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## ON HETEROZYGOSITY AND THE EFFECTIVE SIZE OF POPULATIONS SUBJECT TO SIZE CHANGES<sup>1</sup>

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When a population is subject to fluctuations in size, the effective population number during any time interval is usually approximated by the harmonic mean of the successive generation sizes (Wright, 1938, 1939). If there are no mutations, the population will eventually reach complete homozygosity. The rate at which such a population approaches homozygosity was investigated by Karlin (1968), for stochastic, and also by Chia (1968), for cyclic, deterministic changes in population size. The analysis of homozygosity levels in populations subject to stochastic size changes was extended by Chia and Pollak (1974), who included the possible existence of mutations.

For a population recovering from a great reduction in size, Nei et al. (1975) have concluded, using numerical computations and considering the existence of mutations, that the harmonic mean approximation to the effective population number is quite robust. It is our purpose in this note to extend the analyses of Nei et al. (1975) and of Chakraborty and Nei (1977) concerning the robustness of the harmonic mean approximation in situations which take into account the existence of mutations.

We propose to do this by investigating cases where a population is subject to cyclic, deterministic changes in size. In such a situation, because the mutation rate is not zero, the expected level of heterozygosity, and hence the effective population number, will change in value throughout the cycle. The harmonic mean approxi-

mation, on the other hand, will have, in the steady state, a constant value. However, it will be shown that the harmonic mean is a good approximation in many such cases. Large discrepancies between the expected degree of heterozygosity and the value obtained using the harmonic mean approximation are found in those cases which combine a bottleneck of a very small population size together with a long cycle period. Also demonstrated here is the effect of repeated bottlenecks on greatly reducing the expected level of heterozygosity of the population.

### MATHEMATICAL BACKGROUND

Consider a diploid population of monocious individuals which reproduce by random mating (including the possibility of random selfing). Consider also that generations are discrete, and let  $N_t$  be the effective population size at the  $t$ -th generation. Then, assuming all alleles to be selectively equivalent, and ignoring mutation, the expected homozygosity at generation  $t + 1$  is given by  $f_{t+1} = \frac{1}{2N_t} + \left(1 - \frac{1}{2N_t}\right)f_t$ , where  $f_t$  is the degree of homozygosity at generation  $t$  (Malécot, 1948). Thus,  $f_{t+1} > f_t$  and eventually the population will consist of homozygotes only (fixation of one of the existing alleles).

If  $u$  is the mutation rate per locus per generation, and if each new mutation is different from the pre-existing alleles in the population, then

$$f_{t+1} = \left[ \frac{1}{2N_t} + \left(1 - \frac{1}{2N_t}\right)f_t \right] (1 - u)^2.$$

Assuming that the mutation rate is very small, this can be approximated by

<sup>1</sup> Research supported by N.I.H. Grant (1R01 HD12731).

$$f_{t+1} = \left[ \frac{1}{2N_t} + \left( 1 - \frac{1}{2N_t} \right) f_t \right] (1 - 2u).$$

Hence, for the degree of heterozygosity  $H$ ,

$$H_{t+1} = 2u + (1 - 2u) \left( 1 - \frac{1}{2N_t} \right) H_t.$$

We shall denote by  $y_t$  the value of  $(1 - 2u) \left( 1 - \frac{1}{2N_t} \right)$ . Thus,

$$H_{t+1} = 2u + y_t H_t.$$

Substituting  $H_i$  by  $H_{i-1}$ , successively, we get

$$H_t = 2u \left( 1 + \sum_{j=1}^{t-1} \prod_{i=j}^{t-1} y_i \right) + H_0 \prod_{i=0}^{t-1} y_i. \quad (1)$$

Note that the expected heterozygosity at generation  $t$  is a function of  $N_0, N_1, N_2, \dots, N_{t-1}$ , as well as of  $H_0$  and the mutation rate  $u$ .

If the population size is constant, i.e., if  $N_0 = N_1 = N_2 = \dots = N_{t-1} = N$ , then

$$H_t = \frac{2u(1 - y^t)}{1 - y} + H_0 y^t \quad (2)$$

where  $y = (1 - 2u) \left( 1 - \frac{1}{2N} \right)$ .

$$\begin{aligned} H_\infty &= \lim_{t \rightarrow \infty} H_t \\ &= \frac{2u}{1 - y} = \frac{4Nu}{1 - 2u + 4Nu}. \end{aligned}$$

If  $N$  is large (i.e., if  $4Nu \gg 2u$ ), then, approximately,  $H_\infty = \frac{4Nu}{1 + 4Nu}$ , as obtained by Kimura and Crow (1964).

