RANDOM PROCESSES IN GENETICS

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ABSTRACT. Wright's model of a random process in genetics is modified by supposing that births and deaths occur individually at random so that the generations are no longer simultaneous. An exact solution is then obtained for the distribution of the number of a-genes in a haploid organism when mutation is occurring in both directions. When there is no mutation, the rate of approach to homozygosity is found in more complicated models with two sexes and diploid individuals. This rate is twice that occurring in Wright's models.

Sewell Wright (2), (3) has constructed a mathematical model in order to study the effect of small population size on the random fluctuation of gene frequency under the influence of mutation and selection. Suppose that there are N diploid monoecious individuals each formed from two gametes which are either a or A, and that j of the $2N$ gametes are a, where $j = 0, 1, \ldots, 2N$. We suppose that each of the gametes of the next generation is obtained by a random choice amongst the gametes of the previous generation so that the whole population changes at the one instant (as would happen in a seasonably breeding population with a life span of about one year). This implies, moreover, that self-fertilization is equally likely with fertilization by any other individual. In addition, let there be a probability α_1 of a gamete a mutating to A, and α_2 of a gamete A mutating to a. Then the probability of any particular gamete in the next generation being a is

$$p_j = \frac{j}{2N}(1-\alpha_1) + \left(1-\frac{j}{2N}\right)\alpha_2, \tag{1}$$

and of being A is

$$q_j = \frac{j}{2N}\alpha_1 + \left(1-\frac{j}{2N}\right)(1-\alpha_2). \tag{2}$$

Keeping the population size fixed, the probability of there being k a-gametes in the next generation if there were j in the previous generation is

$$p_{jk} = \binom{2N}{k} p_j^k q_j^{2N-k}. \tag{3}$$

The process can therefore be considered a Markov chain with $2N+1$ states and a transition probability from j to k equal to p_{jk}. The characteristic roots of the matrix of transition probabilities have been shown by W. Feller (1) to be equal to

$$(1-\alpha_1-\alpha_2)^r \binom{2N}{r} \frac{r!}{(2N)^r} \quad (r = 0, \ldots, 2N). \tag{4}$$

The main interest in the case $\alpha_1 \neq 0$, $\alpha_2 \neq 0$ is to estimate the pre-multiplying characteristic vector corresponding to the single unit root, since the elements of this vector are proportional to the probabilities of the states of the system when the latter has reached a stable condition. This vector has never been calculated explicitly, but it

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is possible to give an approximation which holds when $2N$ is large and α_1 and α_2 are small. Feller shows in his paper how Kolmogoroff's theory of random processes can be used to show that in these conditions the process can be approximated by a diffusion process for which the density distribution, $u(x,t)$, of the variable x $(0 \leqslant x \leqslant 1)$ at time t, satisfies the equation

$$u_t(t,x) = \{b(x)\,u(t,x)\}_{xx} - \{a(x)\,u(t,x)\}_x. \tag{5}$$

Here $u(x,t)$ is a continuous approximation to the discrete probability distribution of the random variable $j/2N$ and t is measured in units of N generations. Writing X_t for the random variable $j/2N$ at time t, X_t is approximated by a random variable with a probability density $u(x,t)$ which satisfies the above equations with

$$a(x) = \beta_2 - (\beta_1 + \beta_2)\,x, \tag{6}$$

$$2b(x) = \tfrac{1}{2}x(1-x), \tag{7}$$

where α_1 and α_2 have been put equal to $\beta_1(2N)^{-1}$ and $\beta_2(2N)^{-1}$ before the limit is taken. Then in the stable state we expect the probability distribution of X_t to be approximated by the solution of

$$\{b(x)\,u(t,x)\}_{xx} - \{a(x)\,u(t,x)\}_x = 0. \tag{8}$$

The solution of this equation, obtained as an approximation by Wright in another way, is any multiple of the function

$$u(x) = \frac{\Gamma(2\beta_1 + 2\beta_2)}{\Gamma(2\beta_1)\,\Gamma(2\beta_2)}\,x^{2\beta_2-1}(1-x)^{2\beta_1-1}. \tag{9}$$

Feller points out that if $u(t,x)$ is a solution of (5) which is a probability distribution, it does not follow that the limit of $u(t,x)$ as t increases is (9); for we might have

$$u(t,x) \to \mu u(x),$$

where $0 < \mu < 1$ and concentrations of probability exist at the points $x = 0, 1$. That this does not happen in Wright's model can be easily proved by calculating explicitly the limiting values of the first two moments of X_t and showing that they are equal to the moments of (9).

The case $\alpha_1 = \alpha_2 = 0$ is also of great interest in showing how fast fixation of a gene in a homozygous state can occur in a finite population as a result of random effects alone. There are clearly two unit roots of the matrix in this case, corresponding to fixation in the states $j = 0, j = 2N$, and the next largest root is $\left(1 - \frac{1}{2N}\right)$. From this it follows that in the long run the chance of the population being heterozygous will decline by a factor $\left(1 - \frac{1}{2N}\right)$ in each generation. The characteristic vector corresponding to this root has not been found.

