2. The First Eigenvalues of an Operator Related to Selection in Population Genetics

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1. Introduction. Among the diffusion approximations of 2-allelic gene frequency models in population genetics, one of the simplest is described by the Kolmogorov equation

$$\frac{\partial u}{\partial t}=\frac{x(1-x)}{4N}\frac{\partial^2 u}{\partial x^2}+sx(1-x)\frac{\partial u}{\partial x}. \tag{1}$$

Here we are taking account only of the selection force. x is the space variable running over the interval $0\leq x\leq 1$. x and $1-x$ denote genetically the gene frequencies of 2 allels, say A and A' respectively. t is, genetically the generation, time variable running over the positive real line. $2N$ and s are independent of (t, x). $2N$ (population size) is a large positive integer, and s is a real number ($|s|$ is small). $1+s$ and 1 are relative fitnesses of A and A' respectively. Hence, A is advantageous to A' if $s\geq 0$, and contrarily if $s\leq 0$.

The stochastic process $x(t,\omega)$ starting from $0<x(0,\omega)<1$ reaches almost surely in a finite time to one of the boundary points $x=0$ or $x=1$. If we consider the eigenvalue problem

$$\begin{cases}\dfrac{x(1-x)}{4N}\dfrac{d^2u}{dx^2}+sx(1-x)\dfrac{du}{dx}+\mu u=0, & \text{in } 0<x<1,\\ u(0)=u(1)=0,\end{cases} \tag{2}$$

the first eigenvalue μ_1 is the rate of the absorption to the boundary (see [2] and [3]).

Hence it is of interest to know the magnitude of μ_1 as a function of $2N$ and s. If we change the parameters $(2N, s)$ by

$$4Ns=\sigma \quad \text{and} \quad 4N\mu=\lambda, \tag{3}$$

(2) becomes an equation for spheroidal wave functions ([1])

$$x(1-x)\frac{d^2u}{dx^2}+\sigma x(1-x)\frac{du}{dx}+\lambda u=0, \qquad \text{in } 0<x<1, \tag{4}$$

$$u(0)=u(1)=0. \tag{5}$$

In this note, we will estimate $\mu_1=\mu_1(2N, s)=\lambda_1(4Ns)/(4N)$ as $4Ns$ is large. But the method being the same, we will treat the first $2m$ eigenvalues $\{\lambda_p(\sigma)\}_{p=1}^{2m}$ of (4)–(5), supposing that σ is large (m is arbitrary but fixed). The result will be stated in § 3.

2. Gene frequency model. The original model corresponding to (1) is a Markov chain $\{X_k\}_{k=0}^{\infty}$ whose state space is the finite set $\Omega^{(2N)} = \{0, 1, 2, \cdots, 2N\}$ and the set of times (generations) k is the discrete set $\{0, 1, 2, \cdots\}$. And the one-step transition probability is given by

$$P_{ij}^{(2N)} = \text{Prob}\,[X_{k+1}=j \mid X_k = i] = \binom{2N}{j} p_i^j (1-p_i)^{2N-j}$$

with $p_i = (1+s)i/(2N+si)$, where $i, j \in \Omega^{(2N)}$ and $k=0, 1, 2, \cdots$ (see [2]). In the approximation procedure as $2N$ is large, we identify $i \in \Omega^{(2N)}$ with the point $x^i = i/2N$ in the interval $0 \leq x \leq 1$, and assume that $4Ns = \sigma$ is independent of $2N$. Then we have

$$p_i = x^i + \frac{\sigma}{4N} x^i(1-x^i) + O((2N)^{-2})$$

uniformly on $\Omega^{(2N)}$. And the Markov chain $\{X_k\}$ is approximated by the Markov process $\{x(t, \omega)\}$ whose Kolmogorov equation is (1) with $s = \sigma/4N$ (see [4]). Here the scales of t and k are the same. It should be noticed that this diffusion approximation is no more correct if $4Ns$ is too large (for example if s is a non-zero value independent of $2N$).

