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Effective population size of a population with stochastically varying size

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Abstract For a Wright–Fisher model with mutation whose population size fluctuates stochastically from generation to generation, a heterozygosity effective population size is defined by means of the equilibrium average heterozygosity of the population. It is shown that this effective population size is equal to the harmonic mean of population size if and only if the stochastic changes of population size are uncorrelated. The effective population size is larger (resp. smaller) than the harmonic mean when the stochastic changes of population size are positively (resp. negatively) autocorrelated. These results and those obtained so far for other stochastic models with fluctuating population size suggest that the property that effective population sizes are always larger than the harmonic mean under the fluctuation of population size holds only for continuous time models such as diffusion and coalescent models, whereas effective population sizes can be equal to or smaller than the harmonic mean for discrete time models.

Keywords Population genetics · Effective population size ·
Fluctuation of population size · Wright–Fisher model

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1 Introduction

A large amount of molecular data that estimate the genetic diversity of populations such as the average heterozygosity have been accumulated using recent developments

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in molecular techniques (see Iizuka et al. 2002). The average heterozygosity can be expressed as a simple function of population genetic parameters population size N and mutation rate u under the neutrality assumption (Kimura 1968). This means that it is possible to obtain information on these population genetic parameters from estimates of average heterozygosity under the neutrality assumption. On the other hand, the neutrality assumption can be examined by estimates of the average heterozygosity when the values of these population genetic parameters are known. However, the size of population is hardly constant and it may fluctuate from generation to generation. In such cases, it is important to understand how the fluctuation of population size affects the average heterozygosity. For this purpose, it is necessary to introduce an appropriate effective population size N_e and the properties of the effective population size must be investigated. Then N_e can be used for N in the average heterozygosity formula. Since the harmonic mean of population size N_h has played an important role when the population size is not constant, the relationship between the effective population size and the harmonic mean of population size must be clarified.

Consider a population whose population size fluctuates temporally from generation to generation and the fluctuation is stochastic. There are several definitions of effective population size (see Ewens 1982). In a series of papers (Iizuka 2001; Iizuka et al. 2002; Sano et al. 2004), the relation between effective population sizes and the harmonic mean of fluctuating population size N_h was described. Definition of these effective population sizes and their properties are presented in Appendix 1. For a Wright–Fisher model without mutation, Iizuka (2001) defined an inbreeding effective population size when its population size fluctuates stochastically. This effective population size is denoted by $N_e^{(\mathrm{WF1})}$ in this paper. It was shown that $N_e^{(\mathrm{WF1})}$ is equal to the harmonic mean N_h if the stochastic changes of population size have no correlation between distinct generations, though $N_e^{(\mathrm{WF1})}$ is larger (resp. smaller) than N_h if the stochastic changes of population size are positively (resp. negatively) autocorrelated (Iizuka 2001). For a diffusion model with mutation, Iizuka et al. (2002) defined an effective population size by means of the equilibrium average heterozygosity (heterozygosity effective population size) when its population size fluctuates stochastically. This effective population size is denoted by $N_e^{(D)}$ in this paper. It was shown that $N_e^{(D)}$ is always larger than the harmonic mean N_h (Iizuka et al. 2002). For a coalescent model with fluctuating population size, Sano et al. (2004) defined a coalescent effective population size by means of the mean coalescent time from k genes to $k-1$ genes. In this paper, this effective population size is denoted by $N_e^{(C)}(k)$. It was shown again that $N_e^{(C)}(k)$ is always larger than the harmonic mean N_h (Sano et al. 2004). See Gillespie (2000) and Sjödin et al. (2005) for other definitions of coalescent effective population size with stochastically fluctuating population size.

Is the property of effective population size being always larger than the harmonic mean N_h due to the definition of effective population size such as inbreeding effective population size, heterozygosity effective population size and coalescent effective population size or is it due to the difference between discrete time models such as Wright–Fisher models and continuous time models such as diffusion and coalescent models (Y. Iwasa, personal communication)? In this paper, a heterozygosity effective population size $N_e^{(\mathrm{WF2})}$ is defined by means of the equilibrium average heterozygosity for a Wright–Fisher model with mutation when its population size fluctuates stochastically. It will be shown that $N_e^{(\mathrm{WF2})}$ is equal to the harmonic mean N_h if and only if the stochastic changes of population size have no correlation between distinct generations and $N_e^{(\mathrm{WF2})}$ is larger (resp. smaller) than N_h if the stochastic changes of population size are positively (resp. negatively) autocorrelated. This result together with the results so far obtained suggests that the property of effective population size being always larger than the harmonic mean N_h is that of continuous time models. It will be also discussed how the four effective population sizes $N_e^{(\mathrm{WF1})}$, $N_e^{(\mathrm{WF2})}$, $N_e^{(D)}$ and $N_e^{(C)}(k)$ are related.