In the present paper we obtain a more manageable theory by making a slight modification of the model. Instead of assuming that all the individuals die at the same time we assume that at each instant at which the state of the model may change, one of the gametes, chosen at random, dies and is replaced by a new gamete which is a or A with probabilities p_j, q_j given by (1) and (2), where j is the number of a's prior to

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the event. Strictly speaking this type of model should only apply to a haploid organism, whereas Wright's model, although it appears at first sight to be the same, can in fact be regarded either as a model of a population of N diploid individuals, since these all die and are replaced at the same time, or as a model of a population of $2N$ haploid individuals. However, when $\alpha_1 = \alpha_2 = 0$ we shall remove this restriction later.

The model is again representable as a Markov chain, in which the transitions now occur at the death of a single individual and not of the whole population. The number of steps in the present model equivalent to one generation will therefore be $2N$, although usually not all the $2N$ individuals will be replaced in this time.

It is instructive to observe that the present process, unlike Wright's, can be regarded as a Markov chain embedded in a Markov process in continuous time. We suppose that the probability of any individual 'dying' during an interval $(t, t+dt)$ and then being replaced by a new individual with the probabilities p_j, q_j, is $\lambda\, dt$. The mean number of such events in unit time will be $2N\lambda$ and the mean length of a generation is λ^{-1}, the lifetime distribution being negative exponential. The algebraic equations defining the process are then replaced by a set of ordinary differential equations.

We may summarize the difference between the present model and Wright's by saying that the latter applies to haploid or diploid individuals in a population with a more or less fixed lifetime of one year and a fixed breeding season so that successive generations in different lines of descent never get out of step, whereas the present model applies to a population in which breeding and mortality are occurring all the time. Moreover, the present model only applies strictly to a haploid population, although for $\alpha_1 = \alpha_2 = 0$ we shall remove this restriction later.

Both in Wright's model and in the present model the fact that $2N$ is an even number has no mathematical significance and we shall write M for $2N$ for convenience. The transition probabilities p_{jk} from state j to state k are given by

$$\begin{aligned} p_{j,j-1} &= \frac{j}{M} q_j, \\ p_{j,j} &= \frac{j}{M} p_j + \left(1 - \frac{j}{M}\right) q_j, \\ p_{j,j+1} &= \left(1 - \frac{j}{M}\right) p_j, \\ p_{j,k} &= 0 \quad \text{if} \quad k > j+1 \quad \text{or} \quad k < j-1. \end{aligned}$$

We consider first the case in which $\alpha_1 = \alpha_2 = 0$. Then $p_j = j/M$, $q_j = 1 - j/M$; $j = 0$ and $j = M$ are the two absorbing states and there are two unit characteristic roots corresponding to these. In fact the characteristic roots of the matrix have been proved by Dr E. J. Hannan (see Appendix) to be

$$1 - \frac{s(s-1)}{M^2} \quad (s = 0, 1, \ldots, M).$$

so that the third largest root is $1 - \frac{2}{M^2}$ with a corresponding post-vector of components proportional to

$$-2(M-1)^{-1}, 1, 1, \ldots, 1, 1, -2(M-1)^{-1}.$$

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Asymptotically, the rate of decrease of heterozygosity is therefore $1-\frac{2}{M^2}$ for each event, or

$$\left(1-\frac{2}{M^2}\right)^M$$

per generation. This is approximately $1-\frac{2}{M}$ when M is large, and thus the rate of decrease of heterozygosity is twice that in Wright's model.

The reason for this demands careful consideration. At first sight it might seem to be the result of the fact that we are considering a birth and death process amongst the gametes rather than the zygotes. This is not the case, since Wright's process can itself be regarded as a birth and death process on gametes or on zygotes and, moreover, the zygote birth and death process considered later also shows approximately twice the rate of progress to homozygosity of the Wright model. A clearer understanding of the mathematical reasons for the difference may be seen by considering the random variable $X_t = jM^{-1}$. It is easy to see that

$$E(X_{t+1}-X_t \mid X_t) = M^{-1}\{(1-X_t)X_t - X_t(1-X_t)\} = 0,$$

so that $E(X_t) = X_0$. Similarly

$$E\{(X_{t+1}-X_t)^2 \mid X_t\} = 2M^{-2}X_t(1-X_t).$$

In Wright's model on the other hand, while $E(X_t) = X_0$ as before,

$$E\{(X_{t+1}-X_t)^2 \mid X_t\} = M^{-1}X_t(1-X_t).$$

Thus, per generation, the change in X_t has approximately twice the variance in the present model that it has in Wright's, and when M is large, so that we can represent the model approximately by a diffusion process, the rate of diffusion is twice as large. This arises because randomness enters into the birth and death event not only in the random choice of the offspring but also in the random choice of the individual dying.