3. Statement of a result. Put $w(x) = e^{\sigma x/2} u(x)$. Then the equation (4) becomes

$$Bw(x) = x(1-x)\left\{-w''(x) + \frac{\sigma^2}{4} w(x)\right\} = \lambda w(x). \tag{6}$$

Under the boundary condition (5), B is extended to a positive self-adjoint operator in the Hilbert space H obtained by completing $C_0^\infty(0, 1)$ by the scalar product

$$(u, v)_H = \int_0^1 u(x)\overline{v(x)}\{x(1-x)\}^{-1} dx.$$

We see from this setting that each of the eigenvalues λ is simple and is an increasing function of σ^2, and that the boundary point $x=0$ has the same character as $x=1$. Let us enumerate the eigenvalues of (4)–(5) in increasing order of magnitude: $0 < \lambda_1(\sigma) < \lambda_2(\sigma) < \cdots$. Then we have the following

Theorem. *Let m be any fixed positive integer. Then, $\{\lambda_p(\sigma)\}_{p=1}^{2m}$ behaves in the following manner as $\sigma \to +\infty$:*

$$\overline{\lim_{\sigma \to +\infty}} \left\{\lambda_p(\sigma) - \left[\frac{p+1}{2}\right]\sigma\right\} \leqq 0 \tag{7}$$

$$\lim_{\sigma \to +\infty} \{\lambda_p(\sigma)/\sigma\} = \left[\frac{p+1}{2}\right], \tag{8}$$

where $[(p+1)/2]$ is $(p+1)/2$ if p is odd and $p/2$ if p is even.

4. Preliminaries for the proof. Equation (6) is written as

$$Lw(x) \equiv -w''(x) + \frac{\sigma^2}{4} w(x) = \frac{\lambda}{x(1-x)} w(x). \tag{9}$$

Let $a(x)$ and $b(x)$ be any continuous functions satisfying

$$0 < b(x) \leq x(1-x) \leq a(x), \qquad \text{in } 0 < x < 1. \tag{10}$$

We can compare (9) with the equations

(11) $$Lw(x)=\{\lambda/a(x)\}w(x),$$

(12) $$Lw(x)=\{\lambda/b(x)\}w(x).$$

Let us denote by $\{\bar{\lambda}_p(\sigma)\}_{p=1}^{\infty}$ and $\{\underline{\lambda}_p(\sigma)\}_{p=1}^{\infty}$ the sequencies of eigenvalues of (11)–(5) and (12)–(5) respectively enumerated in increasing order. Then the mini-max principle implies

(13) $$\underline{\lambda}_p(\sigma)\leq\lambda_p(\sigma)\leq\bar{\lambda}_p(\sigma), \qquad \text{for each } p.$$

Therefore an appropriate choice of $a(x)$ or of $b(x)$ will help us to estimate $\lambda_p(\sigma)$'s from above or from below.

The p-th eigenfunction of (9)–(5) is an even (odd) function of $x'=x-1/2$ if p is odd (even respectively). This remains also true for the eigenfunctions of (11)–(5) and (12)–(5) if $a(x)$ and $b(x)$ are even functions of x'. Hence we can look for even eigenfunctions and odd ones separately.

On the other hand, if x is small, the factor $1-x$ in (4) is nearly 1. Therefore we consider a simpler equation

(14) $$u''(z)=u'(z)+(\kappa/z)u(z).$$

The following series is a solution of (14) vanishing at $z=0$:

(15) $$F(\kappa, z)=\sum_{n=0}^{\infty}\binom{\kappa+n}{n}\frac{z^{n+1}}{(n+1)!}.$$