2 The model

Consider a haploid population whose population size in generation t is $N(t)$. The population size changes stochastically from generation to generation. The changes of population size are not independent between distinct generations in general as the case of stochastic fluctuation of selection intensity (see Iizuka 1987; Iizuka and Matsuda 1982 and the citation therein). In other words, stochastic changes of population size may have autocorrelation. In this paper, the following two-valued Markov chain is introduced as a model of autocorrelated stochastic changes of population size (see Iizuka 2001). It is assumed that $\{N(t)\}_{t=0,\pm1,\pm2,\ldots}$ is a stationary Markov chain on $\{N_1, N_2\}$ such that

$$\begin{pmatrix} \mathrm{P}(N(t+1)=N_1) \\ \mathrm{P}(N(t+1)=N_2) \end{pmatrix} = \begin{pmatrix} 1-q_1 & q_2 \\ q_1 & 1-q_2 \end{pmatrix} \begin{pmatrix} \mathrm{P}(N(t)=N_1) \\ \mathrm{P}(N(t)=N_2) \end{pmatrix}, \tag{1}$$

and

$$\mathrm{P}(N(0)=N_i) = p_i^{(st)}, \tag{2}$$

where $1 < N_1 < N_2 < \infty$, $0 \leq q_j \leq 1$, $q_1 + q_2 > 0$ and

$$(p_1^{(st)}, p_2^{(st)}) = \left(\frac{q_2}{q_1+q_2}, \frac{q_1}{q_1+q_2} \right) \tag{3}$$

is the stationary distribution of the Markov chain. Here q_i is the probability that $N(t+1) \neq N(t)$ conditional on $N(t) = N_i$ $(i = 1, 2)$. It is easy to obtain some explicit formulas for this simple Markov chain. Indeed, Iizuka (2001) showed that the covariance of $N(t)$ and $N(t+k)$ is

$$\mathrm{Cov}[N(t), N(t+k)] = (N_2 - N_1)^2 \, \frac{q_1 q_2 (1 - q_1 - q_2)^k}{(q_1+q_2)^2}, \tag{4}$$

$k \geq 0$. By the formulas (1) and (4), we have the following classification of the change of population size. The stochastic change of population size is positively (resp. negatively) autocorrelated, that is, $\mathrm{Cov}[N(t), N(t+k)] > 0$ (resp. $\mathrm{Cov}[N(t), N(t+1)] < 0$)

if $0 < q_1 + q_2 < 1$ and $q_1 q_2 > 0$ (resp. $1 < q_1 + q_2 < 2$). It is uncorrelated if $q_1 + q_2 = 1$ and $q_1 q_2 > 0$. The change of population size is deterministic and cyclic, that is, $N(t) = N(t + 2k) \neq N(t + 1) = N(t + 2k + 1)$, $k = \pm 1, \pm 2, \ldots$ if $q_1 = q_2 = 1$. The population size is constant if $q_1 q_2 = 0$.

Put

$$n_i = 1 - \frac{1}{N_i} \tag{5}$$

for $i = 1, 2$ and denote by E[ ] the operation taking the expectation. By Lemma 2 of Iizuka (2001), it holds that

$$\mathrm{E}\left[\prod_{k=1}^{t}\left\{1 - \frac{1}{N(k)}\right\}\right] = A\alpha_+^{t-1} + B\alpha_-^{t-1} \tag{6}$$

if $q_1 \neq 0$ or $n_1 \neq n_2(1 - q_2)$. Here α_+ and α_- ($\alpha_+ \geq \alpha_-$) are solutions of the quadratic equation

$$\alpha^2 - \{n_1(1 - q_1) + n_2(1 - q_2)\}\alpha + n_1 n_2(1 - q_1 - q_2) = 0 \tag{7}$$

and

$$A = \frac{c_1 q_2 + c_2 q_1}{q_1 + q_2}, \quad B = \frac{d_1 q_2 + d_2 q_1}{q_1 + q_2}, \tag{8}$$

$$c_i = \frac{n_i\{n_i(1 - q_i) + n_j q_i - \alpha_-\}}{\alpha_+ - \alpha_-}, \quad d_i = \frac{-n_i\{n_i(1 - q_i) + n_j q_i - \alpha_+\}}{\alpha_+ - \alpha_-}, \tag{9}$$

$i, j = 1, 2$ ($i \neq j$). Note that α_+ and α_- are real and $\alpha_+ > \alpha_-$ if $n_1 \neq n_2(1 - q_2)$. It is assumed that $n_1 \neq n_2(1 - q_2)$ in this paper. The harmonic mean of $N(t)$ is defined by

$$\frac{1}{N_h} = \mathrm{E}\left[\frac{1}{N(t)}\right] = \frac{p_1^{(st)}}{N_1} + \frac{p_2^{(st)}}{N_2} = \frac{1}{q_1 + q_2}\left(\frac{q_2}{N_1} + \frac{q_1}{N_2}\right). \tag{10}$$

Consider a neutral locus with K alleles $A_1, A_2, \ldots, A_K$. The genetic composition of the population in generation t is $\mathbf{x}(t) = (x_1(t), x_2(t), \ldots, x_{K-1}(t))$ where $x_i(t)$ is the gene frequency of A_i in generation t. Mutation and random genetic drift cause the change of $\mathbf{x}(t)$ in this order. Mutation rate per generation from A_i to A_j is $u/(K - 1)$ ($i \neq j$). In generation t random genetic drift occurs in a finite population of $N(t)$ haploid individuals subject to the standard assumptions of the Wright–Fisher model and it produces $N(t + 1)$ individuals of generation $t + 1$. The explicit probability law of random genetic drift when population size fluctuates stochastically is given in Iizuka (2001) for the case of $K = 2$ and no mutation.

For models with stochastically fluctuating population size, see Araki and Tachida (1997), Chia and Pollak (1974), Donnelly (1986), Heyde and Seneta (1975), Kaj and Krone (2003), Karlin (1968), Klebaner (1988), Seneta (1974) and Tachida (2000).