Let us focus now on the case where population size changes from generation to generation. We begin by defining the effective population number ( $N_e$ ) of such a population.

Consider a population whose sizes at generations  $0, 1, 2, \dots, t - 1$  are  $N_0, N_1, N_2, \dots, N_{t-1}$ , and let  $H_0$  and  $H_t$  be the degrees of heterozygosity at generations  $0$  and  $t$ , respectively. Then the *effective population number* for the epoch  $0$  to  $t - 1$  of that population is the number

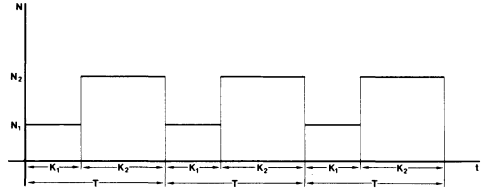


FIGURE 1a

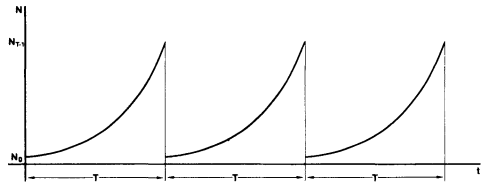


FIGURE 1b

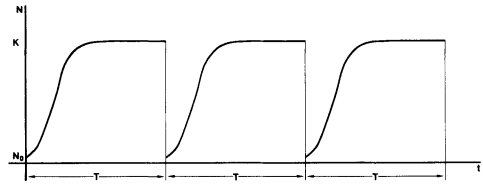


FIGURE 1c

FIG. 1. Examples of cyclic changes in population size: (a) the two-step model, (b) exponential growth, and (c) logistic growth.

$N_e$ , such that if population sizes at generations  $0, 1, 2, \dots, t - 1$  were constant and equal to  $N_e$ , it would yield, for the same  $H_0$  and the same rate of mutation  $u$ , the same expected degree of heterozygosity  $H_t$  at generation  $t$ .

Mathematically speaking,  $N_e$  is the solution to the equation

$$\begin{aligned} H_t(N_e, N_e, N_e, \dots, N_e; H_0; u) \\ = H_t(N_0, N_1, N_2, \dots, N_{t-1}; H_0; u). \quad (3) \end{aligned}$$

Note that  $N_e$  depends on  $N_0, N_1, N_2, \dots, N_{t-1}$ , as well as on  $H_0$  and  $u$ . Employing (1) and (2), equation (3) can be put as follows:

$$\begin{aligned} \frac{2u(1 - y_e^t)}{1 - y_e} + H_0 y_e^t \\ = 2u \left( 1 + \sum_{j=1}^{t-1} \prod_{i=j}^{t-1} y_i \right) + H_0 \prod_{i=0}^{t-1} y_i, \quad (4) \end{aligned}$$

where  $y_e = (1 - 2u) \left( 1 - \frac{1}{2N_e} \right)$ .

If the mutation rate  $u$  is zero, then equation (4) reduces to

$$\left(1 - \frac{1}{2N_e}\right)^t = \prod_{i=0}^{t-1} \left(1 - \frac{1}{2N_i}\right) \quad (5)$$

which is the expression obtained by Wright (1939).

An approximate solution to equation (5), and also to equation (4), is

$$\frac{1}{\bar{N}_e} = \frac{1}{t} \sum_{i=0}^{t-1} \frac{1}{N_i}$$

i.e.,  $\bar{N}_e$  is the harmonic mean of the  $N_i$ 's (Wright, 1938, 1939).

POPULATION WHICH IS SUBJECT TO CYCLICAL CHANGES IN SIZE

Suppose the size of a population changes from generation to generation in a cyclic, deterministic way, and let the cycle length be of  $T$  generations. In other words, let  $N_{kT} = N_{(0)}$ ,  $N_{kT+1} = N_{(1)}$ ,  $N_{kT+2} = N_{(2)}$ , . . . ,  $N_{kT+T-1} = N_{(T-1)}$  for every  $k = 0, 1, 2, \dots$

By defining  $y_{(i)} = (1 - 2u)\left(1 - \frac{1}{2N_{(i)}}\right)$

for  $i = 0, 1, 2, \dots, T - 1$  and substituting in equation (1), we get, after some simple algebra,

$$H_{t=kT} = 2u \frac{1 - r^k}{1 - r} \left(1 + \sum_{j=1}^{T-1} \prod_{i=j}^{T-1} y_{(i)}\right) + H_0 r^k,$$

where  $r = \prod_{i=0}^{T-1} y_{(i)}$ .