Now consider the case $\alpha_1 \neq 0$, $\alpha_2 \neq 0$. By induction it is easy to show that if $\{P_i\}$ is the stable probability distribution ($i = 0, \ldots, M$) then

$$P_k = P_{k-1}\frac{(M-k+1)p_{k-1}}{kq_k},$$

so that

$$P_k = P_0\left\{\frac{M(M-1)\ldots(M-k+1)p_0p_1\ldots p_{k-1}}{k!\,q_1q_2\ldots q_k}\right\}$$

$$= P_0\frac{\Gamma(M+1)\,\Gamma\left(\frac{M\alpha_2}{1-\alpha_1-\alpha_2}+k\right)\Gamma\left(\frac{M(1-\alpha_2)}{1-\alpha_1-\alpha_2}-k\right)}{\Gamma(k+1)\,\Gamma(M-k+1)\,\Gamma\left(\frac{M\alpha_2}{1-\alpha_1-\alpha_2}\right)\Gamma\left(\frac{M(1-\alpha_2)}{1-\alpha_1-\alpha_2}\right)}, \tag{10}$$

which gives us an explicit solution. We next have to find P_0 which we obtain from the equation

$$P_0\left\{1+\sum_{k=1}^{M}\frac{M!\,p_0\ldots p_{k-1}}{M-k!\,k!\,q_1\ldots q_k}\right\} = 1.$$

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To evaluate this we first prove an algebraic identity. Write $u_j = x+jy$, $v_j = 1-x-jy$, where x and y are any numbers. Consider the sum

$$S_M(x,y) = v_1 v_2 \dots v_M + \binom{M}{1} u_0 v_2 \dots v_M + \binom{M}{2} u_0 u_1 v_3 \dots v_M + \dots + u_0 u_1 \dots u_{M-1},$$

where M is a positive integer. We shall prove that

$$S_M(x,y) = (1-y)(1-2y)\dots(1-My).$$

This can easily be verified for small values of M. Assume it true for some value M. Then

$$\begin{aligned} S_{M+1}(x,y) &= v_{M+1} S_M(x,y) + u_0 S_M(x+y,y) \\ &= (1-x-(M+1)y+x)(1-y)(1-2y)\dots(1-My) \\ &= (1-y)(1-2y)\dots(1-(M+1)y). \end{aligned}$$

We now have

$$\left\{1+\sum_{k=1}^{M} \frac{M!\, p_0 \dots p_{k-1}}{k!\,M-k!\, q_1 \dots q_k}\right\}$$

$$= (q_1 \dots q_M)^{-1}\left\{q_1 \dots q_M + \binom{M}{1} p_0 q_2 \dots q_M + \dots + p_0 p_1 \dots p_{M-1}\right\},$$

and using the above identity with $x = \alpha_2$, $y = (1-\alpha_1-\alpha_2)/M$ we find that this is equal to

$$\frac{\left\{1-\frac{1-\alpha_1-\alpha_2}{M}\right\}\left\{1-2\frac{1-\alpha_1-\alpha_2}{M}\right\}\dots\{1-(1-\alpha_1-\alpha_2)\}}{\left\{1-\alpha_2-\frac{1-\alpha_1-\alpha_2}{M}\right\}\left\{1-\alpha_2-2\frac{1-\alpha_1-\alpha_2}{M}\right\}\dots\{1-\alpha_2-(1-\alpha_1-\alpha_2)\}},$$

and so

$$P_0 = \frac{\Gamma\left(\frac{M(1-\alpha_2)}{1-\alpha_1-\alpha_2}\right)\Gamma\left(\frac{M(\alpha_1+\alpha_2)}{1-\alpha_1-\alpha_2}\right)}{\Gamma\left(\frac{M}{1-\alpha_1-\alpha_2}\right)\Gamma\left(\frac{M\alpha_1}{1-\alpha_1-\alpha_2}\right)}. \tag{11}$$

Suppose now that M becomes large and α_1, α_2 tend to zero in such a way that $\alpha_1 = \beta_1 M^{-1}$, $\alpha_2 = \beta_2 M^{-1}$, where β_1, β_2 are fixed. Using Stirling's formula we see that P_0 is asymptotically equal to

$$\frac{\Gamma(\beta_1+\beta_2)}{\Gamma(\beta_1)} M^{-\beta_2}.$$

It follows that P_0 tends to zero in any case, while MP_0 tends to zero, to

$$\frac{\Gamma(\beta_1+\beta_2)}{\Gamma(\beta_1)},$$

or to infinity according as $\beta_2 > 1$, $= 1$ or < 1. Inserting the above value of P_0 in (10) we find that MP_k is asymptotically equal to

$$\frac{\Gamma(\beta_1+\beta_2)}{\Gamma(\beta_1)\Gamma(\beta_2)} X^{\beta_2-1}(1-X)^{\beta_1-1},$$