3 Results

Let

$$H(t) = 1 - \sum_{i=1}^{K} x_i(t)^2 \tag{11}$$

be the heterozygosity of the population in generation t. In the same way as the proof of Lemma 1 of Iizuka (2001), it can be shown that the conditional expectation

$$G(t) = \mathrm{E}[H(t)|H(0), N(k), k \le t] \tag{12}$$

conditional on the values of $H(0)$ and $N(k), k \le t$ satisfies

$$G(t+1) = \left\{1 - \frac{1}{N(t+1)}\right\}\{(1-u_K)^2 G(t) + u(2-u_K)\}, \tag{13}$$

where we put $u_K = Ku/(K-1)$. The solution of the recursion Eq. (13) is

$$\begin{aligned} G(t) = {} & G(0)(1-u_K)^{2t} \prod_{k=1}^{t} \left\{1 - \frac{1}{N(k)}\right\} \\ & + u(2-u_K) \sum_{j=1}^{t} (1-u_K)^{2(t-j)} \prod_{k=j}^{t} \left\{1 - \frac{1}{N(k)}\right\}. \end{aligned} \tag{14}$$

By (14), the stationarity of $\{N(t)\}_{t=0,\pm1,\pm2,\ldots}$ and noting that $\mathrm{E}[G(t)] = \mathrm{E}[H(t)]$ which is a property of the conditional expectation, we have

$$\begin{aligned} \mathrm{E}[H(t)] = {} & \mathrm{E}[H(0)](1-u_K)^{2t} \mathrm{E}\left[\prod_{k=1}^{t} \left\{1 - \frac{1}{N(k)}\right\}\right] \\ & + u(2-u_K) \sum_{j=1}^{t} (1-u_K)^{2(j-1)} \mathrm{E}\left[\prod_{k=j}^{t} \left\{1 - \frac{1}{N(k)}\right\}\right]. \end{aligned} \tag{15}$$

Note that $\mathrm{E}[H(t)]$ is the expectation of $H(t)$ with respect to random genetic drift and the fluctuation of population size, whereas $\mathrm{E}[\prod_{k=1}^{t}\{1 - 1/N(k)\}]$ is the expectation of $\prod_{k=1}^{t}\{1 - 1/N(k)\}$ with respect to the fluctuation of population size only. By (6), we have

$$\begin{aligned} \mathrm{E}[H(t)] = {} & \mathrm{E}[H(0)](1-u_K)^2\{A[(1-u_K)\alpha_+]^{t-1} + B[(1-u_K)\alpha_-]^{t-1}\} \\ & + u(2-u_K)\left\{A\frac{1-[(1-u_K)^2\alpha_+]^t}{1-(1-u_K)^2\alpha_+} + B\frac{1-[(1-u_K)^2\alpha_-]^t}{1-(1-u_K)^2\alpha_-}\right\} \end{aligned} \tag{16}$$

and the expectation of equilibrium average heterozygosity is

$$\mathrm{E}[H(\infty)] = \lim_{t\to\infty} \mathrm{E}[H(t)] = u(2-u_K)\left\{\frac{A}{1-(1-u_K)^2\alpha_+} + \frac{B}{1-(1-u_K)^2\alpha_-}\right\}. \tag{17}$$

The key observation to obtain the relation between the harmonic mean N_h and an effective population size defined by means of the equilibrium average heterozygosity is the following expression for $\mathrm{E}[H(\infty)]$. After tedious calculations, it can be shown that the right-hand side of (17) is equal to

$$\frac{u(2-u_K)\{1-\frac{1}{N_h}-(1-u_K)^2 n_1 n_2 (1-q_1-q_2)\}}{1-(1-u_K)^2\{1-\frac{1}{N_h}-[1-\frac{1}{N_h}-n_1-n_2+(1-u_K)^2 n_1 n_2](1-q_1-q_2)\}}. \tag{18}$$

Note that

$$\mathrm{E}[H(\infty)] = \frac{(N-1)u(2-u_K)}{1+(N-1)u_K(2-u_K)} \tag{19}$$

holds if the population size is constant ($N(t) = N$), where $\mathrm{E}[H(\infty)]$ is the expectation of $H(\infty)$ with respect to random genetic drift only. By this formula, a heterozygosity effective population size $N_e^{(\mathrm{WF2})}$ can be defined by means of the expectation of equilibrium average heterozygosity as follows for the Wright–Fisher model with mutation when population size fluctuates stochastically.

$$\mathrm{E}[H(\infty)] = \frac{(N_e^{(\mathrm{WF2})}-1)u(2-u_K)}{1+(N_e^{(\mathrm{WF2})}-1)u_K(2-u_K)}, \tag{20}$$

where the left-hand side of (20) is given by (18). This definition of heterozygosity effective population size is analogous to that of the heterozygosity effective population size $N_e^{(D)}$ defined for a diffusion model with mutation when its population size fluctuates stochastically (Iizuka et al. 2002). The effective population size $N_e^{(\mathrm{WF2})}$ is an increasing function of $\mathrm{E}[H(\infty)]$ since

$$N_e^{(\mathrm{WF2})} = 1 + \frac{\mathrm{E}[H(\infty)]}{(2-u_K)\{u-u_K\mathrm{E}[H(\infty)]\}}. \tag{21}$$

By (17), (18) and the definition of $N_e^{(\mathrm{WF2})}$, the following result can be proved.

