

## Some invariant properties of a geographically structured finite population: distribution of heterozygotes under irreversible mutation\*

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### SUMMARY

It is shown that the distribution of the sum of heterozygotes, due to mutant gene(s), that appear in a finite population is invariant under geographical structure, provided that the mutant gene has additive effect on fitness and migration does not change the genetic constitution as a whole population. The expected number of heterozygotes is  $2N$  when  $Ns = 0$  and gradually rises to  $4N$  as  $Ns$  increases provided  $s$  remains small, where  $N$  = the total population size and  $s$  = selective advantage of a mutant gene. The distribution of the heterozygosity summed over those generations in which the gene frequency in the entire population is specified, is also shown to be invariant. In the case of a neutral mutant, the density is equal to  $4(1 - Y)$  where  $Y$  is the frequency of the mutant in the whole population, and in the selectively advantageous case, it is approximately equal to a constant function 4, provided that the population size times selection coefficient is sufficiently large. These quantities conditional on the fixation of the mutant are shown to be invariant and some special cases are obtained explicitly.

It is well known that, if alleles are selectively neutral, the heterozygosity in a random mating population of finite size ( $N$ ) decreases by the rate  $1/2N$  per generation, (Wright, 1931, and others). From this theory, we can easily show that the expected sum of heterozygotes formed by a mutant between occurrence and final fixation or loss is  $2N$ . This assumes however, that any heterozygotes between this and any subsequent mutation are not counted. This is an invariant property over geographical structure of the population provided that the mating is locally random and the migration does not change the gene frequency of the entire population, though it may change locally (cf. Maruyama, 1971).

It is shown in this paper that the above invariant property holds for the selective case of 'additive effect', i.e. the fitness of heterozygote is the exactly intermediate of the two homozygotes. Of course the expected sum of heterozygotes depends on the selection coefficient and it is no longer equal to  $2N$ . I shall also derive the variance of the sum of heterozygosity in the whole process and show that, if the gene is addi-

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tive or neutral, the variance, is also invariant over the geographical structure. Furthermore, all the moments of the sum of heterozygosity are shown to be invariant, and the heterozygosity summed over those generations in which the gene frequency in the entire population is specified, that is also invariant, is obtained. Unless the entire population is panmictic, the distribution cannot be calculated directly from the gene frequency of the whole population.

We consider a population subdivided into colonies and let  $N_i(t)$  be the size of colony  $i$  at time  $t$ . We assume that the total population size

$$N \equiv \sum_i N_i(t)$$

is constant, and that selection and random mating are practiced independently in each colony, and no part of the population is completely separated from the other. We consider a locus at which two alleles  $A_1$  and  $A_2$  are segregating and denote by  $x_i(t)$  the frequency of  $A_1$  in colony  $i$  at time  $t$ . Let the fitness of  $A_1A_1$ ,  $A_1A_2$  and  $A_2A_2$  measured in Malthusian parameter be  $2s$ ,  $s$  and  $0$  respectively.

Now let 
$$X(t) \equiv \frac{1}{N} \sum_i N_i(t) x_i(t),$$

which is the gene frequency of the entire population at time  $t$ . We assume that neither mutation nor migration from outside of the population occurs during the time considered. The change of the  $X(t)$  is the stochastic process to be investigated by the diffusion approximation of Wright's model (for the details of the model, see Wright (1969) or Crow & Kimura (1970)). The diffusion process of  $X(t)$  is governed by the two quantities: the variance ( $V_{\Delta X}(t)$ ) and the mean ( $M_{\Delta X}(t)$ ) of the change in  $X(t)$  in one generation. (More precisely we need to compute these quantities for infinitesimally small time interval  $\Delta t$  and divide them by the  $\Delta t$ , but it is custom to use the mean and variance of one generation.) We shall now calculate the  $V_{\Delta X}(t)$  and  $M_{\Delta X}(t)$ . Note that

$$X(t)' = \frac{1}{N} \sum_i N_i(t) x_i(t)' = \frac{1}{N} \sum_i N_i(t) \{x_i(t) + \Delta_i(t)\},$$

where the primes indicate the quantity after the random sampling of gamete and  $\Delta_i(t)$  is the fluctuation in  $x_i(t)$  due to the sampling. By the assumption of independent sampling in each colony,

$$E\{\Delta_i(t) \Delta_j(t)\} = 0 \quad \text{if } i \neq j$$

and

$$E\{\Delta_i(t)^2\} = \frac{x_i(t)\{1-x_i(t)\}}{2N_i(t)}.$$

in which  $E\{\cdot\}$  stands for the expectation. Therefore we have

$$V_{\Delta X}(t) \equiv E\{[X(t)' - X(t)]^2\} = \frac{1}{2N^2} \sum_i x_i(t) \{1-x_i(t)\} N_i(t). \tag{1}$$

