ON A GENETICS MODEL OF MORAN†

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Communicated by M. S. Bartlett

Received 1 July 1961

1. *Introduction.* Wright (14), Feller (2) and others have proposed various stochastic models of genetics to study the fluctuations of gene frequency under the influence of mutation and selection. One of their simplest models has the following structure. There are a fixed number N of gametes each of which may be of two types a or A. The process $X(n)$, $n = 0, 1, 2, \ldots$ which is assumed to have stationary transitions, is said to be in state j when there are j gametes of type a, and $N-j$ of type A. Let γ_1 denote the probability that immediately after formation an a gamete mutates into an A gamete and let γ_2 denote the probability of an A gamete mutating into an a gamete. Each of the gametes of the next generation is independently formed by making a random selection from the gametes of the present generation. The probability of a particular gamete in the next generation being of type a is then

$$p_j = \frac{j}{N}(1-\gamma_1) + \left(1-\frac{j}{N}\right)\gamma_2 \quad (j = 0, 1, \ldots, N) \tag{1}$$

and of type A

$$q_j = \frac{j}{N}\gamma_1 + \left(1-\frac{j}{N}\right)(1-\gamma_2) \quad (j = 0, 1, \ldots, N),$$

where j represents the state of the process. Roughly speaking, the chance of a mating resulting in a gamete of a prescribed kind for the next generation is proportional to the fraction of these gametes present in this generation allowing for mutation effects.

The make-up of the population in the next generation is determined by N independent binomial trials with probability p_j and q_j that the outcome at each trial will be an a-gamete or A-gamete, respectively. Hence, the one-step transition probability matrix is

$$P_{jk} = \binom{N}{k} p_j^k \, q_j^{N-k} \quad (j, k = 0, 1, \ldots, N). \tag{2}$$

This Markoff chain was analysed by Feller (2) who calculated its eigenvalues and determined the rates of convergence of the process to the steady-state distribution (which appears to be unknown). In the case $\alpha_1 = \alpha_2 = 0$, fixation occurs in a population of a single type of gamete.

Letting $N \to \infty$ suitably, Wright and later Feller derived a diffusion process whose solution involves the Jacobi polynomials. The limit analysis was done heuristically.

† This research was supported by National Science Foundation Grants G-9669 and G-6332.

Kimura (9) considered a slight variant of model (2) formulated as follows: each chromosome consists of n sub-units and suppose that a mutation has occurred in one of them. The sub-units duplicate to produce $2n$, which divide at random into two daughter chromosomes of n sub-units. We trace a single line of descent. The state E_i $(i = 0, 1, \ldots, n)$ in each generation designates the number of mutant sub-units contained in the cell. The transition probabilities are given by

$$P_{ij} = \frac{\binom{2i}{j}\binom{2n-2i}{n-j}}{\binom{2n}{n}}. \tag{2a}$$

If n is very large, the proportion of mutant sub-units $x = i/n$ $(0 \leqslant x \leqslant 1)$ is regarded as a continuous variable. Let $\phi(x,t)$ be the probability density of x at time t. If δx is the amount of change in x per generation, then

$$E(\delta x) = 0, \quad E((\delta x)^2) = x(1-x)/(2n-1)$$

and $E((\delta x)^k) = o(1/n)$ for $k \geqslant 3$. A continuous approximation used to obtain $\phi(x,t)$ is furnished by the forward diffusion equation

$$\frac{\partial \phi(x,t)}{\partial t} = \frac{1}{2(2n-1)}\frac{\partial^2}{\partial x^2}[x(1-x)\,\phi(x,t)],$$

where $\phi(x,t)$ has the initial distribution function $\delta(x-1/n)$ and δ is the Dirac function.

Moran (10) devised a continuous time Markoff chain model to study the same phenomenon. This model applies to a population where breeding and mortality occur continuously in time and the generations overlap. In contrast, Wright's model refers to a situation of a fixed duration of life and a fixed breeding season so that generations are kept distinct.

The formulation of the model is as follows: there are N gametes which are either of type a or A. Again, the number $X(t)$ of a-gametes at time t represents the state of the process and the total population size remains constant. Thus $X(t)/N$ is the fraction of a-gametes in the population at time t. A change of state occurs when a single individual reproduces and is replaced by a new individual.

It is assumed that the probability that the state changes during the time interval $(t, t+dt)$ is $\lambda\,dt + o(dt)$. Furthermore, it is assumed that the probability of two or more matings occurring in a time interval of span dt is $o(dt)$. We postulate that the mechanism of mating has the following structure. At the occurrence of mating an individual from the population is selected at random to be fertilized. Another individual also chosen at random, does the fertilizing, is called the fertilizer (self-fertilization is allowed) and this individual dominates the outcome. More precisely, if an A-gamete fertilizes an a-gamete or an A-gamete the result is always an A-gamete. A similar situation prevails when an a-gamete acts as fertilizer; in this case an a-gamete is always produced. Immediately following fertilization the progeny may mutate into the other type of gamete. Let γ_1 denote as before the probability that an a-gamete mutates to an A-gamete and let γ_2 denote the probability of an A-gamete mutating into an a-gamete.