5. Proof of (7). Let us consider the problem (11)–(5) with

(16) $$a(x) = \operatorname{Min}(x, 1-x) \qquad \text{in } 0\leq x\leq 1.$$

Let us define $w_1(x)$ and $w_2(x)$ by

(17) $$\begin{cases} w_1(x)=w_2(x)=w_0(x) & \text{in } 0\leq x\leq 1/2, \text{ and} \\ w_1(x)=-w_2(x)=w_0(1-x) & \text{in } 1/2< x\leqq 1, \\ \text{where } w_0(x)=e^{-\sigma x/2}F(-\lambda/\sigma, \sigma x). \end{cases}$$

$w_1(x)$ ($w_2(x)$) is an eigenfunction of (11)-(5) if and only if $w_1'(1/2\pm 0)=0$ ($w_2(1/2\pm 0)=0$). This condition is equivalent to

(18) $$F(-\lambda/\sigma, \sigma/2)=2F'(-\lambda/\sigma, \sigma/2)$$

(19) $$(F(-\lambda/\sigma, \sigma/2)=0 \text{ respectively,})$$

where $F'(\kappa, z)=(\partial F/\partial z)(\kappa, z)$. Therefore, it suffices to investigate the position of real roots κ of the equation

(20) $$F(\kappa, z)=\theta F'(\kappa, z), \qquad \text{where } \theta \text{ is 2 or 0}.$$

We see that, for any fixed positive integer m and for sufficiently large z, there are exactly m roots $\{\kappa_p(\theta, z)\}_{p=1}^{m}$ in the interval $-m-1/2\leq\kappa\leq m+1/2$, and that each of $|\kappa_p(\theta, z)+p|$ decays exponentially as $z\to+\infty$. Since $\bar{\lambda}_{2p-1}(\sigma)=-\sigma\kappa_p(2, \sigma/2)$ and $\bar{\lambda}_{2p}(\sigma)=-\sigma\kappa_p(0, \sigma/2)$ for $1\leq p\leq m$, we have proved (7).

6. Proof of (8). We proceed to the problem (12)–(5), where

(21) $$b(x)=\operatorname{Min}\{\alpha x, \alpha\beta, \alpha(1-x)\}, \qquad \text{in } 0\leq x\leq 1.$$

The inequality (10) holds if the constants α and β satisfy $0<\alpha<1$, $0<\beta<1/2$ and $\alpha+\beta\leq 1$. Similarly to (17), we put

$$(22)\quad \begin{cases} v_0(x)=e^{-\sigma x/2}F\left(-\dfrac{\lambda}{\alpha\sigma}, \sigma x\right), \\ v_1(x)=\cosh\left\{\mu\left(\dfrac{1}{2}-x\right)\right\} \quad \text{and} \quad v_2(x)=\sinh\left\{\mu\left(\dfrac{1}{2}-x\right)\right\}, \end{cases}$$

where $\mu=\{(\sigma^2/4)-(\lambda/(\alpha\beta))\}^{1/2}$. And define $W_1(x)$ and $W_2(x)$ by

$$(23)\quad \begin{cases} W_1(x)=W_2(x)=v_0(x) \quad \text{in } 0\leq x<\beta, \\ W_j(x)=A_j v_j(x) \quad \text{in } \beta<x<1-\beta,\ j=1,2, \\ W_1(x)=-W_2(x)=v_0(1-x) \quad \text{in } 1-\beta<x\leq 1. \end{cases}$$

$W_j(x)$ is an eigenfunction of (12)–(5) if and only if $W_j(\beta+0)=W_j(\beta-0)$ and $W_j'(\beta+0)=W_j'(\beta-0)$ with some constant A_j, that is,

$$(24)\quad F'\left(-\frac{\lambda}{\alpha\sigma}, \alpha\beta\right)=F\left(-\frac{\lambda}{\alpha\sigma}, \sigma\beta\right)\left[\frac{1}{2}-\frac{\mu}{\sigma}\tanh\left\{\mu\left(\frac{1}{2}-\beta\right)\right\}\right],$$