Result 1 *If the successive population sizes are positively autocorrelated* ($0 < q_1 + q_2 < 1$ *and* $q_1 q_2 \neq 0$)*, then*

$$N_e^{(\mathrm{WF2})} > N_h. \tag{22}$$

If the successive population sizes are uncorrelated ($q_1 + q_2 = 1$ *and* $q_1 q_2 \neq 0$)*, then*

$$N_e^{(\mathrm{WF2})} = N_h. \tag{23}$$

If the successive population sizes are negatively autocorrelated ($1 < q_1 + q_2 < 2$)*, then*

$$N_e^{(\mathrm{WF2})} < N_h. \tag{24}$$

The proof of Result 1 is given in Appendix 2.

The dependence of $N_e^{(\mathrm{WF2})}$ on the jump probabilities is given as the next result for the case of symmetric jump probabilities ($q = q_1 = q_2$).

Result 2 *Assume that* $q = q_1 = q_2$*. Then the heterozygosity effective population size* $N_e^{(\mathrm{WF2})}$ *is a decreasing function of the jump probability* q*.*

The proof of Result 2 is given in Appendix 2. This property corresponds to that for the inbreeding effective population size $N_e^{(\mathrm{WF1})}$ for the Wright–Fisher model without mutation when its population size fluctuates stochastically (put $c = 1$ in Theorem 4 of Iizuka 2001). The proof of Result 2 in Appendix 2 implies that the expectation of equilibrium average heterozygosity $\mathrm{E}[H(\infty)]$ is a decreasing function of the jump probability q.

Finally, we consider how the four effective population sizes $N_e^{(\mathrm{WF1})}$, $N_e^{(\mathrm{WF2})}$, $N_e^{(D)}$ and $N_e^{(C)}(k)$ are related (see Appendix 1 for definition and properties of $N_e^{(\mathrm{WF1})}$, $N_e^{(D)}$ and $N_e^{(C)}(k)$). Assume that the population size fluctuates between two distinct states N_1 and N_2 ($N_1 < N_2$) for the four models. The jump rate from N_i to N_j is denoted by γ_i ($i, j = 1, 2, i \neq j$) for the diffusion and coalescent models (see (46) and (49)). The jump probability from N_i to N_j is q_i for the discrete time models ($i, j = 1, 2$, $i \neq j$). Note that the parameter N in (33) of Sano et al. (2004) is a scaling parameter and we can put $N = 1$ in this formula without loss of generality. Let

$$\widetilde{N}_e^{(\mathrm{WF2})} = \lim_{u \to 0} N_e^{(\mathrm{WF2})}, \tag{25}$$

and

$$\widetilde{N}_e^{(D)} = \lim_{u \to 0} N_e^{(D)}. \tag{26}$$

Then the following result holds.

Result 3 *It holds that*

$$\widetilde{N}_e^{(\mathrm{WF2})} = N_h + \frac{(N_h - N_1)(N_2 - N_h)(1 - q_1 - q_2)}{N_1 N_2 (q_1 + q_2) + N_h (1 - q_1 - q_2)}, \tag{27}$$

though

$$\widetilde{N}_e^{(\mathrm{WF2})} \neq N_e^{(\mathrm{WF1})} \tag{28}$$

in general. Further

$$\widetilde{N}_e^{(D)} = N_h + \frac{(N_h - N_1)(N_2 - N_h)}{N_1 N_2(\gamma_1 + \gamma_2) + N_h} = N_e^{(C)}(2) \tag{29}$$

holds.

The proof of Result 3 is given in Appendix 2. By (27) and (29), it holds that

$$\widetilde{N}_e^{(\mathrm{WF2})} = \widetilde{N}_e^{(D)} \tag{30}$$

if $\gamma_1 + \gamma_2 = (q_1 + q_2)/(1 - q_1 - q_2)$ and $q_1 + q_2 < 1$. This equality implies that the hererozygosity effective population size of the diffusion model approximates the heterozygosity effective population size of the Wright–Fisher model when $q_1 + q_2 < 1$.

4 Discussion

When the population size varies, it is usually described in the literature that the effective population size is equal to the harmonic mean of the population size (see Crow 1954; Gillespie 1998; Nei et al. 1975; Wright 1938). For the Wright–Fisher model without mutation whose population size fluctuates stochastically, however, I showed that the inbreeding effective population size $N_e^{(\mathrm{WF1})}$ is not equal to the harmonic mean N_h unless the stochastic changes of population size are uncorrelated from generation to generation (see Theorem 2 of Iizuka 2001). By Result 1, this property holds for the heterozygosity effective size $N_e^{(\mathrm{WF2})}$ of the Wright–Fisher model with mutation when its population size fluctuates stochastically.