For  $k$  very large,

$$H_{kT} \cong \frac{2u}{1 - r} \left(1 + \sum_{j=1}^{T-1} \prod_{i=j}^{T-1} y_{(i)}\right).$$

Also,

$$H_{kT+m} \cong \frac{2u}{1 - r} \left(1 + \sum_{j=1}^{T-1} \prod_{i=j}^{T-1} y_{(i+m)}\right),$$

for  $m = 0, 1, 2, \dots, T - 1$  and  $y_{(T)} = y_{(0)}$ .

Denoting by  $\phi_m$  the expression in the

parentheses of the right-hand side of  $H_{kT+m}$ , we have

$$H_{kT+m} \cong 2u \frac{\phi_m}{1 - r}$$

for  $m = 0, 1, 2, \dots, T - 1$ .

Thus, we see that after a sufficiently long repetition of these cyclical size changes, the degree of heterozygosity also changes in a cyclic way, having the same period as that of the changes in the population size, and

$$\frac{H_{kT+m}}{H_{kT+n}} = \frac{\phi_m}{\phi_n}$$

for  $m, n = 0, 1, 2, \dots, T - 1$ .

As for the effective population numbers, we have

$$N_{e_{(kT+m)}} = \frac{H_{kT+m}}{4u(1 - H_{kT+m})} = \frac{\phi_m}{2(1 - r - 2u\phi_m)},$$

for  $m = 0, 1, 2, \dots, T - 1$ .

These numbers also change in a cyclic way, with the same period  $T$ , and

$$\frac{N_{e_{(kT+m)}}}{N_{e_{(kT+n)}}} = \frac{\phi_m(1 - r - 2u\phi_n)}{\phi_n(1 - r - 2u\phi_m)},$$

for  $m, n = 0, 1, 2, \dots, T - 1$ .

If  $u$  is small,

$$\frac{N_{e_{(kT+m)}}}{N_{e_{(kT+n)}}} \cong \frac{\phi_m}{\phi_n}.$$

Note that if we consider the harmonic mean of the population sizes  $N_0, N_1, N_2, \dots, N_{t-1}$ , this harmonic mean will tend, as  $t$  gets larger and larger, to be a constant value  $\bar{N}_e$ , equal to the harmonic mean of the  $T$  repetitive sizes  $N_{(0)}, N_{(1)}, N_{(2)}, \dots, N_{(T-1)}$ . This is because of the cyclic nature of the population size changes.  $\bar{H}_t$ , the heterozygosity calculated using the harmonic mean of the  $t$  population sizes, also tends to a constant value, namely,  $\frac{4\bar{N}_e u}{1 + 4\bar{N}_e u}$ .

To conclude, if population size changes from generation to generation in a repet-

TABLE 1. *The two-step model.  $u = 10^{-6}$ .*

Population size		Cycle length			Minimal values		Maximal values		Using the Harmonic Mean Approximation		$R = \text{Max}H/\text{Min}H$	Number of cycles to reach steady state (see text)
$N_1$	$N_2$	$K_1$	$K_2$	$T = K_1 + K_2$	$H$ (%)	$N_e$	$H$ (%)	$N_e$	$\bar{H}$ (%)	$\bar{N}_e$		
2	$10^6$	1	99	100	0.06	151	0.08	200	0.08	200	1.33	41
2	$10^6$	3	97	100	0.01	37	0.03	86	0.03	67	2.30	15
2	$10^6$	1	9,999	10,000	5.52	14,598	7.36	19,850	7.27	19,608	1.33	23
2	$10^6$	3	9,997	10,000	1.42	3,591	3.36	8,681	2.58	6,623	2.37	9
2	$10^6$	100	9,900	10,000	0.00	2	1.96	4,989	0.08	200	2,445.62	1
$10^3$	$10^6$	1	99	100	26.67	90,941	26.69	91,002	26.68	90,992	1.00	7,492
$10^3$	$10^6$	500	500	1,000	0.75	1,877	0.84	2,129	0.79	1,998	1.13	38
$10^3$	$10^6$	5,000	5,000	10,000	0.49	1,220	1.47	3,739	0.79	1,998	3.03	4
$10^4$	$10^8$	5,000	5,000	10,000	6.96	18,695	7.88	21,390	7.40	19,980	1.13	27
$10^4$	$10^8$	50,000	50,000	100,000	4.57	11,980	13.63	39,459	7.40	19,980	2.98	3