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where $X = kM^{-1}$ is kept fixed. Hence the random variable X has asymptotically a continuous probability distribution with density

$$\frac{\Gamma(\beta_1+\beta_2)}{\Gamma(\beta_1)\,\Gamma(\beta_2)}\,X^{\beta_2-1}(1-X)^{\beta_1-1},$$

and there is no concentration of probability at $X = 0$, $X = 1$. This is the same form as in Wright's model, with his β_1 and β_2 replaced by $\frac{1}{2}\beta_1$, $\frac{1}{2}\beta_2$. This distribution will be a good approximation so long as $\beta_1 > 0, \beta_2 > 0$ are not too small. If they are very small so that the distribution is very U-shaped, the approximation may break down at each end point since in the discrete model there is a positive concentration of probability at $k = 0$, $k = M$.

We now show how consideration of the moments of X_t can be used to provide information about the roots of the matrix of transition probabilities. We have

$$\begin{aligned} E(X_{t+1}-X_t) &= M^{-1}\{(1-X_t)\,p_k - X_t q_k\} \\ &= M^{-1}\{\alpha_2 - X_t(\alpha_1+\alpha_2)\} \\ &= 0 \quad \text{if} \quad \alpha_1 = \alpha_2 = 0. \end{aligned}$$

Hence when $\alpha_1 = \alpha_2 = 0$ the probability of absorption in $X = 1$ is X_0 and of absorption in $X = 0$ is $(1-X_0)$. If $\alpha_1 \neq 0$, $\alpha_2 \neq 0$ we can solve the difference equation to obtain

$$E(X_t) = \alpha_2\left\{1-\left(1-\frac{\alpha_1+\alpha_2}{M}\right)^t\right\}(\alpha_1+\alpha_2)^{-1} + X_0\left(1-\frac{\alpha_1+\alpha_2}{M}\right)^t, \tag{12}$$

so that $E(X_t)$ then tends to $\alpha_2(\alpha_1+\alpha_2)^{-1}$.

Now consider

$$\begin{aligned} E(X_{t+1}^2) &= E(X_t^2) + E(X_{t+1}-X_t)^2 + 2E\{(X_{t+1}-X_t)\,X_t\} \\ &= E(X_t^2)\{1-2M^{-2}(1-\alpha_1-\alpha_2) - 2M^{-1}(\alpha_1+\alpha_2)\} \\ &\qquad + E(X_t)\{M^{-2}(2-\alpha_1-3\alpha_2) + 2\alpha_2 M^{-1}\} + \alpha_2 M^{-2}.) \end{aligned}$$

Inserting the value of $E(X_t)$ and solving this difference equation we obtain

$$E(X_t^2) = a_0 + a_1(1-M^{-1}(\alpha_1+\alpha_2))^t + a_2(1-2M^{-2}(1-\alpha_1-\alpha_2) - 2M^{-1}(\alpha_1+\alpha_2))^t, \tag{13}$$

where a_0, a_1 and a_2 are rather complicated non-zero constants depending on α_1, α_2 and M.

Now consider how we can use formulae for the moments to obtain information about the roots. Suppose that $\lambda_0, \lambda_1, \ldots, \lambda_s$ are the roots of the matrix, with

$$1 = \lambda_0 > |\lambda_1| \geqslant |\lambda_2| \geqslant |\lambda_3| \geqslant \ldots \geqslant |\lambda_s|,$$

and with multiplicities $m_0, m_1, \ldots, m_s$, where $m_0 + \ldots + m_s = M+1$. All states are accessible from the states $k = 1, \ldots, M-1$ and if $\alpha_1 = \alpha_2 = 0$ the states $k = 0$, $k = M$ are absorbing. Then for any particular value of j satisfying $1 \leqslant j \leqslant M-1$ we have

$$p_{jk}^{(n)} = a_0^{(k)} + a_1^{(k)}(n)\,\lambda_1^n + \ldots + a_s^{(k)}(n)\,\lambda_s^n,$$

where $a_n^{(k)}(n)$ $(r = 1, \ldots, s)$ is a polynomial of degree at most $m_r - 1$ in n.