The definition of $N_e^{(\mathrm{WF2})}$ is essentially the same as that of $N_e^{(D)}$ for the diffusion model with mutation when its population size fluctuates stochastically. Though the definitions of these heterozygosity effective population sizes are essentially the same, the relations of these effective population sizes to the harmonic mean of population size are not the same. The heterozygosity effective population size $N_e^{(D)}$ for the diffusion model is always larger than the harmonic mean (see Iizuka et al. 2002), whereas the heterozygosity effective population size $N_e^{(\mathrm{WF2})}$ for the Wright–Fisher model can be equal to or smaller than the harmonic mean. Further Sano et al. (2004) showed for the coalescent model with fluctuation of population size that the coalescent effective population size $N_e^{(C)}(k)$ defined by means of the mean coalescent time from k genes to $k - 1$ genes is always larger than the harmonic mean. These results suggest that the property that the effective population sizes are always larger than the harmonic mean under the stochastic fluctuation of population size holds only for continuous time models such as diffusion and coalescent models and the effective population sizes can be equal to or smaller than the harmonic mean for discrete time models.

Let

$$\Theta = \frac{(N_h - 1)u(2 - u_K)}{1 + (N_h - 1)u_K(2 - u_K)} \tag{31}$$

be the equilibrium average heterozygosity when the population size is constant and it is N_h $(N(t) = N_h)$. Then the proof of Result 1 in Appendix 2 implies that $\mathrm{E}[H(\infty)] > \Theta$, $\mathrm{E}[H(\infty)] = \Theta$ and $\mathrm{E}[H(\infty)] < \Theta$ for positively autocorrelated stochastic changes, uncorrelated stochastic changes and negatively autocorrelated stochastic changes of population size, respectively. These results suggest that the stochastic changes of population size are likely to have positive (resp. negative) autocorrelation when it is known that the observed heterozygosity is larger (resp. smaller) than Θ.

The effective population sizes $N_e^{(\mathrm{WF2})}$ and $N_e^{(D)}$ depend on mutation rate. It may be preferable that the effective population sizes do not depend on mutation parameter. The limits $\widetilde{N}_e^{(\mathrm{WF2})}$ and $\widetilde{N}_e^{(D)}$ can be regarded as the appropriate effective population sizes when the effect of mutation is weak for the Wright–Fisher model with mutation and the diffusion model with mutation when the population size fluctuates stochastically, respectively. These limits are given in Result 3 (see (27) and (29)). By Result 2 it holds that $\widetilde{N}_e^{(\mathrm{WF2})} > N_h$ (resp. $\widetilde{N}_e^{(\mathrm{WF2})} < N_h$) if the successive population sizes are positively (resp. negatively) autocorrelated and $\widetilde{N}_e^{(\mathrm{WF2})} = N_h$ if they are uncorrelated. Also it holds that $\widetilde{N}_e^{(D)} > N_h$. Note that the formula (27) tells that the difference $\widetilde{N}_e^{(\mathrm{WF2})} - N_h$ has the maximal negative value in the case of deterministic demographics with $q_1 = q_2 = 1$ (cyclic change).

It is easy to see that

$$\lim_{N_1(q_1+q_2)\to\infty} \frac{N_e^{(\mathrm{WF2})}}{N_h} = 1 \tag{32}$$

and

$$\lim_{N_2(q_1+q_2)\to 0} \frac{\widetilde{N}_e^{(\mathrm{WF2})}}{N_a} = 1, \tag{33}$$

where

$$N_a = \mathrm{E}[N(t)] = N_1 p_1^{(st)} + N_2 p_2^{(st)} = \frac{N_1 q_2 + N_2 q_1}{q_1 + q_2} \tag{34}$$

is the arithmetic mean of the fluctuating population size $N(t)$ $(N_h < N_a)$. The same properties as (32) and (33) hold for the heterozygosity effective population size $N_e^{(D)}$ of the diffusion model with mutation when its population size fluctuates stochastically (see (51) and (52) of Iizuka et al. 2002) and for the coalescent effective population size $N_e^{(C)}(k)$ of the coalescent model with fluctuating population size (see (31) and (32) of Sano et al. 2004). For the inbreeding effective population size $N_e^{(\mathrm{WF1})}$ of the Wright–Fisher model without mutation the same property as (32) holds though the property as (33) does not hold (see Theorem 5 of Iizuka 2001).

The equality (32) and the same properties of the other three models imply that the effective population sizes are close to the harmonic mean if the population size fluctuates between two large values and the probability of the change is not weak (the autocorrelation of population sizes in two distinct generations is weak) in the sense that $N_1(q_1 + q_2)$ is large. Sjödin et al. (2005) considered the three cases that fluctuations of population size are fast, intermediate and slow compare to coalescent time scale. Their coalescent effective population size only exists when fluctuations are fast and the population sizes are large enough and it is asymptotically equal to the harmonic mean (Jagers and Sagitov 2004 obtained a much more general asymptotic result providing $N(t)$ being a finite Markov chain and exchangeable reproduction laws introduced by Cannings 1974). This is consistent with a result of present paper since the equality (32) implies that the heterozygosity effective population size $N_e^{(\mathrm{WF2})}$ becomes asymptotically equal to the harmonic mean N_h as N_1, N_2 and $N_1(q_1 + q_2)$ tend to infinity (the essentially the same property holds for the other three effective population sizes $N^{(\mathrm{WF1})}$, $N_e^{(D)}$ and $N_e^{(C)}(k)$). The condition that $N_1(q_1 + q_2)$ tends to infinity corresponds to fast fluctuations of population size in the sense of Sjödin et al. (2005). Note that fluctuations of population size are intermediate in the sense of Sjödin et al. (2005) for the coalescent model of Sano et al. (2004). On the other hand, the equality (33) implies that under weak mutation the heterozygosity effective population size $N_e^{(\mathrm{WF2})}$ is close to the arithmetic mean if the population size fluctuates between moderate or small values and the probability of the change is weak (the autocorrelation of population sizes in two distinct generations is strong) in the sense that $N_2(q_1 + q_2)$ is small.