If mating occurs at time t, the conditional probability of the event

$$X(t+) = X(t)+1$$

(the a-gamete population increases; only increases of magnitude ± 1 are possible) is

$$\left(1-\frac{j}{N}\right)\frac{j}{N}(1-\gamma_1)+\left(1-\frac{j}{N}\right)\left(1-\frac{j}{N}\right)\gamma_2, \quad \text{where} \quad X(t)=j. \tag{3}$$

We reason this formula in the following manner: The a-gamete population size can enlarge only if an A-gamete is fertilized and transforms into an a-gamete. Since matings occur at random, the chance of selecting an A-gamete when $X(t)=j$ is $1-j/N$. Now if an a-gamete fertilizes the selected A-gamete the outcome is a new a-gamete provided no mutation occurs. The first term in (3) is the probability of this contingency. Another combination which also gives rise to a new a-gamete is that an A-gamete fertilizes an A-gamete and the progeny mutates into an a-gamete. The second term in (3) is the probability of this contingency.

In a similar way we find that the probability of the event

$$X(t+) = X(t)-1$$

under the condition of a mating at time t is

$$\frac{j}{N}\left[\left(1-\frac{j}{N}\right)(1-\gamma_2)+\frac{j}{N}\gamma_1\right], \quad \text{where} \quad X(t)=j. \tag{4}$$

The stochastic process described above is recognized as an example of a birth and death process (5) with birth rates

$$\lambda_j = \gamma\left(1-\frac{j}{N}\right)\left[\frac{j}{N}(1-\gamma_1)+\left(1-\frac{j}{N}\right)\gamma_2\right] \tag{5}$$

and death rates

$$\mu_j = \lambda\frac{j}{N}\left[\frac{j}{N}\gamma_1+\left(1-\frac{j}{N}\right)(1-\gamma_2)\right] \tag{6}$$

corresponding to an a-gamete population of size j, $0 \leqslant j \leqslant N$.

For a complete discussion of birth and death processes we refer the reader to (4), (5). It is shown in (4) that the transition probability function of the process

$$P_{ij}(t) = \Pr\{X(t)=j \mid X(0)=i\}$$

can be represented in the form

$$P_{ij}(t) = \pi_j\int_0^\infty e^{-xt}R_i(x)\,R_j(x)\,d\psi(x), \tag{7}$$

where

$$\pi_0 = 1, \quad \pi_k = \frac{\lambda_0\lambda_1\dots\lambda_{k-1}}{\mu_1\mu_2\dots\mu_k} \quad (k=1,2,\dots),$$

and $R_k(x)$ are a system of polynomials determined by the recursion relations

$$\left.\begin{aligned} R_0(x) = 1, \quad R_{-1}(x)=0, \\ -xR_k(x) = -(\lambda_k+\mu_k)R_k(x)+\lambda_k R_{k+1}(x)+\mu_k R_{k-1}(x) \quad (k=0,1,\dots). \end{aligned}\right\} \tag{8}$$

Here λ_k and μ_k are defined in (5) and (6). Since $\lambda_N = 0$ there exists only the finite system $R_0(x), R_1(x), \dots, R_N(x)$ which are orthogonal with respect to a unique measure

$\psi(x)$ with exactly $N+1$ points of increase and with total mass one. The measure $\psi(x)$ is called the spectral measure of the process and the spectrum of the process is identified with the spectrum of ψ.

We shall identify the measure ψ and the polynomials $R_i(x)$ $(i = 0, 1, \ldots, N)$ for the birth and death process at hand. The polynomials $R_i(x)$ are expressible in terms of the dual Hahn polynomials whose properties are described in § 2. From the representation (7) and our knowledge of the properties of $R_i(x)$ we then derive various probabilistic consequences.

In § 3 we display the representation formula (7) for the transition matrix. It is necessary to distinguish four cases. In Case 1 we assume that $\gamma_1, \gamma_2 > 0$ and $1-\gamma_1-\gamma_2 > 0$. Here the two linear factors contained in the formula of the birth and death rates (5) and (6) oppose each other, one exhibiting attraction, the other repulsion towards the same end state. Case 2 is characterized by the conditions $\gamma_1, \gamma_2 > 0$ and $1-\gamma_1-\gamma_2 < 0$ and now the two linear factors extend their force in the same direction. In Case 3 ($\gamma_1, \gamma_2 > 0$, $1 = \gamma_1+\gamma_2$) the birth and death rates are linear. The associated polynomials are expressed in terms of the familiar Krawtchouk polynomials. In Case 4, $\gamma_1 = \gamma_2 = 0$, the process manifests two absorbing states corresponding to fixation in homozygous populations of a- of A-gametes.

