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Advance of advantageous genes for a multiple-allele population genetics model

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HIGHLIGHTS

- ▶ We extend the classical result of Fisher from two alleles to multiple alleles.
- ▶ We show that the advantageous allele has a positive propagation speed c^*.
- ▶ We show that traveling wave solutions with speed c exist for $|c| \geq c^*$.
- ▶ Under certain conditions, we show that c^* has an explicit formula.

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ABSTRACT

This paper extends the classical result of Fisher (1937) from the case of two alleles to the case of multiple alleles. Consider a population living in a homogeneous one-dimensional infinite habitat. Individuals in this population carry a gene that occurs in k forms, called alleles. Under the joint action of migration and selection and some additional conditions, the frequencies of the alleles, $p_i, i = 1, \ldots, k$, satisfy a system of differential equations of the form (1.2). In this paper, we first show that under the conditions A_1A_1 is the most fit among the homozygotes, (1.2) is cooperative, the state that only allele A_1 is present in the population is stable, and the state that allele A_1 is absent and all other alleles are present in the population is unstable, then there exists a positive constant, c^*, such that allele A_1 propagates asymptotically with speed c^* in the population as $t \to \infty$. We then show that traveling wave solutions connecting these two states exist for $|c| \geq c^*$. Finally, we show that under certain additional conditions, there exists an explicit formula for c^*. These results allow us to estimate how fast an advantageous gene propagates in a population under selection and migration forces as $t \to \infty$. Selection is one of the major evolutionary forces and understanding how it works will help predict the genetic makeup of a population in the long run.

1. Introduction

In 1937, R.A. Fisher studied the traveling wave solutions of the equation

$$u_t = du_{xx} + mu(1-u),$$

in order to study the propagation of an advantageous gene in a population living in a homogeneous one-dimensional infinite habitat (Fisher, 1937). He showed that traveling wave solutions of speed c exist for $|c| \geq 2\sqrt{dm}$. Kolmogoroff et al. (1988) studied the equation

$$u_t = du_{xx} + f(u),$$

where f satisfies the conditions

$$f \in C^1[0,1], \quad f(0) = f(1) = 0, \quad f(u) > 0 \quad \text{in } (0,1),$$

$$\text{and} \quad f'(u) \leq f'(0) \quad \text{in } [0,1]. \tag{1.1}$$

They proved, among other things, that traveling wave solutions of speed c exist for $|c| \geq c^* = 2\sqrt{df'(0)}$ and that c^* is the asymptotic speed of propagation of the advantageous gene. This equation is now called Fisher's equation.

Fisher's equation is based on the assumption that certain gene resides at an autosomal locus with two alleles A_1 and A_2. Let p_i be the frequency of allele A_i. Then, assuming that genotype A_1A_1 is more fit than genotype A_2A_2, fitness of the heterozygote A_1A_2 is between the homozygotes, population density is spatially independent, and Hardy–Weinberg equilibrium holds, it can be shown that p_1 satisfies Fisher's equation (Aronson and Weinberger, 1975, 1978).

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The papers of Fisher and Kolmogoroff, Petrovsky, and Piscounoff prompted a flurry of research activities in the area of reaction–diffusion equations. For Fisher's equation, Aronson and Weinberger (1975, 1978) proved that c^* is indeed the asymptotic speed of propagation of the advantageous gene A_1 under weaker assumptions than (1.1). The purpose of this paper is to extend Fisher's and Aronson and Weinberger's results to the case of multiple alleles.

Suppose there are k alleles residing at the locus; then there are $k(k+1)/2$ genotypes $A_iA_j, i,j=1,\dots,k$, where $A_iA_j = A_jA_i$. Let the fitness (or reproductive success rate) of genotype A_iA_j be denoted by r_{ij}. Suppose the dispersal rate is the same for all individuals (scaled to one). Fife (1979) and Nagylaki (1975, 1989) showed that under the assumption that both migration and selection are weak, the allele frequencies p_i, $i=1,\dots,k$, satisfy the reaction–diffusion system

$$\frac{\partial p_i}{\partial t} = \frac{\partial^2 p_i}{\partial x^2} + p_i(r_i - r), \quad i=1,\dots,k, \tag{1.2}$$

where $r_i = \sum r_{ij}p_j$ is the marginal fitness of allele A_i and $r = \sum r_i p_i = \sum r_{ij}p_i p_j$ is the mean fitness of the population. For the rest of this paper, we let $R=(r_{ij})$ be the fitness matrix which is symmetric since A_iA_j is the same as A_jA_i. Since $\sum p_i = 1$, (1.2) is a system of $k-1$ equations. It is easy to see that $f_i := p_i(r_i - r)$ is a cubic polynomial in p_i and is unchanged if we add a constant to all the r_{ij}. By relabeling the alleles, we assume that

$$r_{kk} < r_{(k-1)(k-1)} < \cdots < r_{22} < r_{11}. \tag{1.3}$$

Strict inequalities are assumed in (1.3) to avoid degeneracies. We also assume in this paper that the r_{ij}'s are distinct.