The assumption of independent selection in each colony implies

$$\Delta x_i(t) \equiv x_i'(t) - x_i(t) = s x_i(t) \{1-x_i(t)\},$$

where the prime indicates the quantity after the selection. Thus

$$\begin{aligned}
 M_{\Delta X}(t) &\equiv X'(t) - X(t) = \frac{1}{N} \sum_i \Delta x_i(t) N_i(t), \\
 &= \frac{s}{N} \sum_i x_i(t) \{1 - x_i(t)\} N_i(t).
 \end{aligned}
 \tag{2}$$

Now let

$$h(X(t)) \equiv \frac{2}{N} \sum_i x_i(t) \{1 - x_i(t)\} N_i(t)
 \tag{3}$$

and

$$H^{(1)}(X) \equiv E \left\{ \int_0^\infty h(X(t)) dt \right\},$$

where  $E\{\cdot\}$  stands for the expectation taken over a collection of populations with  $X(0) = X$ . Then  $h(X(t))$  gives the average heterozygosity at time  $t$ , and  $H^{(1)}(X)$  gives the expected sum of heterozygosity in the whole process, and  $NH^{(1)}(X)$  gives the expected sum of heterozygotes. It is important to note that all the three quantities given in (1), (2) and (3) have the same factor

$$\sum_i x_i(t) \{1 - x_i(t)\} N_i(t)$$

and this is what leads us to the invariant property claimed.

Let  $P(t, X, Y)$  be the probability density that the  $X(t)$  moves from  $X$  to  $Y$  in time interval  $t$ . For the migration may change the local distribution of genes, colony, number and colony size, it may change  $M_{\Delta X}(t)$  and  $V_{\Delta X}(t)$ . Thus  $V_{\Delta X}(t)$  and  $M_{\Delta X}(t)$  are time dependent. However, by assumption, the  $X(t)$  is not altered by the migration. Thus the  $P \equiv P(t, X, Y)$  satisfies the following Kolmogorov backward equation

$$\frac{\partial P}{\partial t} = \frac{V_{\Delta X}(t)}{2} \frac{d^2 P}{dX^2} + M_{\Delta X}(t) \frac{dP}{dX}.$$

This is a diffusion process with time dependent coefficients. Let

$$\mathbf{G} \equiv \frac{V_{\Delta X}(t)}{2} \frac{d^2}{dX^2} + M_{\Delta X}(t) \frac{d}{dX}.$$

Then general theory of stochastic processes tells us that the  $H(X)$  is the unique solution of the differential equation

$$\mathbf{G}H^{(1)}(X) + h(X) = 0,
 \tag{4}$$

with boundary condition  $H^{(1)}(0) = H^{(1)}(1) = 0$  (cf. Dynkin, 1965, chapter 10; Maruyama & Kimura 1971). Because the same factor

$$\sum_i x_i(t) \{1 - x_i(t)\} N_i(t) \quad \text{in } \mathbf{G} \text{ and in } h(X(t))$$

can be cancelled, we have

$$\frac{d^2 H^{(1)}(X)}{dX^2} + 4Ns \frac{dH^{(1)}(X)}{dX} + 8N = 0,
 \tag{5}$$

in which the time dependent factor disappeared. Therefore the  $H^{(1)}(X)$  is independent of the geographical structure. The appropriate solution of (5) is

$$H^{(1)}(X) = \frac{2S(X)}{sS(1)} - \frac{2X}{s}, \quad (6)$$

where  $S(X) = 1 - \exp(-4NsX)$ . Formula (6) is the same as that for a panmictic population of size  $N$  and initial frequency  $X$ , (cf. Kimura, 1969). If  $s = 0$ , the  $H(X)$  is reduced to

$$H^{(1)}(X) = 4NX(1-X) \quad \text{and} \quad H^{(1)}(1/2N) \approx 2.$$

The above argument incidentally implies that, since the solution of  $\mathbf{GH}(X) = 0$  is the ultimate fixation probability, it is also an invariant property under the assumption of this paper (cf. Maruyama 1970).