Section 4 is devoted to discussing some probabilistic consequences of the representation. We determine the rates of convergence of the transition probability function $P_{ij}(t)$ to the stationary distribution in Cases 1, 2 and 3; the rate of convergence to homozygosity in Case 4. These results are immediate once the spectrum of the process is known, which is the case here. Moran (**10**) obtained some of these results. We also characterize the direction of convergence of $P_{ij}(t)$ to the limiting probabilities π_j in Cases 1, 2 and 3. This depends on the sign of the polynomials $R_i(x)$ at the smallest positive value in the spectrum.

In paragraph 2 of this section we write out some formulas for recurrence time and absorption time distributions. We close by discussing several limit behaviours as $N \to \infty$. In this way we derive a diffusion process associated with each of the discrete models. The details are made explicit for Cases 1 and 4 but the methods are applicable to the other cases also. The derived processes are essentially the same as those dealt with by Feller (**2**) and Kimura (**9**); they emerge very naturally from our set up and the limit procedure is completely rigorous. The limit relations for the probability functions have their counterpart in a classical limit relation which takes the Hahn polynomials into the Jacobi polynomials (**1**).

Moran has developed various extensions (**12**), (**13**) of these models involving diploid and bisexual populations. These are processes whose state space is now naturally described by at least two variables. Moran also has dealt (**11**) with the original haploid model as formulated above where there exists a definite selectivity factor. We shall return in another publication to a discussion of these processes exploiting the methods developed here.

2. *The Hahn polynomials and their dual system.* For ready reference we review some of the properties of the Hahn polynomials and their dual system. We refer the reader to (**8**) for detailed discussion and proofs. Some new results are included which

were inspired by the Moran model. The Hahn polynomials are defined by the explicit formula

$$\begin{aligned} Q_n(x) &= Q_n(x; a, b, N) \\ &= {}_3F_2(-n, -x, n+a+b+1; a+1, -N+1; 1) \\ &= \sum_{k=0}^{n} \frac{(-n)_k (-x)_k (n+a+b+1)_k}{(a+1)_k (-N+1)_k k!} \quad (a, b > -1), \end{aligned} \tag{9}$$

where $(c)_0 = 1$, $(c)_k = c(c+1)\dots(c+k-1)$ for $k \geqslant 1$ and $N > n$. These polynomials are orthogonal with respect to the measure which has jumps at $x = 0, 1, \dots, N-1$ of magnitudes

$$\rho(x) = \rho(x; a, b, N) = \frac{\binom{a+x}{x}\binom{b+N-1-x}{N-1-x}}{\binom{N+a+b}{N-1}} \quad (x = 0, 1, 2, \dots, N-1).$$

In addition to a standard recurrence formula they also satisfy a difference equation

$$-\omega_n Q_n(y) = D(y) Q_n(y-1) - [B(y) + D(y)] Q_n(y) + B(y) Q_n(y+1), \tag{10}$$

where
$$B(y) = (N-1-y)(a+1+y), \quad D(y) = y(N+b-y), \tag{11}$$
$$\omega_n = n(n+a+b+1)$$

and (10) is valid for $n = 0, 1, \dots, N-1$ and all complex values of y.

Let
$$\tilde{P}_k(x, a, b; N) = \tilde{P}_k(x) \quad (k = 0, 1, \dots, N-1), \tag{12}$$

denote the finite system of N polynomials determined by the recurrence formula

$$-\lambda \tilde{P}_k(\lambda) = D(k) \tilde{P}_{k-1}(\lambda) - [D(k) + B(k)] \tilde{P}_k(\lambda) + B(k) \tilde{P}_{k+1}(\lambda)$$
$$(k = 0, 1, \dots, N-1), \tag{13}$$

with the initial condition $\tilde{P}_0(\lambda) \equiv 1$. Since $D(0) = B(N-1) = 0$, the terms involving $\tilde{P}_{-1}(\lambda)$ and $\tilde{P}_{N-1}(\lambda)$ are to be ignored. By comparison with the difference equation (10) we have

$$\tilde{P}_k(\omega_n; a, b, N) = Q_n(k; a, b; N).$$

The polynomials $\tilde{P}_n$ are orthogonal with respect to the measure ψ with jumps at the points $\omega_k = k(k+a+b+1)$ $(k = 0, 1, \dots, N-1)$ of magnitudes

$$\begin{aligned} \psi_{k,N} &= \psi_{k,N}(a, b, N) \\ &= \frac{\binom{N-1}{k}}{\binom{N+a+b+k}{k}} \frac{\Gamma(b+1)}{\Gamma(a+1)\Gamma(a+b+1)} \frac{\Gamma(k+a+1)\Gamma(k+a+b+1)}{\Gamma(k+b+1)\Gamma(k+1)} \\ &\qquad \times \frac{(2k+a+b+1)}{a+b+1}. \end{aligned} \tag{14}$$

(If $a+b = -1$, the above formula for ψ_0 is indeterminate and is to be taken $= 1$.) The normalizing constant C, chosen so that $C \Sigma \psi_k = 1$ is

$$C = \rho(0; a, b, N) = \binom{b+N-1}{N-1} \Big/ \binom{N+a+b}{N-1}.$$

A variant of the recurrence law (13) needed below will now be obtained.