itive, cyclic way, then, at the steady state (i.e., after a large enough number of cycles so that the influence of the initial conditions fades away) the effective population number and the expected degree of heterozygosity both change periodically, with the same period as that of the size fluctuations. On the other hand, the harmonic mean approximation to the effective population number brings about a constant effective number and a constant expected heterozygosity.

The question arises as to how good the harmonic mean is as an approximation to the effective number and also how good  $\frac{4\bar{N}_{eu}}{1 + 4\bar{N}_{eu}}$  is as an approximation to the expected level of heterozygosity in the case of cyclical changes in population size. Some examples are given in the following section.

EXAMPLES

I. *The Two-Step Model*

This is the least realistic example of the three cases considered in this section, but it clearly demonstrates the possibility of large differences between the time-changing values and the time-constant approximation for the expected heterozygosity.

We assume that population size changes in a cyclic way, with a period of  $T$  gen-

erations. During the first  $K_1$  generations, the size is constant and equal to  $N_1$ , whereas it is  $N_2$  during the remaining  $K_2 = T - K_1$  generations (Fig. 1a). Without loss of generality, we let  $N_2 > N_1$ .

In the steady state situation, the effective population number and the degree of heterozygosity also change periodically, reaching their maximal values at the end of the  $K_2$  generations during which the population size is the larger. The minimal values are obtained at the end of the  $K_1$  generations of the smaller population size.

In Table 1 some illustrative examples for the two-step model are tabulated.

II. *Cycles of Exponential Growth*

Here we consider populations whose size increases geometrically for  $T$  generations, from size  $N_0$  at the beginning of the period to  $N_{T-1} = N_0(1 + r)^{T-1}$  at the end of the period, where  $r > 0$  is the constant growth rate. This pattern is repeated periodically (Fig. 1b), and Table 2 gives some examples of expected values of heterozygosity and effective population number at the steady state situation.

III. *Cycles of Logistic Growth*

Population size changes periodically, in a logistic way.  $N_0$  is the initial size,  $K$  is the carrying capacity,  $r$  is the growth rate, and  $T$  is the cycle length (Fig. 1c). Some

TABLE 2. Cycles of exponential growth.

Population size		Cycle length <i>T</i>	Growth rate <i>r</i>	Mutation rate <i>u</i>	Maximal values		Using the Harmonic Mean Approximation		$\bar{R} = \text{Max}H/\bar{H}$	Number of cycles to reach steady state (see text)
<i>N</i> <sub>0</sub>	<i>N</i> <sub><i>T</i>-1</sub>				<i>H</i> (%)	<i>N</i> <sub><i>e</i></sub>	$\bar{H}$ (%)	$\bar{N}_e$		
2	10 <sup>6</sup>	10	3.298	10 <sup>-6</sup>	0.01	16	0.01	15	1.05	40
				10 <sup>-7</sup>	0.00	16	0.00	15	1.05	46
				10 <sup>-8</sup>	0.00	16	0.00	15	1.05	52
		100	0.142	10 <sup>-6</sup>	0.02	51	0.01	25	2.05	7
				10 <sup>-7</sup>	0.00	51	0.00	25	2.05	8
				10 <sup>-8</sup>	0.00	51	0.00	25	2.05	9
	1,000	0.013	10 <sup>-6</sup>	0.15	366	0.01	26	14.01	1	
			10 <sup>-7</sup>	0.01	366	0.00	26	14.01	1	
			10 <sup>-8</sup>	0.00	366	0.00	26	14.01	1	
	10,000	0.001	10 <sup>-6</sup>	1.11	2,796	0.01	26	105.43	1	
			10 <sup>-7</sup>	0.11	2,783	0.00	26	105.97	1	
			10 <sup>-8</sup>	0.01	2,781	0.00	26	106.02	1	
2	10 <sup>8</sup>	10	6.169	10 <sup>-6</sup>	0.01	18	0.01	17	1.03	44
		100	0.196	10 <sup>-6</sup>	0.02	58	0.01	33	1.78	8
		1,000	0.018	10 <sup>-6</sup>	0.16	409	0.01	35	11.62	1
		10,000	0.002	10 <sup>-6</sup>	1.37	3,465	0.01	35	96.48	1
10 <sup>3</sup>	10 <sup>6</sup>	10	1.154	10 <sup>-6</sup>	2.10	5,362	2.10	5,361	1.00	8,866
				10 <sup>-8</sup>	0.02	5,362	0.02	5,361	1.00	13,990
		100	0.072	10 <sup>-6</sup>	2.63	6,764	2.63	6,746	1.00	1,080
				10 <sup>-8</sup>	0.03	6,763	0.03	6,746	1.00	1,730
		1,000	0.007	10 <sup>-6</sup>	2.75	7,082	2.69	6,898	1.03	110
				10 <sup>-8</sup>	0.03	7,077	0.03	6,898	1.03	177
	10,000	0.001	10 <sup>-6</sup>	3.45	8,924	2.69	6,913	1.28	11	
			10 <sup>-8</sup>	0.04	8,860	0.03	6,913	1.28	18	