Let us now investigate the  $n$ th moment of the sum of heterozygosity defined by

$$H^{(n)}(X) \equiv E \left\{ \left[ \int_0^\infty h(X(t)) dt \right]^n \right\} \quad (n = 1, 2, 3, \dots).$$

Then it can be shown that the  $H^{(n)}(X)$  is the solution of

$$\mathbf{GH}^{(n)}(X) + nh(X)H^{(n-1)}(X) = 0 \quad \text{for} \quad n \geq 2,$$

with boundary condition  $H^{(n)}(0) = H^{(n)}(1) = 0$ . As in (4), the time dependent factor in the above equation can be cancelled and we have

$$\frac{d^2 H^{(n)}(X)}{dX^2} + 4Ns \frac{dH^{(n)}(X)}{dX} + 8nNH^{(n-1)}(X) = 0.$$

Therefore all the moments  $H^{(n)}(X)$  are independent of the geographical structure, and therefore the distribution of the sum of heterozygosity that appears in the whole process is also invariant. The second moment is given by

$$H^{(2)}(X) = \frac{32NS(X)}{sS(1)} \left\{ \frac{1+e^{-B}}{BS(1)} - \frac{2}{B^2} - \frac{1}{2B} + \frac{1}{B^2} - \frac{S(1)}{B^3} \right\} - \frac{32N}{s} \left\{ \frac{X(1+e^{-BX})}{BS(1)} - \frac{2S(X)}{B^2S(1)} - \frac{X^2}{2B} + \frac{X}{B^2} - \frac{S(X)}{B^3} \right\}, \quad (7)$$

where  $B = 4Ns$ . If  $s = 0$ ,

$$H^{(2)}(X) = 16N^2(X - 2X^3 + X^4)/3.$$

As far as the first moment is concerned the invariance of the sum of heterozygosity can be demonstrated very simply by an alternative way. Equation (2) asserts that the expected change in gene frequency in any generation is equal to the selection coefficient times the half of heterozygosity, i.e.  $M_{\Delta X}(t) = sh(X(t))/2$ . Therefore, summing both sides of this equation over generations, we have

$$2(u(X) - X)/s = H^{(1)}(X),$$

as is shown in equation (6), where  $u(X) = (1 - e^{-BX})/(1 - e^{-B})$  is the fixation proba-

bility of the mutant gene, and it has been shown to be invariant to population structure (cf. Maruyama, 1970). (This derivation was given by one of the referees.)

We shall next consider the following quantity defined by

$$\Phi^{(1)}(X, Y) \equiv E \left\{ \int_0^\infty h(X(t)) \delta(X(t) - Y) dt \right\},$$

where  $\delta(\cdot)$  is Dirac's delta function. The  $\Phi^{(1)}(X, Y)$  gives the heterozygosity summed over those generations in which the gene frequency in the entire population is  $Y$ . Then  $\Phi^{(1)}(X, Y)$  satisfies

$$G\Phi^{(1)}(X, Y) + \delta(X - Y) h(X) = 0.$$

This equation can be integrated and

$$\begin{aligned} \Phi^{(1)}(X, Y) &= \frac{2S(1 - Y)S(X)}{sS(1)} \quad \text{for } Y > X, \\ &= \frac{2S(1 - Y)S(X)}{sS(1)} - \frac{2S(X - Y)}{s} \quad \text{for } Y < X. \end{aligned} \tag{8}$$

If  $s = 0$ , this is reduced to

$$\begin{aligned} \Phi^{(1)}(X, Y) &= 8N(1 - Y)X \quad \text{for } Y > X, \\ &= 8N(1 - Y)X - 8N(X - Y) \quad \text{for } Y < X \end{aligned}$$

and the particular case of  $X = 1/2N$  is

$$\Phi^{(1)}\left(\frac{1}{2N}, Y\right) = 4(1 - Y) \quad \text{for } \frac{1}{2N} < Y < 1. \tag{9}$$

With  $s \neq 0$  and  $X = 1/2N$ ,

$$\Phi^{(1)}\left(\frac{1}{2N}, Y\right) = \frac{2S(1 - Y)(1 - e^{-2s})}{sS(1)} \quad \text{for } \frac{1}{2N} < Y < 1.$$