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It is possible that $|\lambda_1| = |\lambda_2|$ if these roots are conjugate complex, but in the expansion of $p_{jk}^{(r)}$ the term

$$a_1^{(k)}(n)\lambda_1^n + a_2^{(k)}(n)\lambda_2^n$$

must be real. Thus, whatever the nature of λ_1, when $\alpha_1 = \alpha_2 = 0$, $a_0^{(k)} = 0$ for $k = 1, \ldots, M-1$ and the probabilities of the system being in the states $k = 1, \ldots, M-1$ will all ultimately be non-zero and decreasing asymptotically in a geometric progression whose ratio is $|\lambda_1|$ for each birth-death event. Thus an explicit formula for any expression such as $E(X_t - rM^{-1})^2$ $(r = 1, \ldots, M-1)$ must ultimately be increasing and contain λ_1^n in one of its terms. Any other term of the form λ^n must be such that either $|\lambda| = \lambda_1$ or λ is one of the other roots. In this way we can prove once again that $(1-2M^{-2})$ is a root of the matrix when $\alpha_1 = \alpha_2 = 0$, and this technique can be applied to much more complicated models.

When $\alpha_1 \neq 0$, $\alpha_2 \neq 0$ we see from (13) that

$$1 - M^{-1}(\alpha_1 + \alpha_2) \quad \text{and} \quad 1 - 2M^{-2}(1 - \alpha_1 - \alpha_2) - 2M^{-1}(\alpha_1 + \alpha_2)$$

are roots of the matrix. The above method of argument does not then show that these are the second and third largest roots but this will certainly be true for α_1 and α_2 small since they then tend to 1 and $1 - 2M^{-2}$ which are the second and third roots when $\alpha_1 = \alpha_2 = 0$, and the roots are clearly continuous functions of α_1 and α_2.

We now construct a model without mutation in which each individual subject to death and birth is diploid. We consider zygotes which are aa, Aa or AA. Let there be k, $N-k-l$ and l of these respectively, so that we are now dealing with a bivariate model with two random variables, k and l. Successive events will each consist of one of these zygotes dying at random and being replaced by a new zygote whose gametes are independently chosen to be a or A with probabilities proportional to the numbers of a and A gametes in the population before death. Once again this model, which is clearly a Markov chain with $\frac{1}{2}(N+1)(N+2)$ states, could be regarded as embedded in a continuous Markov process in which each individual zygote has a negative exponential distribution of its life time. The states of the Markov chain are defined by the two variates k and l such that $k, l = 0, 1, \ldots, N$ and $k + l \leqslant N$. The number of a gametes is $N + k - l$ and thus we see that the transition probabilities are

$(k,l) \to (k+1, l+1)$: 0.

$(k,l) \to (k+1, l)$: $(N-k-l)(N+k-l)^2(4N^3)^{-1}$.

$(k,l) \to (k+1, l-1)$: $l(N+k-l)^2(4N^3)^{-1}$.

$(k,l) \to (k, l-1)$: $l(N^2-(k-l)^2)(2N^3)^{-1}$.

$(k,l) \to (k-1, l-1)$: 0.

$(k,l) \to (k-1, l)$: $k(N^2-(k-l)^2)(2N^3)^{-1}$.

$(k,l) \to (k-1, l+1)$: $k(N+l-k)^2(4N^3)^{-1}$.

$(k,l) \to (k, l+1)$: $(N-k-l)(N+l-k)^2(4N^3)^{-1}$.

$(k,l) \to (k,l)$: $\{k(N+k-l)^2 + 2(N-k-l)(N^2-(k-l)^2) + l(N+l-k)^2\}(4N^3)^{-1}$.

The matrix of these transition probabilities could be written with some suitable convention for ordering the states but appears to be too complicated to consider

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directly. There are two absorbing states ($k = N, l = 0$) and ($k = 0, l = N$), and the other states are all transient. All states are accessible from any state which is not an absorbing state. It follows that there are exactly two unit roots and our aim is to find the next largest root. Suppose that the system starts in some transient state and that the probability of state (k, l) is $P^{(n)}_{(k,l)}$ when n births have occurred. Then $P^{(n)}_{N,0}$ and $P^{(n)}_{0,N}$ will continually increase and the $P^{(n)}_{k,l}$, other than these will ultimately decrease in such a way that $P^{(n+1)}_{k,l}(P^{(n)}_{k,l})^{-1}$ will tend to $|\lambda_3|$, the modulus of the third largest root.

Define random variables, X_t and Y_t, equal to the values of kN^{-1} and lN^{-1} at the time t. We have $X_t + Y_t \leqslant 1$ and (using k and l for the values at time t)

$$\begin{aligned} E(X_{t+1} - X_t) &= (4N^4)^{-1} E\{N^3 - 2N^2(k+l) - N(k-l)^2\} \\ &= (4N)^{-1} E\{1 - 2(X_t + Y_t) + (X_t - Y_t)^2\}. \end{aligned}$$