Considering effects of selection on the genetic diversity of populations, effects of weak selection depend on population size (Ohta 1973, 1992). The fluctuation of population size must be incorporated in weak selection models when population size is not constant. It is difficult, however, to develop the mathematical analysis of these complex models. One of mathematically tractable ways is introducing an appropriate effective population size and replacing the population size by the effective population size in the weak selection models without fluctuation of population size. The results of this paper show that the harmonic mean of population size cannot be used as the effective population size in general.

The classical result that the effective population size is equal to the harmonic mean was originally obtained asymptotically as the census population sizes tend to infinity. Therefore, it is a remarkable fact that the effective population size is exactly equal to the harmonic mean when the population size changes stochastically and the successive changes are uncorrelated.

An advantage of discrete time models is that it is easy to incorporate stochastic change of a model parameter such as the population size into the models since the cases of positive autocorrelation, negative autocorrelation and no correlation can be formulated in a unified way (see Iizuka 1987). In this paper, a two-state Markov chain is considered for population evolution since various explicit formulas can be obtained for this simple Markov chain. It is a future problem to see whether the conclusions of the present paper on the effective population size hold for more general Markov chains.

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Appendix 1 Definition and properties of $N_e^{(\mathrm{WF1})}$, $N_e^{(D)}$ and $N_e^{(C)}(k)$

Definition of three effective population sizes and their properties of the Wright–Fisher model without mutation, the diffusion model with mutation and coalescent model under stochastic fluctuation of population size are presented. The different notations and terminologies from the original papers (Iizuka 2001; Iizuka et al. 2002; Sano et al. 2004) may be used here to unify them with those of the main text of this paper.

A.1.1 Wright–Fisher model without mutation under stochastic fluctuation of population size (Iizuka 2001)

The definition of this model is the same as that of the main text of this paper (Wright–Fisher model with mutation under stochastic fluctuation of population size) except that $u = 0$. By (15) and $u = 0$,

$$\mathrm{E}[H(t)] = \mathrm{E}[H(0)]\mathrm{E}\left[\prod_{k=1}^{t}\left\{1 - \frac{1}{N(k)}\right\}\right] \tag{35}$$

for this model. Since it holds that

$$\mathrm{E}[H(t)] = \mathrm{E}[H(0)]\left(1 - \frac{1}{N}\right)^{t} \tag{36}$$

when the population size is a constant ($N = N(t)$), the inbreeding effective population size $N_e^{(\mathrm{WF1})}$ of this model is defined by

$$1 - \frac{1}{N_e^{(\mathrm{WF1})}} = \lim_{t\to\infty}\left(\mathrm{E}\left[\prod_{k=1}^{t}\left\{1 - \frac{1}{N(k)}\right\}\right]\right)^{\frac{1}{t}}. \tag{37}$$

Then $N_e^{(\mathrm{WF1})}$ has the following concrete expression.

$$N_e^{(\mathrm{WF1})} = \frac{1}{1-\alpha_+}, \tag{38}$$

where α_+ is the largest solution of the quadratic equation

$$\begin{aligned}\alpha^2 - \left\{\left(1 - \frac{1}{N_1}\right)(1-q_1) + \left(1 - \frac{1}{N_2}\right)(1-q_2)\right\}\alpha + \left(1 - \frac{1}{N_1}\right)\\ \times\left(1 - \frac{1}{N_2}\right)(1 - q_1 - q_2) = 0.\end{aligned} \tag{39}$$

It holds that $N_e^{(\mathrm{WF1})} > N_h$ (resp. $N_e^{(\mathrm{WF1})} < N_h$) if $0 < q_1 + q_2 < 1$ and $q_1 q_2 \neq 0$ (resp. $q_1 + q_2 > 1$) and $N_e^{(\mathrm{WF1})} = N_h$ if $q_1 + q_2 = 1$ and $q_1 q_2 \neq 0$, where is N_h is defined by (10). Though two allele case is considered for simplicity in Iizuka (2001), it is obvious that this model can be extended to K allele case ($K \geq 2$).

A.1.2 Diffusion model with mutation under stochastic fluctuation of population size (Iizuka et al. 2002)

For this diffusion model, time parameter t is continuous ($-\infty < t < \infty$) and $N(t)$ is the population size of a haploid population at time t. Consider a neutral locus with K alleles ($2 \leq K \leq \infty$) and with symmetric mutation between them. If the population size is constant ($N = N(t)$), the average heterozygosity of the population $\mathcal{H}(t)$ at time t satisfies

$$\frac{d\mathcal{H}(t)}{dt} = -\frac{1}{N}\mathcal{H}(t) + 2\{u - u_K\mathcal{H}(t)\}, \tag{40}$$

where u is the total mutation rate of an allele and $u_K = Ku/(K-1)$. Then $\mathcal{H}(t)$ and $\mathcal{H}(\infty) = \lim_{t\to\infty} \mathcal{H}(t)$ are given by

$$\mathcal{H}(t) = \frac{2Nu}{1+2Nu_K} + \left\{\mathcal{H}(0) - \frac{2Nu}{1+2Nu_K}\right\} e^{-(2u_K+1/N)t}, \tag{41}$$

and

$$\mathcal{H}(\infty) = \frac{2Nu}{1+2Nu_K}. \tag{42}$$

Let $N(t)$ be a stationary process. The diffusion model under stochastic fluctuation of population size is defined replacing N by $N(t)$ and this is a diffusion model with a random parameter $N(t)$. For this diffusion model, the average heterozygosity of the population $\mathcal{H}(t)$ at time t satisfies

$$\frac{d\mathcal{H}(t)}{dt} = -\frac{1}{N(t)}\mathcal{H}(t) + 2\{u - u_K\mathcal{H}(t)\}. \tag{43}$$

