach.

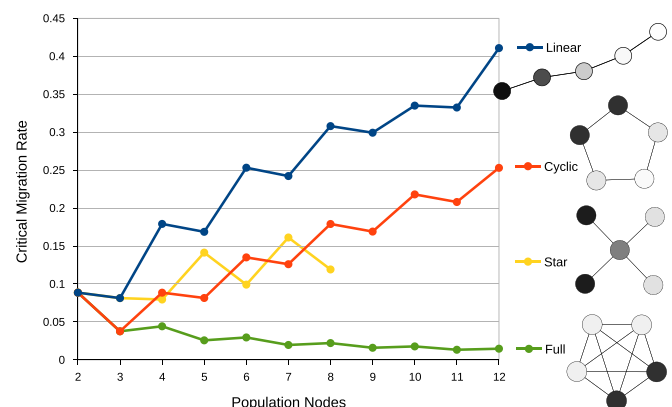
The frequencies, adjusted for migration, are then paired into genotypes and undergo the effects of selection. The remaining allelic transmission sum is normalized by the total transmission of all alleles to the next generation to render an allele frequency from zero to one.

$$p'_{i,g} = \frac{p_{i,g}^2 + \omega p_{i,g}(1 - p_{i,g})}{p_{i,g}^2 + 2\omega p_{i,g}(1 - p_{i,g}) + (1 - p_{i,g})^2}$$

Note that here for simplicity we set the relative fitness of the homozygotes to one,  $w_{AA} = w_{BB} = 1$  and the heterozygote fitness is represented by  $w_{AB} = \omega$ .

### 2.1. Analytic results

Underdominance in a single population has one central unstable equilibrium and two trivial stable equilibria at  $p=0$  and  $p=1$ . When one considers multiplying the three fixed points of a



**Fig. 1.** The stability of some simple network configurations. For each number of nodes and network topology (linear in blue, cyclic in red, star-like in yellow, and fully interconnected in green) the critical migration rate allowing polymorphic underdominant polymorphism to persist at  $\omega = 1/2$  is plotted. Examples of each type of network at  $V=5$  are plotted as graphs in the legend to the right. The shading of the nodes represents the allele frequency between zero and one of each population near the critical migration rate value. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

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