The Hahn polynomials are well defined for complex a, b, x provided $a \neq -1, -2, \ldots, -N$, and satisfy (10) for all x if $a > -1$ and $b > -1$. Hence (10) is also satisfied by analytic continuation for all a, b with $a \neq -1, -2, \ldots, -N$. Suppose $a < -N$, $b < -N$ and let

$$\left.\begin{aligned} a &= -(N+b'+1), \\ b &= -(N+a'+1), \end{aligned}\right\} \quad \text{where} \quad a', b' > -1. \tag{14a}$$

Then consulting (11), we have

$$\left.\begin{aligned} D(x) &= -x(a'+1+x), \\ B(x) &= -(N-1-x)(N+b'-x), \\ \omega_n &= -\omega'_n = -n(2N+a'+b'+1-n). \end{aligned}\right\} \tag{15}$$

The difference equation (10) reduces to

$$\begin{aligned} -\omega'_n Q_n(x) = x(a'+1+x)\,Q_n(x-1) + (N-1-x)(N+b'-x)\,Q_n(x+1) \\ -[x(a'+1+x)+(N-1-x)(N+b'-x)]\,Q_n(x) \end{aligned} \tag{16}$$

and $Q_n(x) = Q_n(x; a, b, N)$ is given explicitly by (9) as before.

Let $S_k(\lambda) = S_k(\lambda, a', b', N)$ comprise the polynomial system obeying the recurrence relation

$$-\lambda S_k(\lambda) = -D(k)\,S_{k-1}(\lambda) + [D(k)+B(k)]\,S_k(\lambda) - B(k)\,S_{k+1}(\lambda), \tag{17}$$

$S_0(\lambda) = 1$ where $D(k)$ and $B(k)$ are now defined by (15). By comparison with (16), we see that

$$S_k(\omega'_n, a', b', N) = Q_n(k; a, b, N) \tag{18}$$

and a, b are connected to a', b' according to (14 a).

The polynomials (9) can be regarded as a discrete analogue of the infinite system of Jacobi polynomials. Similarly, the difference equation (10) can be regarded as a discrete approximation of the differential equation satisfied by the Jacobi polynomials.

3. *Representation formula for the Moran genetic model.* The background preparations are now complete and we return to the study of the Moran probability model set forth in § 1. We distinguish four cases.

Case 1. $\gamma_1, \gamma_2 > 0$, $1-\gamma_1-\gamma_2 > 0$. Some appropriate transformations on (8) and comparison with (10) show that

$$R_k(c\omega_n) = Q_n(k; a, b, N+1) \quad (n, k = 0, 1, \ldots, N), \tag{19}$$

where the right-hand side is (9) with

$$\left.\begin{aligned} a &= \frac{N\gamma_2}{1-\gamma_1-\gamma_2} - 1, \quad b = \frac{N\gamma_1}{1-\gamma_1-\gamma_2} - 1, \\ \omega_n &= n(n+a+b+1), \quad c = \frac{\lambda(1-\gamma_1-\gamma_2)}{N^2}. \end{aligned}\right\} \tag{20}$$

The representation formula (7) reduces to

$$P_{ij}(t) = \pi_j \sum_{n=0}^{N} \exp(-c\omega_n t)\, R_i(c\omega_n)\, R_j(c\omega_n)\, \psi_{n,N+1}\rho(0; a, b, N+1) \quad (i, j, = 0, 1, \ldots, N), \tag{21}$$

where $R_i(\lambda)$ are given in (19), $\psi_{n,N}$ is expressed in (14), $\rho(0; a, b, N+1)$ is the normalizing constant for ψ, and

$$\pi_j = \frac{\lambda_0 \lambda_1 \dots \lambda_{j-1}}{\mu_1 \mu_2 \dots \mu_j}.$$

Case 2. $\gamma_1, \gamma_2 > 0$, $\gamma_1 + \gamma_2 - 1 > 0$. Comparison of (8) with (16) shows that

$$R_k(c\omega'_n) = S_k(c\omega'_n) = Q_n(k; a, b, N+1), \tag{22}$$

where the right-hand side is (9) with

$$\left.\begin{gathered} a = -(N+b'+2), \quad b = -(N+a'+2), \\ a' = \frac{N(1-\gamma_2)}{\gamma_1+\gamma_2-1} - 1, \quad b' = \frac{N(1-\gamma_1)}{\gamma_1+\gamma_2-1} - 1, \quad c = \frac{\lambda(\gamma_1+\gamma_2-1)}{N^2}, \\ \omega'_n = n(2N+a'+b'+3-n). \end{gathered}\right\} \tag{23}$$

The representation formula (7) reduces to

$$P_{ij}(t) = \pi_j \sum_{n=0}^{N} \exp(-c\omega'_n) S_i(c\omega'_n) S_j(c\omega'_n) \psi_{n,N+1} \rho(0; a, b, N+1), \quad (i, j = 0, 1, \dots, N), \tag{24}$$

where the various symbols are defined explicitly in (22) and (23), $\psi_{n,N+1}(a, b, N)$ being expressed in (14).