If  $s$  in the above formula is small but positive, and  $4Ns \gg 1$ , it becomes the following very simple distribution

$$\Phi^{(1)}\left(\frac{1}{2N}, Y\right) \approx 4. \tag{10}$$

It is worth noting that, if  $4Ns$  is large, the expected sum of heterozygotes is  $4N$  and the expected conditional sum of heterozygosity for all given  $Y = 1/2N, 2/2N, \dots$ , is  $4/2N$  and this quantity is independent of  $Y$ , while if  $s = 0$  the expectation is  $2N$  and the conditional heterozygosity is given by the density  $4(1 - Y)/2N$ . If  $4Ns \ll -1$  and  $|s| \ll 1$ ,

$$\Phi^{(1)}\left(\frac{1}{2N}, Y\right) \approx \frac{4}{e^{-B}} S(1 - Y). \tag{11}$$

The second moment ( $\Phi^{(2)}(X, Y)$ ) of the quantity given by the formula  $\Phi^{(1)}(X, Y)$  of (8) is also invariant under the geographical structure and is the solution of the differential equation

$$G\Phi^{(2)}(X, Y) + 2\delta(X - Y) h(X) \Phi^{(1)}(X, Y) = 0,$$

where  $\Phi^{(1)}(X, Y)$  is given in (8). Thus

$$\begin{aligned} \Phi^{(2)}(X, Y) &= \frac{16NS(1 - Y) e^{-BX} S(1 - X) \Phi^{(1)}(Y, Y)}{BS(1)} \quad \text{for } Y > X \\ &= \frac{16N\Phi^{(1)}(Y, Y)}{B} \left\{ \frac{S(1 - Y) e^{-BX} S(1 - X)}{S(1)} - e^{BY} S(X) \right\} \quad \text{for } Y < X. \end{aligned} \tag{12}$$

Assuming steady situation, formulae (9) ~ (12) may be applied to existing data of protein polymorphisms. Namely, if the majority of them are maintained, in populations, due to mutation and random drift or selectively advantageous mutants, the sum of heterozygosity for each gene frequency class should be approximately equal. Yamazaki & Maruyama (1972) have examined data of some 400 protein polymorphisms from several organisms and have obtained exactly this pattern of the distribution of heterozygosity. However, since the invariant property is not valid for non-additive genes, this kind of test will not exclude other possibilities. Ewens (1972) has given a different statistical method to examine the neutrality of protein polymorphisms.

The above analyses give the sum of heterozygotes including both eventually fixed and lost cases. However, we can obtain these quantities on the assumption that the allele under consideration is eventually fixed in the population (excluding the cases where the extinction of the allele occurs). The above method can be extended to this conditional situation (cf. Maruyama and Kimura, 1971). Let

$$H_1^{(n)}(X) \equiv E \left\{ \left[ \int_0^\infty h(X(t)) dt \right]^n \middle| X(\infty) = 1 \right\}.$$

Then  $H_1^{(n)}(X)$  is the  $n$ th moment of the sum of heterozygosity in those cases where the fixation of  $A_1$  occurs. Still considering the same population model as above and assuming the additive fitnesses, it can be shown that the  $H_1^{(n)}(X)$  is the solution of differential equation

$$GH_1^{(n)}(X) u(X) + nh(X) H_1^{(n-1)}(X) u(X) = 0,$$

where  $H_1^{(0)}(X) u(X) = u(X) = S(X)/S(1) =$  the ultimate fixation probability of  $A_1$ , and the boundary condition is  $H_1^{(n)}(0) u(0) = H_1^{(n)}(1) u(1) = 0$  provided  $n > 1$ . Therefore we see immediately that like in (4) and (5) all the moments  $H_1^{(n)}(X)$  are invariant under the geographical structure. As a special case, if  $s = 0$ , we have  $H_1^{(1)}(X) = 4N(1 - X^2)/3$  and  $H_1^{(2)}(X) = 112N^2/45 + 32N^2(X^4/10 - X^2/3)/3$ . Thus, regardless the population structure, if a neutral mutant is fixed by random drift, it produces  $4N^2/3$  heterozygotes on the average. We can also obtain the expected sum of heterozygotes for the extinction cases by solving equation

$$(4N^2/3) (1/2N) + (1 - 1/2N) x = 2N,$$

which turn out to be  $x \approx 4N/3$ . Therefore we can conclude that of the expected sum ( $2N$ ) of heterozygotes due to a single mutant, one-third ( $1/2N \times 4N^2/3$ ) will occur in populations in which it is eventually fixed, and two-thirds ( $(1 - 1/2N) \times 4N/3$ ,