This paper is organized as follows. In Section 2, we summarize some existing theories which will be used to study (1.2). In Section 3, we show under the conditions that (1.2) is cooperative, the state that only allele A_1 is present in the population is stable, and the state that allele A_1 is absent but all other alleles are present in the population is unstable, then there exists $c^*>0$ such that A_1 propagates asymptotically with speed c^* in the population as $t \to \infty$. Furthermore, monotone traveling wave solutions connecting these two states exist for $|c| \ge c^*$. In Section 4, we impose additional conditions on the fitness matrix such that (1.2) is linearly determinate, implying that there is an explicit formula for c^*. Numerical examples are given in Section 5. Section 6 is conclusion where we summarize our results and discuss other issues not addressed in this paper.

2. Mathematical preliminaries

Consider the following reaction–diffusion system

$$\frac{\partial u_i}{\partial t} = d_i \frac{\partial^2 u_i}{\partial x^2} + F_i(u_1, u_2, \dots, u_k), \quad d_i > 0 \text{ for } 1 \le i \le k. \tag{2.1}$$

Let $\mathbf{F} = (F_1,\dots,F_k)$ be a C^1– function that satisfies $\mathbf{F}(\mathbf{0}) = \mathbf{0}, \mathbf{F}(\boldsymbol{\beta}) = \mathbf{0}$ for some constant vector $\boldsymbol{\beta} \gg \mathbf{0}$ (i.e., $\beta_i > 0$ for each i). Let $\mathcal{C}_{\boldsymbol{\beta}} = \{\mathbf{u} : 0 \le u_i \le \beta_i, \text{ for } i=1,\dots,k\}$. Given $\mathbf{u}_0 \in \mathcal{C}_{\boldsymbol{\beta}}$, we assume that a unique smooth solution to (2.1) with initial condition $\mathbf{u}_0$ exists for all $t>0$. System (2.1) is said to be cooperative in $\Omega \subset \mathbb{R}^k$ if

$$\frac{\partial F_i}{\partial u_j}(\mathbf{u}) \ge 0 \quad \text{for all } \mathbf{u} \in \Omega \text{ and } i \ne j. \tag{2.2}$$

Comparison principle holds for cooperative systems. This means that if $\mathbf{u}_0(x) \le \mathbf{v}_0(x)$ on $\mathbb{R}$, then solutions of (2.1) with initial conditions $\mathbf{u}_0$ and $\mathbf{v}_0$ satisfy $\mathbf{u}(x,t) \le \mathbf{v}(x,t)$ on $\mathbb{R}$ for as long as both solutions exist. It can be shown that if (2.2) holds in $\mathcal{C}_{\boldsymbol{\beta}}$, then $\mathcal{C}_{\boldsymbol{\beta}}$ is an invariant set with respect to (2.1). In other words, if initial condition lies in $\mathcal{C}_{\boldsymbol{\beta}}$, then solutions of (2.1) lie in $\mathcal{C}_{\boldsymbol{\beta}}$ for $t>0$.

Let us assume further that $\mathbf{F}$ does not vanish for any other vector in $\mathcal{C}_{\boldsymbol{\beta}}$ besides $\mathbf{0}$ and $\boldsymbol{\beta}$, and that $\mathbf{0}$ is unstable and $\boldsymbol{\beta}$ is stable with respect to the system $d\mathbf{u}/dt = \mathbf{F}(\mathbf{u})$. Let $\mathbf{Q}_\tau$ be the time—τ map of system (2.1). That is, given $\mathbf{u} \in \mathcal{C}_{\boldsymbol{\beta}}$, $\mathbf{Q}_\tau[\mathbf{u}]$ is the solution of (2.1) at time $\tau > 0$ with $\mathbf{u}$ as the initial condition. Then it is clear that Theorems 3.1 and 3.2 in Lui (1989) are valid which imply that there exists $c_\tau^* > 0$ such that if $0 \le \mathbf{u}_0 \ll \boldsymbol{\beta}$, $\mathbf{u}_0$ is nontrivial and has compact support, $\mathbf{u}_{n+1} = \mathbf{Q}_\tau[\mathbf{u}_n]$ for $n \ge 0$, then for any $\epsilon > 0$

$$\lim_{n\to\infty}\left[\max_{|x| \ge n[c_\tau^*+\epsilon]} |\mathbf{u}_n(x)|\right] = 0. \tag{2.3}$$

Also, for any $\boldsymbol{\omega} \gg \mathbf{0}$, there is a positive constant $R_{\boldsymbol{\omega}}$ such that if $\mathbf{u}_0 \ge \boldsymbol{\omega}$ on an interval of length $2R_{\boldsymbol{\omega}}$, then for any $\epsilon > 0$

$$\lim_{n\to\infty}\left[\max_{|x| \le n[c_\tau^*-\epsilon]} |\boldsymbol{\beta} - \mathbf{u}_n(x)|\right] = 0. \tag{2.4}$$

The constant c_τ^* is commonly called the *asymptotic speed of propagation* or the *spreading speed* in theoretical ecology. Once we verified that (2.3) and (2.4) hold, we can apply (Weinberger et al., 2002, Theorem 4.1) to obtain the following theorem.