Case 3. $\gamma_1 + \gamma_2 = 1$, $\gamma_1, \gamma_2 > 0$. The birth and death rates become linear in j rather than quadratic,

$$\lambda_j = \frac{\lambda\gamma_2}{N^2}(N-j), \quad \mu_j = \frac{\lambda}{N^2}(1-\gamma_2)j.$$

The polynomials $R_k(x)$ are now identified in terms of the Krawtchouk polynomials. Specifically,

$$R_n\left(\frac{\lambda x}{N^2}\right) = K_n(x; \gamma_2, N),$$

where $K_n(x; p, N)$ denote the Krawtchouk polynomials normalized so $K_n(0; p, N) = 1$; see (1). The representation formula (7) takes the form

$$P_{ij}(t) = \pi_j \sum_{n=0}^{N} \exp\left(-\frac{\lambda n}{N^2}\right) K_n(i; \gamma_2, N) K_n(j; \gamma_2, N) \psi_{n,N}, \tag{25}$$

where now $$\psi_{n,N} = \binom{N}{n} \gamma_2^{N-n} (1-\gamma_2)^n, \quad \pi_j = \binom{N}{j} \left(\frac{\gamma_2}{1-\gamma_2}\right)^n.$$

Case 4. $\gamma_1 = \gamma_2 = 0$. The homozygous states $j = 0, j = N$ act as absorbing barriers. To analyse this case we appeal to a standard method in the theory of birth and death processes for converting a reflecting barrier process into an absorbing barrier process ((5), p. 384). Consider the reflecting barrier process on the state space $0, 1, \dots, N-1$ characterized by the birth and death rates

$$\lambda_k^* = \lambda\left(1 - \frac{k+1}{N}\right)\left(\frac{k+1}{N}\right), \quad \mu_k^* = \lambda\frac{k}{N}\left(1 - \frac{k}{N}\right) \quad (k = 0, 1, \dots, N-1). \tag{26}$$

The corresponding polynomial system is $R_k(\lambda\omega_n/N^2) = Q_n(k; 0, 0, N)$ which obey the recurrence law (10) with $a = b = 0$, and $\omega_n = n(n+1)$. We form the polynomials

$$H_k\left(\frac{\lambda\omega_n}{N^2}\right) = \frac{\lambda_k^*\pi_k^*\left[R_{k+1}\left(\frac{\lambda\omega_n}{N^2}\right) - R_k\left(\frac{\lambda\omega_n}{N^2}\right)\right]}{-\frac{\lambda}{N^2}\omega_n}$$

$$= \frac{N^2\lambda_k^*\,\pi_k^*}{\lambda}\,\frac{Q_n(k+1; 0, 0, N) - Q_n(k; 0, 0, N)}{-\omega_n}$$

$$= \frac{N^2}{\lambda}\,\frac{\lambda_k^*\,\pi_k^*}{N-1}\,Q_{n-1}(k; 1, 1, N-1) \quad (k = 0, 1, \ldots, N-2) \tag{27}$$

valid for $n = 0, 1, \ldots, N-1$. The last identity is proved in (6). The polynomials (27) satisfy the usual recursion relation (8) with birth and death rates respectively

$$\lambda_k = \mu_k = \left(1 - \frac{k+1}{N}\right)\left(\frac{k+1}{N}\right)\lambda \quad (k = 0, 1, \ldots, N-2).$$

This is a process exhibiting an absorbing state at -1 and at $N-1$.

In carrying out the operations of (27) it transpires that the states of the process are shifted so that state -1 now is identified with the zero state of the original process and is ignored in our set-up and similarly state $N-1$ (also ignored) corresponds to state N in the original formulation. Here $P_{ij}(t)$ can be interpreted as the conditional probability of transitions from i to j in time t without absorption having occurred in the intervening time. Whenever the process occupies states 0 or $N-2$ then with probability $\mu_0 dt$ and $\lambda_{N-2}dt$ absorption takes place in the next dt time units into the -1 and $N-1$ state, respectively. The representation formula (7) has the form

$$P_{ij}(t) = \pi_j \sum_{n=1}^{N-1} \exp\left[-\frac{\lambda}{N^2}\omega_n t\right] H_i\left(\frac{\lambda}{N^2}\omega_n\right) H_j\left(\frac{\lambda}{N^2}\omega_n\right) \frac{\lambda\omega_n}{N^2\lambda_0^*}\,\psi_{n,N}\rho(0; 0, 0, N), \tag{28}$$

where $\omega_n = n(n+1)$ and $\psi_{n,N}$ is defined in (14) with $a = b = 0$.