examples of the steady state situation are given in Table 3.

IV. Conclusions

The examples presented in this section show the possibility of significant deviations of the expected level of heterozygosity from the approximate, constant value obtained by using the harmonic mean as the effective population number. The magnitude of these deviations depends very much on the existence of bottlenecks. The smaller the bottleneck size and the longer it lasts, the larger the ratio ( $\bar{R}$ ) between the maximal and the minimal values of  $H$  (Table 1) or the ratio ( $\bar{R}$ ) between the maximal and the approximate values of  $H$  (Tables 2 and 3).

In each case, we have changed the mutation rate from 10<sup>-6</sup> to 10<sup>-7</sup> and to 10<sup>-8</sup>

per generation. These changes affect  $H$  (which decreases as  $u$  decreases), but have very minor effect on the values of  $R$  or  $\bar{R}$ .

It should be noted that in most of the examples presented in Table 1 and in those presented in Table 3, the population maintains a constant size of 10<sup>6</sup> or 10<sup>8</sup> for almost all the time, but because of the strong effect of the bottlenecks, heterozygosity is reduced to a far lower level than the constant value of 80% or 99.75% expected in the case of a constant population size of 10<sup>6</sup> and 10<sup>8</sup>, respectively ( $u = 10^{-6}$ ). The long lasting consequences of a bottleneck were clearly demonstrated by Nei et al. (1975). Here we observe the very strong effect of repeated bottlenecks on the perpetual reduction of the expected level of heterozygosity.

In all our examples of cyclic variations

TABLE 3. *Cycles of logistic growth.*

Population size		Growth rate $r$	Cycle length $T$	Mutation rate $u$	Maximal values		Using the Harmonic Mean Approximation		$\bar{R} = \frac{\text{Max}H}{\bar{H}}$	Comments
$N_0$	Carrying capacity $K$				$H$ (%)	$N_e$	$\bar{H}$ (%)	$\bar{N}_e$		
2	$10^8$	0.1	5,000	$10^{-6}$	1.05	2,642	0.36	909	2.88	After 118 generations population size is already larger than $.99K$ . Exp. het. if pop. size was constant and equal to $K$ : 99.75%.
			10,000	$10^{-6}$	2.08	5,319	0.72	1,818	2.88	
2	$10^8$	0.2	5,000	$10^{-6}$	1.24	3,131	0.66	1,667	1.87	After 230 generations population size is already larger than $.99K$ . Exp. het. if pop. size was constant and equal to $K$ : 99.75%.
			10,000	$10^{-6}$	2.46	6,297	1.32	3,333	1.87	
$10^3$	$10^8$	0.1	20,000	$10^{-7}$	41.78	$1.794 \times 10^6$	41.67	$1.786 \times 10^6$	1.00	After 165 generations population size is already larger than $.99K$ . Exp. het. if pop. size was constant and equal to $K$ : 97.56%.

in population size, we have considered the steady state situation, when the expected level of heterozygosity oscillates with the same period as the population size fluctuations. The question is, how long does it take to approach the steady state situation? This time depends, among other factors, on the initial conditions. Thus, if we begin with the “least favorable” conditions, we can get, for each example, the least upper bound for the time it takes to be in a specified neighborhood of the steady state. For each example, we have calculated the number of cycles it takes (beginning with  $H_0 = 1$ ) for the percentage difference between the maximal value of  $H$  and its steady state value to be less than 1%. This number depends on the severity, both in terms of size and extent, of the bottleneck and on the cycle length. It can be quite large (e.g., 7,492 for example 6 in Table 1 or even 13,990 for example 18 in Table 2), but in some cases, the neigh-

borhood of the steady state is reached already in the first cycle.