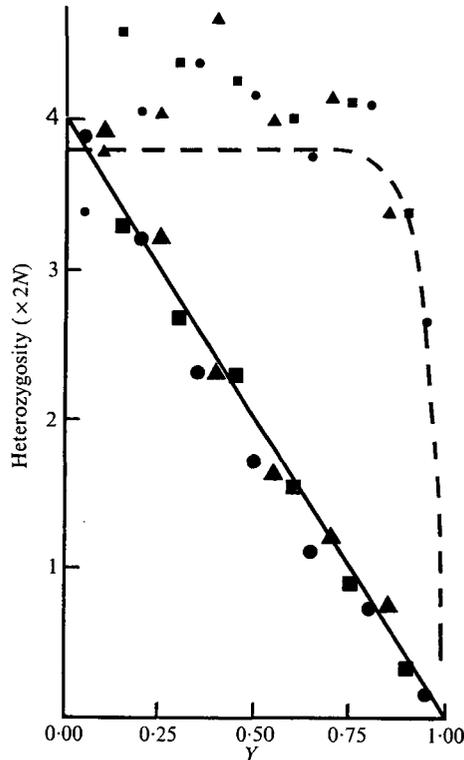


Fig. 1. The distribution of heterozygosity  $\Phi^{(1)}(X, Y)$ , formula (8), with  $X$  (initial frequency) =  $1/2N$  and  $Y$  (the gene frequency in entire population) =  $1/2N, 2/2N, \dots, (2N-1)/2N$ . The dots indicate simulation results. The simulation data were taken from those presented in Table 1.  $\bullet$  = sim. no. 1;  $\blacktriangle$  = sim. no. 2;  $\blacksquare$  = sim. no. 3;  $\bullet$  = sim. no. 4;  $\blacktriangle$  = sim. no. 5;  $\blacksquare$  = sim. no. 6. The broken curve indicates the theoretical expectation for simulations nos. 1-3, and the solid line indicates the expectation for simulations nos. 4-6.

approximately) in those in which it is lost. We can also obtain similarly the conditional distributions analogous to  $\Phi^{(1)}(X, Y)$  and  $\Phi^{(2)}(X, Y)$ .

In order to show the validity of the analyses, I have carried out several computer simulations using the following three different models of population structure. Model I consists of circularly arranged ten colonies of equal size and geographically adjacent colonies exchange their members at the rate  $m$ ; Model II consists of ten colonies of variable size (but the total size is fixed) and an individual moves from one colony to any other colony with probability  $m$  per generation; Model III is a random mating population. The generations are discrete in all the three models and a mutant gene is introduced into the population when and only when it becomes homallelic. The simulation results agreed well with the theoretical expectation. Six examples of such comparisons are presented in Table 1 and in Fig. 1. In the table, the mean and the second moment of the sum of heterozygosity due to a single mutant gene are compared with the theoretical expectations under various conditions, and in order to show the structural difference, the mean fixation time of mutants is also given. In Fig. 1 the distributions of the sum of heterozygosity

Table 1. Some of the simulation results ( $H^{(1)}(X)$ ,  $H^{(2)}(X)$ ,  $H^{\text{Q}}(X)$  and  $u(X)$ ) are compared with their theoretical expectations derived in this paper

(In all the simulations given here, the initial frequency was set to  $1/2N (= X)$ . The fixation time is given for purpose of showing the effect of population structure.)

Simula- tion no.	Popula- tion size (N)	Migra- tion rate (m)	Selec- tion coeffi- cient(s)	$H^{(1)}(1/2N)$		$H^{(2)}(1/2N)$		$H^{\text{Q}}(1/2N)$		$u(1/2N)$		Fixation time	Model§
				Sim.*	Th.†	Sim.	Th.	Sim.	Th.	Sim.‡	Th.		
1	100	0.01	0.05	3.88	3.61	150.4	136.3	37.33	36.00	199/2000 = 0.0995	0.0952	627.0	I
2	100	0.01	0.05	3.75	3.61	145.6	136.3	34.04	36.00	170/1594 = 0.1067	0.0952	396.1	II
3	100	—	0.05	3.76	3.61	153.3	136.3	37.90	36.00	200/2122 = 0.0943	0.0952	141.6	III
4	50	0.02	0	1.88	2.00	120.0	133.3	60.28	66.67	62/7000 = 0.0089	0.01	842.9	I
5	50	0.06	0	2.05	2.00	140.3	133.3	62.63	66.67	71/6972 = 0.0102	0.01	342.3	II
6	50	—	0	1.78	2.00	108.9	133.3	59.80	66.67	200/20936 = 0.0096	0.01	174.4	III

† Th. = theoretical expectation. \* Sim. = simulation result. ‡ Fixation probability in this column is given by the number of fixations occurred/the number of runs. § See the text for the models.