There are two further cases ($\gamma_1 = 0$, $0 < \gamma_2 < 1$; $\gamma_2 = 0$, $0 < \gamma_1 < 1$) which can be handled by the methods of Case 4 above. We do not enter into details.

4. *Applications of the representation formula.* With the aid of the representation formula and the properties of the associated orthogonal polynomials we may deduce several probabilistic consequences. Three topics will be discussed which are typical of our method.

(*a*) *Rates of convergence to the stationary distributions.* In Cases 1, 2 and 3 the process tends to a stationary distribution

$$\lim_{t\to\infty} P_{ij}(t) = C\pi_j \quad (j = 0, 1, \ldots, N),$$

where

$$\pi_j = \frac{\lambda_0\lambda_1 \ldots \lambda_{j-1}}{\mu_1\mu_2 \ldots \mu_j},$$

λ_i, μ_i are the appropriate birth and death rates, and C is a normalizing constant.

Inspection of the representation formula reveals that the rate of approach is governed by the smallest positive point in the spectrum of the ψ measure. This is the second value in the spectrum when a stationary distribution exists. Specifically the rate of approach is of the order of magnitude $\exp[-c\omega_1 t]$, where c and ω_1 are defined in (20) for Case 1, (23) for Case 2, and (25) for Case 3. Actually, we can as well ascertain the direction of approach to the limit stationary probabilities. For example, we clearly infer by examination of the representation formula that $P_{ij}(t) \gtrless C\pi_j$ for t sufficiently large if and only if $R_i(c\omega_1) R_j(c\omega_1) \lessgtr 0$, where R_i denotes the relevant polynomial system defined in (8). In particular, we always have $R_{n-1}(c\omega_1) < 0$ and hence

$$P_{0,N-1}(t) < C\pi_{N-1} \quad \text{for} \quad t \text{ large.} \tag{29}$$

In fact, more is true. We know by (3) that $P_{0j}(t)$ is unimodal as a function of t. This fact combined with (29) implies that (29) holds indeed for all t. More generally, let $0 < j_0 < N-1$ be determined as the first j value for which $R_j(c\omega_1) \leqslant 0$. Now, the theory of orthogonal polynomials tells us that $R_j(c\omega_1) > 0$ for $j < j_0$ and $R_j(c\omega_1) < 0$ for $j > j_0$. Then $P_{0j}(t) < C\pi_j$ for all t provided $j > j_0$. On the other hand, $P_{0j}(t) > C\pi_j$ for t sufficiently large and $j < j_0$.

We conclude this paragraph by noting the rate of convergence for the model of Case 4. In fact, examination of (28), reveals that the rate of fixation is of the order of magnitude $\exp[-(2\lambda/N^2)t]$ as $t \to \infty$.

(*b*) *Recurrence and first passage distributions.* We indicate two examples. Consider the models corresponding to Cases 1, 2 or 3. Appealing to a general theorem (5) we know that the Laplace transform of the first passage time from state i to state $j > i$ is $R_i(-s)/R_j(-s)$ where R_i denotes the polynomial system of the process. This formula may be used routinely to get moments and other properties of the first passage distribution. In our case this is all the more useful since we have identified $R_i(.)$. Using the symmetry relation

$$Q_n(N-1-x; a, b, N) = \frac{Q_n(x; b, a, N)}{Q_n(N-1; b, a, N)}$$

valid for the polynomials (9), we possess an analogous formula for the Laplace transform of the first passage time from i to $j < i$.

Consider now the model of Case 4 where -1 and $N-1$ represent absorbing states. We can write immediately the probability distribution of the time of absorption into state -1 following the rules of (5), § 6. Thus, $\mu_0 P_{i0}(t)$ is the density function of fixation on a-gametes where i denotes the initial state. We will refer to this fact in the following paragraph. Similarly, the density function of the absorption time for fixation in state $N-1$ is $\lambda_{N-2} P_{i,N-2}(t)$. The functions $P_{i0}(t)$ and $P_{i,N-2}(t)$ are known explicitly by (27).

(*c*) *Limiting diffusion processes.* By using the known limiting relations

$$\lim_{N\to\infty} Q_n((N-1)x; a, b, N) = P_n(1-2x;\ a, b), \tag{30}$$

where $P_n(.\,; a, b)$ denotes the renormalized Jacobi polynomials

$$P_n^{a,b}(x)/P_n^{a,b}(1) = {}_2F_1(-n, n+a+b+1, a+1, \tfrac{1}{2}(1-x)),$$

we can now let $N \to \infty$ and obtain a diffusion process. This can be done for each of the models studied in § 3 but we will limit our discussions to the case of models 4 and 1.