if $j=1$ (we replace tanh by coth if $j=2$). Let us take a large positive M independent of σ, put $\alpha=1-M/\sigma$ and $\beta=M/\sigma$, and assume that σ/M is large. We regard (24) as an equation in $\kappa=-\lambda/(\alpha\sigma)$. Then, there are exactly m roots $\{\kappa_{2p-1}'(\sigma)\}_{p=1}^m$ for $j=1$ and m roots $\{\kappa_{2p}'(\sigma)\}_{p=1}^m$ for $j=2$ in the interval $-m-1/2\leq\kappa\leq m+1/2$. Moreover, taking both of M and σ/M large enough, $|\kappa_{2p-1}'(\sigma)+p|$ and $|\kappa_{2p}'(\sigma)+p|$ can be made arbitrarily small. Since $\lambda_q(\sigma)=(M-\sigma)\kappa_q'(\sigma)$, we have

$$\varliminf_{\sigma\to+\infty}\lambda_q(\sigma)/\sigma\geq\left[\frac{q+1}{2}\right] \qquad \text{for } 1\leq q\leq 2m.$$

Combining this with (7), we have (8). Theorem is now established.

7. An improvement of the result. A better upper bound for $\lambda_1(\sigma)$ and $\lambda_2(\sigma)$ is obtained in the following way. We put

$$R(w)=(Bw, w)_H/(w, w)_H$$

(see the context of (6)). Then we have $\lambda_1(\sigma)\leq R(w_\rho)$ and $\lambda_2(\sigma)\leq R(v_\rho)$, where $w_\rho(x)=x(1-x)\cosh\{\rho(x-1/2)\}$, $v_\rho(x)=x(1-x)\sinh\{\rho(x-1/2)\}$ and ρ is a positive parameter. Computing the minima of $R(w_\rho)$ and $R(v_\rho)$ as functions of ρ, we have the following bound for $\lambda_1(\sigma)$ and $\lambda_2(\sigma)$ as σ is large:

$$(25)\quad \lambda_1(\sigma) \ \text{and} \ \lambda_2(\sigma)\leq\sigma-2-4\sigma^{-1}-24\sigma^{-2}-O(\sigma^{-3}).$$

8. A multi-dimensional analogue. For the d-allelic ($d\geq 3$) gene frequency model analogous to (1), the reduced eigenvalue problem corresponding to (4)–(5) is the following:

$$(26)\quad \begin{cases} \displaystyle\sum_{j,k=1}^{n}(\delta_{jk}x_j-x_jx_k)\left(\frac{\partial^2 u}{\partial x_j\partial x_k}+\sigma_j\frac{\partial u}{\partial x_k}\right)+\lambda u=0, \text{ in } \Omega, \\ u(x)=0, \text{ on } \partial\Omega. \end{cases}$$

Here $n=d-1$, $\sigma=(\sigma_1, \sigma_2, \cdots, \sigma_n)$ are real constants and Ω is the n-simplex in $\boldsymbol{R}^n$ defined by $x_j>0$, $1\leq j\leq n$, and $\sum_{j=1}^n x_j<1$. Let $\lambda_1(\sigma)$ be the first eigenvalue of this problem. If $|\sigma|$ tends to infinity keeping the ratio $\sigma_1:\sigma_2:\cdots:\sigma_n$ fixed, the following inequality holds

$$(27)\quad C\leq\lambda_1(\sigma)\Big/\min_{1\leq j\leq d}\sum_{k=1}^{d}|\sigma_j-\sigma_k|\leq 1+o(1), \qquad \text{with } \sigma_d=0,$$

where C is a positive constant depending only on d.

References

[1] Erdélyi, A. *et al.*: Higher Transcendental Functions. Vol. 3, chap. XVI, McGraw-Hill (1955).
[2] Karlin, S.: A First Course in Stochastic Processes. Chap. 13, Academic Press (1966).
[3] Maruyama, T.: Stochastic Problems in Population Genetics. Lect. Notes in Biomath., vol. 17, Springer (1977).
[4] Sato, K.: A class of Markov chains related to selection in population genetics. J. Math. Soc. Japan, **28**(4), 621–637 (1976).