A similar result holds for $E(Y_{t+1} - Y_t)$. Writing $u_t = E(X_t + Y_t)$, $v_t = E(X_t - Y_t)^2$, we have

$$u_{t+1} = (2N)^{-1} + (1 - N^{-1})\, u_t + (2N)^{-1} v_t. \tag{14}$$

Next, we have

$$\begin{aligned} v_{t+1} = E(X_{t+1} - Y_{t+1})^2 = E(X_t - Y_t)^2 + E(X_{t+1} - Y_{t+1} - X_t + Y_t)^2 \\ + 2E\{(X_{t+1} - Y_{t+1} - X_t + Y_t)(X_t - Y_t)\}, \end{aligned}$$

in which the third term is zero. Evaluating the second term by enumerating all the cases, we find

$$\begin{aligned} v_{t+1} - v_t &= (4N^5)^{-1} E\{2(k+l)(N^2 - (k-l)^2) + 4k(N + l - k)^2 \\ &\quad + 4l(N + k - l)^2 + (N - k - l)((N + l - k)^2 + (N + k - l)^2)\} \\ &= (4N^2)^{-1}\{4u_t + 2 - 6v_t\}. \end{aligned} \tag{15}$$

The solution of the pair of difference equations (14) and (15) will be of the form

$$\begin{aligned} u_t &= a_0 + a_1 \lambda_1^t + a_2 \lambda_2^t, \\ v_t &= b_0 + b_1 \lambda_1^t + b_2 \lambda_2^t, \end{aligned}$$

where the λ's are the roots of the quadratic equation

$$\begin{vmatrix} \lambda - 1 + N^{-1} & (2N)^{-1} \\ N^{-2} & \lambda - 1 + 3(2N^2)^{-1} \end{vmatrix}$$

$$= \lambda^2 - \{2 - N^{-1} - 3(2N^2)^{-1}\}\lambda + \{1 - N^{-1} - 3(2N^2)^{-1} + N^{-3}\} = 0.$$

These roots are

$$1 - (2N)^{-1} - 3(4N^2)^{-1} \pm (2N)^{-1}\sqrt{\{1 - N^{-1} + 9(4N^2)^{-1}\}}.$$

For N large these are equal to $1 - N^{-2} + o(N^{-3})$ and $1 - N^{-1} + o(N^{-2})$. The smaller of these two roots, $1 - N^{-1} + o(N^{-2})$, is apparently connected with rate of approach to a state in which the Hardy–Weinberg relation holds approximately. We can show that the larger root, $1 - N^{-2} + o(N^{-3})$, gives the rate of approach to homozygosity by observing that all the states with $X_t + Y_t < 1$ are transient, and the probabilities of these states will ultimately decrease in the ratio λ, where λ is the rate of decrease of heterozygosity. Thus the explicit formula for u_t must contain a factor λ^t, and this will

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be the largest factor of this form in u_t. However a_2 can be verified to be non-zero by explicit calculation from u_0, u_1, u_2, v_0, v_1 and v_2 provided the initial state is not an absorbing one.

Thus the rate of approach to homozygosity is $1-N^{-2}$ per birth, or approximately $1-N^{-1}$ per generation of N births, which is again twice that of Wright's model; and the reason for this is the same, namely that an additional element of randomness is introduced by the random choice of the element which is to die.

Now consider a model with two sexes. Suppose that there are N_1 males of which k, N_1-k-l, and l are aa, Aa and AA respectively, and N_2 females of which r, N_2-r-s, s are aa, Aa and AA. Then the proportion of a's in males and females are

$$(2N_1)^{-1}(N_1+k-l) \quad \text{and} \quad (2N_2)^{-1}(N_2+r-s).$$

At each transition one of the $N = N_1+N_2$ individuals, chosen at random, dies and is replaced by an individual of the same sex one of whose gametes is chosen at random from the male population before death, and the other from the female population. The state of the system is then defined by the set of four numbers (k,l,r,s) where $k,l = 0,\ldots,N_1$ $(k+l \leqslant N_1)$ and $r,s = 0,\ldots,N_2$ $(r+s \leqslant N_2)$. The system is a Markov chain, and if there is no mutation there are exactly two absorbing states, $(N_1,0,N_2,0)$ and $(0,N_1,0,N_2)$.

The probabilities of death of a male individual aa, Aa, AA and of a female individual, aa, Aa and AA are then kN^{-1}, $(N_1-k-l)N^{-1}$, lN^{-1}, rN^{-1}, $(N_2-r-s)N^{-1}$ and sN^{-1} respectively where $N = N_1+N_2$. If a male dies, the probabilities that the replacing male is aa, Aa or AA are

$$\begin{gathered}(N_1+k-l)(N_2+r-s)(4N_1N_2)^{-1},\\ \{(N_1+k-l)(N_2-r+s)+(N_1-k+l)(N_2+r-s)\}(4N_1N_2)^{-1},\\ (N_1-k+l)(N_2-r+s)(4N_1N_2)^{-1},\end{gathered}$$

respectively, and the corresponding female probabilities are obtained by replacing N_1, N_2, k, l, r, s by N_2, N_1, r, s, k, l. Then apart from the transition $(k,l,r,s) \to (k,l,r,s)$ the possible states to which there can be a transition from (k,l,r,s), together with their probabilities, are as follows:

$(k+1,l,r,s)$: $(N_1-k-l)(N_1+k-l)(N_2+r-s)(4NN_1N_2)^{-1}$.