We begin with model 4. Let x and y denote arbitrary real numbers for which $0 < x,\ y < 1$. We determine $i, j < N$ and N increasing to infinity preserving the relationship $i = [Nx]$ and $j = [Ny]$ where the square brackets signify as customary the integral part of the number bracketed. Inspection of (26) shows that $\lambda_i^* \pi_i^* \sim \lambda x(1-x)$ as $N \to \infty$ and by virtue of (27) and (30) we have

$$H_i\left(\frac{\lambda \omega_n}{N^2}\right) \sim Nx(1-x)\, P_{n-1}(1-2x;\, 1, 1) \quad (N \to \infty). \tag{31}$$

Similarly,

$$H_j\left(\frac{\lambda \omega_n}{N^2}\right) \sim Ny(1-y)\, P_{n-1}(1-2y;\, 1, 1) \quad (N \to \infty). \tag{32}$$

In the same way we obtain that

$$\pi_j \sim \frac{1}{Ny(1-y)}. \tag{33}$$

It is essential at this point to relate the parameter λ (which is the rate of mating in the whole population) with the size of the population. Since mating involves selecting a pair at random it is justifiable to postulate that $\lambda = \alpha N^2$ where N^2 is the number of possible pairs.

Now starting with (28) and taking account of (31), (32) and (33) we obtain

$$\begin{aligned} \lim_{N \to \infty} NP_{ij}(t) &= p(t;\, x, y) \\ &= \frac{1}{y(1-y)} \sum_{n=1}^{\infty} e^{-\alpha n(n+1)t} [x(1-x)\, P_{n-1}(1-2x;\, 1, 1)] \\ &\qquad \times [y(1-y)\, P_{n-1}(1-2y;\, 1, 1)]\, n(n+1)\,(2n+1). \end{aligned} \tag{34}$$

This limit assertion follows by virtue of dominated convergence with the aid of the crude estimates

$$|Q_n(x)| \leqslant (2+n)^{2n} \quad (x = 0, 1, \ldots, N-1),$$

$$\psi_{N,n} = O(n) \quad (n \geqslant 1).$$

The reader should consult (7) where a similar limit procedure is carried out with complete details.

It follows from (34) that

$$\lim_{N \to \infty} \sum_{Nv_1 \leqslant j \leqslant Nv_2} P_{ij}(t) = \int_{v_1}^{v_2} p(t;\, x, y)\, dy.$$

In particular $p(t;\, x, y)$ may be interpreted as the density function of a Markoff process whose realizations describe the fluctuation of the gene frequency of type a-gametes in an infinite population. More precisely if the proportion of a-gametes at time 0 is x then $p(t;\, x, y)$ denotes the density function of the proportion of a-gametes in the population at time t. The points 0 and 1 act as absorbing barriers. The density

$p(t; x, y)$ satisfies the forward diffusion equation and backward diffusion equation respectively

$$\frac{\partial p}{\partial t} = \alpha \frac{\partial^2}{\partial y^2}[y(1-y)\,p], \tag{35a}$$

$$\frac{\partial p}{\partial t} = \alpha x(1-x)\frac{\partial^2 p}{\partial x^2}, \tag{35b}$$

which can be checked directly with reference to the differential equation satisfied by $P_n(x; 1, 1)$. The boundary condition in (35*b*) is $p(t; 0, y) = p(t, 1, y) = 0$.

This continuous state diffusion process characterized by the diffusion equation (35) should be compared with a model of Kimura (9) described in the introduction of this paper.

Kimura investigates the diffusion model (35) for purposes of making computations which are difficult to do directly on the discrete model. The formulae obtained from (35) are to be taken as approximately valid. Moreover, the diffusion model (35) as explained by Kimura merely corresponds to the Markoff chain with matrix (2*a*) in that the mean displacement and the mean variance of displacement coincide. This was the main justification offered for its relevance. On the other hand our approach leads to (35) in a natural and completely rigorous manner based on the Moran model by letting the population size tend to infinity.

In general, it is difficult to evaluate various important distributions of functionals on the diffusion processes. For example, it would be desirable to calculate the distribution of the time for absorption into the 0 state (fixation of A-gametes). As far as we know this has not been evaluated; Kimura only obtained some approximations. We now show the strength of our method by determining this distribution explicitly.

As pointed out in paragraph (*b*) of this section, the probability density of the time of absorption into state -1 (i.e. fixation of A-gametes) in the finite population with initial state i is

$$\phi_N(i, t)\,dt = \mu_0 P_{i0}(t)\,dt.$$

Let $N \to \infty$ and $i = [Nx]$ in the manner of (34). We obtain the density function of the absorption time for fixation of A-gametes where the initial a-gamete gene frequency is x; viz.

$$\phi(x, t) = x(1-x)\,\alpha \sum_{n=1}^{\infty} \exp[-\alpha n(n+1)\,t]\,P_{n-1}(1-2x; 1, 1)\,n(n+1)\,(2n+1), \tag{36}$$

where $P_k(.; 1, 1)$ is the Jacobi polynomial with indicated parameters normalized so $P_k(1; 1, 1) = 1$.