Then $\mathcal{H}(t)$ is given by

$$\mathcal{H}(t) = 2u\int_0^t e^{-\int_z^t \{2u_K+1/N(s)\}\mathrm{d}s}\mathrm{d}z + \mathcal{H}(0)e^{-\int_0^t \{2u_K+1/N(s)\}\mathrm{d}s}. \tag{44}$$

The expectation of a quantity X with respect to the stochastic fluctuation of population size is denoted by $\mathrm{E}[X]$. By (42), the heterozygosity effective population size $N_e^{(D)}$ is defined by

$$\mathrm{E}[\mathcal{H}(\infty)] = \frac{2N_e^{(D)}u}{1+2N_e^{(D)}u_K}, \tag{45}$$

where $\mathcal{H}(\infty) = \lim_{t\to\infty} \mathcal{H}(t)$. This effective population size has the property that $N_h < N_e^{(D)} < N_a$, where N_h and N_a are the harmonic mean and the arithmetic mean of population size, that is, $1/N_h = \mathrm{E}[1/N(t)]$ and $N_a = \mathrm{E}[N(t)]$.

For the special case that $N(t)$ is a two-valued Markov chain on $\{N_1, N_2\}$ such that

$$\begin{pmatrix} \mathrm{P}(N(t+\triangle t) = N_1) \\ \mathrm{P}(N(t+\triangle t) = N_2) \end{pmatrix} = \begin{pmatrix} 1 - \gamma_1 \triangle t + o(\triangle t) & \gamma_2 \triangle t + o(\triangle t) \\ \gamma_1 \triangle t + o(\triangle t) & 1 - \gamma_2 \triangle t + o(\triangle t) \end{pmatrix} \times \begin{pmatrix} \mathrm{P}(N(t) = N_1) \\ \mathrm{P}(N(t) = N_2) \end{pmatrix}, \tag{46}$$

($\triangle t \downarrow 0$), this effective population size has a concrete expression

$$N_e^{(D)} = N_h + \frac{(N_2 - N_h)(N_h - N_1)}{(\gamma_1 + \gamma_2 + 2u_K)N_1 N_2 + N_h} \tag{47}$$

Here $N_1 < N_2$ and γ_i is the jump rate of $N(t)$ conditional on $N(t) = N_i$ $(i = 1, 2)$.

A.1.3 Coalescent model under stochastic fluctuation of population size (Sano et al. 2004)

For this coalescent model, time parameter t is continuous ($-\infty < t < \infty$) and $N(t)$ is the population size of a haploid population at time t. Here $N(t)$ is a continuous time Markov chain on $\{N_1, N_2, \ldots, N_L\}$ with $N_1 < N_2 < \cdots < N_L$ and

$$\mathrm{P}(N(t+\triangle t) = N_j \mid N(t) = N_i) = \gamma_{ij} \triangle t + o(\triangle t), \tag{48}$$

($\triangle t \downarrow 0$), which is assumed to be an ergodic and reversible Markov chain with respect to the stationary distribution $\nu = (\nu_1, \nu_2, \ldots, \nu_L)$. Let K be a fixed positive integer. A $(K \times L) \times (K \times L)$ matrix $Q = \left(\gamma_{(k,i)(l,j)}\right)$ with

$$\gamma_{(k,i)(l,j)} = \begin{cases} \frac{k(k-1)}{2N_i}, & \text{if } \ l = k-1,\ j = i \\ \gamma_{ij}, & \text{if } \ l = k,\ j \neq i \\ -\frac{k(k-1)}{2N_i} - \sum_{m \neq i} \gamma_{im}, & \text{if } \ l = k,\ j = i \\ 0, & \text{otherwise} \end{cases} \tag{49}$$

is the generator of a continuous time Markov chain $(k(t), N(t))$ on $\{(k, N_i) : k = 1, 2, \ldots, K;\ i = 1, 2, \ldots, L\}$. Measuring the time backward, $(k(t), N(t))$ is the coalescent model under fluctuation of population size. Let $A(t)$ be the standard Kingman's ancestral process (see Tavaré 1984) and $I(t) = \int_0^t \frac{1}{N(u)} \mathrm{d}u$. Kaj and Krone (2003) constructed a coalescent model $(A(I(t)), N(t))$ under fluctuation of population size. Two coalescent models $(k(t), N(t))$ and $(A(I(t)), N(t))$ can be regarded as the same Markov chain (Sano et al. 2004). Let $T_k = \inf\{t > 0 \mid A(t) = k-1, A(0) = k\}$ be the coalescent time from k genes to $k-1$ genes. Let $\mathrm{E}[T_k]$ be the expectation of T_k with respect to coalescent events and the stochastic fluctuation of population size. The coalescent effective population size from k genes to $k-1$ genes $N_e^{(C)}(k)$ is defined by

$$\mathrm{E}[T_k] = \frac{2}{k(k-1)} N_e^{(C)}(k), \tag{50}$$

since $\mathrm{E}[T_k] = \frac{2}{k(k-1)}N$ when the population size is constant $(N(t) = N)$. For this effective population size, it holds that $N_h < N_e^{(C)}(k) < N_a$ where $N_h = \left(\sum_{i=1}^{L} \nu_i/N_i\right)^{-1}$ and $N_a = \sum_{i=1}^{L} N_i\nu_i$ are the harmonic mean and the arithmetic mean of population size.