DISCUSSION

The purpose of this work was to develop mathematical formulae for the effective population number and the expected level of heterozygosity of populations changing in size during time. This problem was treated by Karlin (1968) and by Chia (1968) for cases where there are no mutations. Chia and Pollak (1974) considered the same problem, taking into account the existence of a positive, constant mutation rate, where they assumed the population sizes to be states in a finite irreducible Markov chain. The cases treated here extend, in a sense, a special case of Chia and Pollak’s work. We have considered the steady state situation of populations whose size changes in a repeated, cyclic way. In such cases we see that the effective population number and the expected degree of heterozy-

gosity both oscillate with the same period as the population size fluctuations. Under Chia and Pollak's assumptions of large population sizes and small cycle length, the different levels of heterozygosity are approximately equal, so they considered the degree of heterozygosity to be the average of these values. Their definition of the effective population number, which, for the monoecious case, is the reciprocal of the asymptotic average, over population sizes, of the probabilities that two gametes uniting to form an individual came from the same individual one generation earlier, leads to a fixed number. The definition of the effective population number used in our work as the constant size which would yield, under similar circumstances, the same change in heterozygosity as expected in our varying-size population (see, e.g., Crow and Kimura, 1970), gives a time-dependent value. Since in the steady state of our cyclic model, the harmonic mean approximation yields a constant effective number, and consequently, a constant expected level of heterozygosity, differences between the actual expected heterozygosity and the approximated value always exist. Unless there are substantial bottlenecks accompanied by sufficiently long cycle lengths, these differences are relatively small, and Wright's approximation is very satisfactory.

Large deviations of the periodically changing heterozygosity from the constant value obtained by using the harmonic mean as the effective population number are demonstrated in cases where a bottleneck is present in the cycle. These deviations are more conspicuous the longer the cycle length, but still large deviations are found for cycle lengths very much smaller than  $1/u$ . (In fact, the examples treated show that changing the mutation rate  $u$  from  $10^{-6}$  to  $10^{-7}$  and to  $10^{-8}$  per generation has almost no effect on the relative size of these deviations.)

The effect of a bottleneck on the expected heterozygosity of the population in subsequent generations was convincingly demonstrated by Nei et al. (1975). In their example the effect of a one-time bottleneck

is to dramatically reduce the expected heterozygosity of the population. Heterozygosity decreases monotonically for some generations until it reaches a minimal value, and then increases again to the steady-state value  $\frac{4Nu}{1 + 4Nu}$ . But the rate of approach to the limit is very slow—it takes many generations (the number depends, of course, on the growth rate and also on the mutation rate) to reach the neighborhood of the steady state value; much longer than is needed for the population to restore its original size. In other words, although the population maintains an almost constant size for a very long period, the expected heterozygosity still exhibits the consequences of the apparently "long forgotten" bottleneck.

In this work we have demonstrated the effect of repeated bottlenecks on the degree of heterozygosity. These, combined with long enough cycle length, not only produce large deviations from the widely used approximated values, but also greatly reduce the heterozygosity level at all stages in the cycle. This reduction in heterozygosity is well demonstrated in some of the examples in the previous section, especially those of the logistic growth model. There we see that although the population size is very close to  $10^6$  for about 99% of the time, heterozygosity hardly reaches 5% of the value that we would expect if population size was constant and equal to  $10^6$ .

As a concluding remark, we would point out that it is unrealistic to assume that populations will experience cyclic fluctuations in size of the constant periodicity as investigated in this work. We have considered such situations for the sake of mathematical simplicity. Nevertheless, we believe that the general effects illustrated here will also be produced for less regular variations in population size.

#### SUMMARY

The effective population size and the expected level of heterozygosity are considered here for populations whose size



changes in a deterministic, cyclic way. Repeated bottlenecks, combined with long enough cycle length, not only provide large deviations from the widely used approximated values, but also greatly reduce the heterozygosity level at all stages of the cycle.

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