By the identical limiting analysis other distributions of the process can be evaluated. The success of this method rests on our detailed knowledge of the fine structure of the underlying discrete birth and death process.

We conclude the paper by indicating as a further application of our method the nature of the limiting transition density as $N \to \infty$ of the mutation model (Case 1) set forth in § 3. Again, we postulate for the rate of mating $\lambda = \alpha N^2$. Its justification was indicated earlier in this paragraph. Also we require that the probabilities of mutation per individual γ_1 and γ_2 tend to zero as $N \to \infty$ so that $\gamma_1 N \to \kappa_1$ and

$\gamma_2 N \to \kappa_2$. (We assume $0 < \kappa_1, \kappa_2 < \infty$.) Thus κ_1 and κ_2 signify the mutation rate of the whole population per unit time.

We now investigate the limit of the terms in (21). Observe from their very definition that as $N \to \infty$

$$\left.\begin{aligned} a &\to \kappa_2 - 1, \quad b \to \kappa_1 - 1, \\ \omega_n &\to n(n+\kappa_1+\kappa_2-1), \quad c \to \alpha. \end{aligned}\right\} \tag{37}$$

Combining these limit relations with (30) shows that

$$R_i(c\omega_n) = Q_n(i; a, b, N+1) \to P_n(1-2x; \kappa_2 - 1, \kappa_1 - 1), \tag{38}$$

where $i = [Nx]$, and the right-hand side represents Jacobi polynomials normalized at $x = 0$ to equal 1 (see (1)). We verify directly that as $N \to \infty$,

$$\left.\begin{aligned} \psi_{n,N} &\to \frac{\Gamma(\kappa_1)}{\Gamma(\kappa_2)\,\Gamma(\kappa_1+\kappa_2-1)} \cdot \frac{\Gamma(n+\kappa_2)\,\Gamma(n+\kappa_1+\kappa_2-1)}{\Gamma(n+\kappa_1)\,\Gamma(n+1)} \cdot \frac{2n+\kappa_1+\kappa_2-1}{\kappa_1+\kappa_2-1}, \\ \rho(0, a, b, N+1) &\sim \frac{\Gamma(\kappa_1+\kappa_2-1)}{\Gamma(\kappa_1)\,N^{\kappa_2}}. \end{aligned}\right\} \tag{39}$$

Finally, we need to compute

$$\pi_j = \frac{\lambda_0 \lambda_1 \dots \lambda_{j-1}}{\mu_1 \mu_2 \dots \mu_j},$$

where

$$\lambda_j \sim \frac{\lambda}{N^2}(1-\gamma_1-\gamma_2)\,(N-j)\,(j+\kappa_2),$$

$$\mu_j \sim \frac{\lambda}{N^2}(1-\gamma_1-\gamma_2)\,j(N+\kappa_1-j).$$

Taking logarithms and executing obvious asymptotic estimates we deduce that

$$\pi_j \sim M' N^{\kappa_2-1} x^{\kappa_2-1}(1-x)^{\kappa_1-1}, \tag{40}$$

where M' is a suitable constant.

We now have available the ingredients to permit $N \to \infty$ in (21). The interchange of limit with summation is easily justified since the exponential factor converges like $\exp(-n^2 t)$. It follows for $i = [yN], j = [xN]$ that

$$\begin{aligned} \lim_{N\to\infty} NP_{ij}(t) &= p(t; y, x) \\ &= Mx^{\kappa_2-1}(1-x)^{\kappa_1-1} \sum_{n=0}^{\infty} \exp[-\alpha n(n+\kappa_1+\kappa_2-1)\,t] \\ &\quad \times P_n(1-2y; \kappa_2-1, \kappa_1-1)\,P_n(1-2x; \kappa_2-1, \kappa_1-1) \\ &\quad \times \frac{\Gamma(n+\kappa_2)\,\Gamma(n+\kappa_1+\kappa_2-1)}{\Gamma(n+\kappa_1)\,\Gamma(n+1)}(2n+\kappa_1+\kappa_2-1) \end{aligned}$$

and M is a suitable constant. This is the transition density function of a diffusion process in the interval $0 < x < 1$, where 0 and 1 are reflecting barriers. The backward equation of the process is

$$\frac{\partial p}{\partial t} = \beta(x(1-x))\frac{\partial^2 p}{\partial x^2} - [\kappa_2(1-x) + \kappa_1 x]\frac{\partial p}{\partial x},$$

where β is an appropriate constant. The stationary distribution of the process is

$$Cx^{\kappa_2-1}(1-x)^{\kappa_1-1}\,dx.$$

We wish to thank J. Gani, who brought the Moran papers to our attention.

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