Theorem 2.1 (*Asymptotic speed of propagation*). *Suppose* $\mathbf{F} = (F_1,\dots,F_k)$ *is a* C^1*-function that satisfies* (*i*) *there exists* $\boldsymbol{\beta} \gg 0$ *such that* $\mathbf{F}(\mathbf{0}) = \mathbf{0}, \mathbf{F}(\boldsymbol{\beta}) = \mathbf{0}$, (*ii*) *condition* (2.2) *holds in* $\mathcal{C}_{\boldsymbol{\beta}}$, (*iii*) $\mathbf{F}$ *does not have any other zero in* $\mathcal{C}_{\boldsymbol{\beta}}$ *besides* $\mathbf{0}$ *and* $\boldsymbol{\beta}$, *and* (*iv*) $\mathbf{0}$ *is unstable and* $\boldsymbol{\beta}$ *is stable with respect to the system* $d\mathbf{u}/dt = \mathbf{F}(\mathbf{u})$. *Then there exists* $c^* > 0$ *such that given* $\mathbf{0} \ll \boldsymbol{\omega} \ll \boldsymbol{\beta}$, *there exists* $R_{\boldsymbol{\omega}} > 0$ *such that if the initial condition* $\mathbf{u}_0 \in \mathcal{C}_{\boldsymbol{\beta}}$ *has compact support, exceeds* $\boldsymbol{\omega}$ *on an interval of length greater than* $2R_{\boldsymbol{\omega}}$, *then* (2.3) *and* (2.4) *hold with n replaced by t*, c_τ^* *replaced by* $c^* := c_1^*$, *and* $\mathbf{u}_n(x)$ *replaced by* $\mathbf{u}(x,t)$, *the solution of* (2.1).

Remark 2.2. In Theorem 2.1, the condition that $\mathbf{u}_0$ has to exceed $\boldsymbol{\omega}$ on a sufficiently large interval is called the threshold condition. It may be replaced by the condition $\mathbf{u}_0$ is positive on an open interval if $\mathbf{Q}_\tau$ satisfies $\mathbf{Q}_\tau[\rho\mathbf{u}] \ge \rho\mathbf{Q}_\tau[\mathbf{u}]$ for all $0 \le \rho \le 1, \tau > 0$ and any function $\mathbf{u} \in \mathcal{C}_{\boldsymbol{\beta}}$.

The following theorem follows from Li et al. (2005, Theorem 4.1) since $\mathcal{C}_{\boldsymbol{\beta}}$ does not contain any other equilibrium besides $\mathbf{0}$ and $\boldsymbol{\beta}$.

Theorem 2.3 (*Existence of traveling wave solutions*). *Let the conditions of* Theorem2.1 *hold. Then for* $c \ge c^*$, *there exists a nonincreasing function* $\mathbf{w}_c(z)$ *such that* $\mathbf{w}_c(x-ct)$ *satisfies system* (2.1), $\mathbf{w}_c(-\infty) = \boldsymbol{\beta}$ *and* $\mathbf{w}_c(\infty) = \mathbf{0}$. *The function* $\mathbf{w}_c(z)$ *is called a traveling wave solution with speed c.*

Remark 2.4. Let $\mathbf{w}_c(z)$ be the traveling wave solution in Theorem 2.3 and let $\overline{\mathbf{w}}_c(z) = \mathbf{w}_c(-z)$. Then $\overline{\mathbf{w}}_c(z)$ is a nondecreasing traveling wave solution which exists for $c \le -c^*$ with $\overline{\mathbf{w}}_c(-\infty) = \mathbf{0}$ and $\overline{\mathbf{w}}_c(\infty) = \boldsymbol{\beta}$. Therefore, monotone traveling wave solutions exist for $|c| \ge c^*$.

We now turn to the question of linear determinacy which means that the asymptotic speed of propagation, c^*, for the nonlinear system (2.1) is the same as that of the linear system

$$\frac{\partial \mathbf{v}}{\partial t} = D\frac{\partial^2 \mathbf{v}}{\partial x^2} + \mathbf{F}'(\mathbf{0})\mathbf{v}, \tag{2.5}$$

where $D = \mathrm{diag}(d_1,\dots,d_k)$ and $\mathbf{F}'(\mathbf{u})$ is the Jacobian matrix of $\mathbf{F}$ evaluated at $\mathbf{u}$. This concept is important because the asymptotic speed of propagation for (2.5) can be computed so there is an explicit formula for c^* if linear determinacy holds (Weinberger et al., 2002, Section 4). Because of condition (2.2), the matrix $\mathbf{F}'(\mathbf{0})$ has nonnegative off-diagonal entries. Suppose it is also irreducible. (A $k \times k$ matrix is said to be irreducible if the set $\{1,\dots,k\}$ cannot be split into two nonempty disjoint subsets with the