$(k+1,l-1,r,s)$: $l(N_1+k-l)(N_2+r-s)(4NN_1N_2)^{-1}$.

$(k,l-1,r,s)$: $l\{(N_1+k-l)(N_2-r-s)+(N_1-k+l)(N_2+r-s)\}(4NN_1N_2)^{-1}$.

$(k-1,l,r,s)$: $k\{(N_1+k-l)(N_2-r+s)+(N_1-k+l)(N_2+r-s)\}(4NN_1N_2)^{-1}$.

$(k-1,l+1,r,s)$: $k(N_1-k+l)(N_2-r+s)(4NN_1N_2)^{-1}$.

$(k,l+1,r,s)$: $(N_1-k-l)(N_1-k+l)(N_2-r+s)(4NN_1N_2)^{-1}$.

$(k,l,r+1,s)$: $(N_2-r-s)(N_1+k-l)(N_2+r-s)(4NN_1N_2)^{-1}$.

$(k,l,r+1,s-1)$: $s_1(N_1+k-l)(N_2+r-s)(4NN_1N_2)^{-1}$.

$(k,l,r,s-1)$: $s\{(N_1+k-l)(N_2-r+s)+(N_1-k+l)(N_2+r-s)\}(4NN_1N_2)^{-1}$.

$(k,l,r-1,s)$: $r\{(N_1+k-l)(N_2-r+s)+(N_1-k+l)(N_2+r-s)\}(4NN_1N_2)^{-1}$.

$(k,l,r-1,s+1)$: $r(N_1-k+l)(N_2-r+s)(4NN_1N_2)^{-1}$.

$(k,l,r,s+1)$: $(N_2-r-s)(N_1-k+l)(N_2-r+s)(4NN_1N_2)^{-1}$.

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Now write X_t, Y_t, W_t, Z_t for kN_1^{-1}, lN_1^{-1}, rN_2^{-1}, sN_2^{-1}, and

$$\begin{aligned} p_t &= E(X_t+Y_t), \\ q_t &= E(W_t+Z_t), \\ v_t &= E(X_t-Y_t)(W_t-Z_t), \\ a_t &= E(X_t-Y_t)^2, \\ b_t &= E(W_t-Z_t)^2. \end{aligned}$$

Enumerating the various possibilities we see that

$$E(X_{t+1})-E(X_t) = (4NN_1N_2)^{-1}\{N_1N_2+N_1(r-s)+N_2(k-l)+(k-l)(r-s)-4kN_2\},$$

where k, l, r, s are the values at time t. From this it follows that

$$p_{t+1} = (1-N^{-1})p_t+(2N)^{-1}\{1+v_t\}.$$

By a similar enumeration of possibilities we get

$$\begin{aligned} q_{t+1} &= (1-N^{-1})q_t+(2N)^{-1}(1+v_t), \\ v_{t+1} &= (1-N^{-1})v_t+(2N)^{-1}(a_t+b_t), \\ a_{t+1} &= (2NN_1)^{-1}(1-2a_t+2p_t-v_t)+N^{-1}(v_t-a_t)+a_t, \\ b_{t+1} &= (2NN_2)^{-1}(1-2b_t+2q_t-v_t)+N^{-1}(v_t-b_t)+b_t. \end{aligned}$$

The five quantities p_t, q_t, v_t, a_t and b_t thus satisfy a five-variable first-order difference equation, and they approach their asymptotic values at a rate which is ultimately determined by the modulus of the largest root of the matrix

$$\begin{pmatrix} 1-N^{-1} & 0 & (2N)^{-1} & 0 & 0 \\ 0 & 1-N^{-1} & (2N)^{-1} & 0 & 0 \\ 0 & 0 & 1-N^{-1} & (2N)^{-1} & (2N)^{-1} \\ (NN_1)^{-1} & 0 & N^{-1}-(2NN_1)^{-1} & 1-N^{-1}-(NN_1)^{-1} & 0 \\ 0 & (NN_2)^{-1} & N^{-1}-(2NN_2)^{-1} & 0 & 1-N^{-1}-(NN_2)^{-1} \end{pmatrix}.$$

Let λ be the largest root of this matrix and put

$$\lambda = 1-\mu N^{-1} \quad \text{and} \quad M = (2N_1)^{-1}+(2N_2)^{-1} = N(2N_1N_2)^{-1}.$$

Then the determinant of the matrix equation turns out to be

$$\begin{aligned} \mu^5 - (5+2M)\mu^4+(9-\tfrac{17}{2}M+2MN^{-1})\mu^3-(7+12M+7MN^{-1})\mu^2 \\ +(2+\tfrac{13}{2}M+7MN^{-1})\mu-(M+2MN^{-1}) = 0. \end{aligned}$$

We are looking for the smallest root of this equation, and, if N_1, N_2 are not small, M is of the order of the smaller of N_1^{-1} and N_2^{-1}; and the smallest root of the equation is approximately $\frac{1}{2}M = N(4N_1N_2)^{-1}$ and the largest root of the original matrix is approximately

$$\left(1-\frac{1}{4N_1N_2}\right). \tag{16}$$

By a similar argument to that used in the case of a diploid monoecious population it follows that (16) gives the asymptotic rate of decrease of heterozygosity provided

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N_1 and N_2 are not too small. This is again just twice the rate of decrease in Wright's two sex model, when we remember that one generation in his model must correspond on the average to $N_1 + N_2$ events in this model.

In subsequent papers we shall consider models involving two sexes and diploid individuals, and models for selection.

APPENDIX

By E. J. Hannan

The transition matrix in the first model has roots $1 - s(s-1)M^{-2}$ $(s = 0, 1, \ldots, M)$. This is equivalent to asserting that the matrix A

$$\begin{pmatrix} 0 & (M-1) & & & & \\ 0 & -2(M-1) & 2(M-2) & & & \\ & (M-1) & -4(M-2) & 3(M-3) & & \\ & & 2(M-2) & -6(M-3) & \ldots & \\ & & & \ldots & -2(M-1) & 0 \\ & & & & (M-1) & 0 \end{pmatrix}$$

(with zeros elsewhere) has characteristic roots $s(s-1)$ $(s = 0, 1, \ldots, M)$. To show this we construct a sequence of similarity transformations by matrices $P_0, P_1, \ldots$, so that

$$A_s = P_s P_{s-1} \ldots P_0 A P_0^{-1} \ldots P_s^{-1}$$

is of the form $$\begin{pmatrix} B_s & 0 \\ C_s & D_s \end{pmatrix},$$

where B_s is a lower triangular matrix of order $s+1$ with the elements

$$0, \quad 0, \quad 2.1, \quad 3.2, \quad \ldots, \quad s(s-1)$$

in its main diagonal, while $(C_s\ D_s)$ is the same as the corresponding rows of A except for its first row (which corresponds to the $(s+2)$th row of A) which consists of s zeros followed by

$$s(m-s), \quad -2(s+1)(M-s-1) - \binom{s+1}{1} s(M-s), \quad (s+2)(M-s-2) - \binom{s+2}{2} s(M-s)$$

and then by $$-\binom{s+j-1}{j-1} s(M-s)$$

in the $(s+j)$th column, where $j = 4, 5, \ldots, M+1-s$.

We define P_{s+1} to be $I + Q_s$, where Q_s is a matrix with $\binom{s+2}{1}$, $\binom{s+3}{2}$ in the $(s+3)$th and $(s+4)$th place of the $(s+2)$th row and zeros elsewhere. Then P_{s+1}^{-1} is equal to $I - Q_s$. Clearly P_0 performs what is required of it. The proof is completed by an induction so that we must show that the application of the similarity transformation based on P_{s+1} to the matrix A_s results in A_{s+1}.

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The application of P_{s+1} on the left affects only the $(s+2)$th row, which now becomes a row consisting of s zeros followed, in order, by the following terms

$$s(m-s) \qquad = s(m-s),$$

$$-2(s+1)(m-s-1)-\binom{s+1}{1}s(m-s)+\binom{s+2}{1}(s+1)(m-s-1) = -s(s+1),$$

$$(s+2)(m-s-2)-\binom{s+2}{2}s(m-s)-2\binom{s+2}{1}(s+2)(m-s-2)$$

$$+\binom{s+3}{2}(s+2)(m-s-2) \qquad = -\binom{s+2}{1}s(s+1),$$

.....

$$\binom{s+j-1}{j-1}s(m-s)+\binom{s+j-2}{j-3}(s+j-1)(m-s-j+1)$$

$$-2\binom{s+j-1}{j-2}(s+j+1)(m-s-j+1)+\binom{s+j}{j-1}(s+j-1)(m-s-j+1)$$

$$= -\binom{s+j-1}{j-2}s(s+1),$$

.....

The application of P_{s+1}^{-1} on the right, which affects only rows $(s+2)$ and $(s+3)$, then results in M_{s+1}. The lower triangular matrix M_m then has $-s(s-1)$ in the main diagonal, $(s-1)(m-s+1)$ in the sub-diagonal and zeros elsewhere. Moreover, $P_m P_{m-1} \dots P_0$ is a matrix whose (i,j) element is $\binom{j}{j-1}$ $(i,j = 0, \dots, M)$ for $i < j$ and zero elsewhere. From this the right characteristic vectors of M_m can be found.

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