For the special case that $N(t)$ is a two-valued Markov chain on $\{N_1, N_2\}$ $(N_1 < N_2)$, the coalescent effective population size from two genes to one gene is expressed as

$$N_e^{(C)}(2) = N_h + \frac{(N_h - N_1)(N_2 - N_h)}{N_1N_2(\gamma_1 + \gamma_2) + N_h}, \tag{51}$$

where $\gamma_1 = \gamma_{12}$, $\gamma_2 = \gamma_{21}$ and $N_h = (\gamma_1 + \gamma_2)\left(\frac{\gamma_2}{N_1} + \frac{\gamma_1}{N_2}\right)^{-1}$.

Appendix 2 Proof of Results 1, 2 and 3

A.2.1 Proof of Result 1

Note that $(L-l)/(M+m) > L/M$ if and only if $Lm + lM < 0$, $(L-l)/(M+m) = L/M$ if and only if $Lm + lM = 0$, and $(L-l)/(M+m) < L/M$ if and only if $Lm + lM > 0$. Put

$$L = 1 - \frac{1}{N_h}, \tag{52}$$

$$l = (1-u_K)^2 n_1 n_2 (1 - q_1 - q_2), \tag{53}$$

$$M = 1 - \left(1 - \frac{1}{N_h}\right)(1-u_K)^2, \tag{54}$$

$$m = (1-u_K)^2 \left\{1 - \frac{1}{N_h} - n_1 - n_2 + (1-u_K)^2 n_1 n_2\right\}(1 - q_1 - q_2). \tag{55}$$

Then it holds that

$$Lm + lM = -(1-u_K)^2 \left(\frac{1}{N_1} - \frac{1}{N_h}\right)\left(\frac{1}{N_h} - \frac{1}{N_2}\right)(1 - q_1 - q_2), \tag{56}$$

$$\frac{L}{M} = \frac{N_h - 1}{1 + (N_h - 1)u_K(2 - u_K)}, \tag{57}$$

$$\frac{L-l}{M+m} = \frac{\mathrm{E}[H(\infty)]}{u(2-u_K)}, \tag{58}$$

by noting (18). Since $Lm + lM < 0$ if and only if $0 < q_1 + q_2 < 1$, $Lm + lM = 0$ if and only if $q_1 + q_2 = 1$, and $Lm + lM > 0$ if and only if $q_1 + q_2 > 1$, it holds that

$$\mathrm{E}[H(\infty)] > \frac{(N_h - 1)u(2 - u_K)}{1 + (N_h - 1)u_K(2 - u_K)} = \Theta \tag{59}$$

if and only if $0 < q_1 + q_2 < 1$,

$$\mathrm{E}[H(\infty)] = \Theta \tag{60}$$

if and only if $q_1 + q_2 = 1$,

$$\mathrm{E}[H(\infty)] < \Theta \tag{61}$$

if and only if $q_1 + q_2 > 1$. Here Θ is the equilibrium average heterozygosity when the population size is constant and $N(t) = N_h$ (see (31)). The conclusion of Result 1 holds since the heterozygosity effective population size $N_e^{(\mathrm{WF2})}$ is an increasing function of $\mathrm{E}[H(\infty)]$ (see (21)). □

A.2.2 Proof of Result 2

It is enough to show that $\mathrm{E}[H(\infty)]$ is a decreasing function of q since $N_e^{(\mathrm{WF2})}$ is an increasing function of $\mathrm{E}[H(\infty)]$. For the symmetric case that $q = q_1 = q_2$,

$$1 - \frac{1}{N_h} = \frac{n_1 + n_2}{2} \tag{62}$$

and $\mathrm{E}[H(\infty)]$ can be expressed as

$$g(q) = \mathrm{E}[H(\infty)] = \frac{u(1 - u_K)\{n_1 + n_2 - (1 - u_K)^2 n_1 n_2 (1 - 2q)\}}{1 - (1 - u_K)^2 (n_1 + n_2)(1 - q) + (1 - u_K)^4 n_1 n_2 (1 - 2q)}. \tag{63}$$

Here $\mathrm{E}[H(\infty)]$ is denoted by $g(q)$ as a function of q. After tedious calculations, it can be shown that the derivative of $g(q)$ with respect to q is

$$g'(q) = -\frac{u(1 - u_K)(n_1 - n_2)^2}{\{1 - (1 - u_K)^2 (1 - q) + (1 - u_K)^4 n_1 n_2 (1 - 2q)\}^2} < 0. \tag{64}$$

Then $\mathrm{E}[H(\infty)]$ is a decreasing function of q. □

A.2.3 Proof of Result 3

By (18) and (21), it can be shown that

$$\widetilde{N}_e^{(\mathrm{WF2})} = N_h + \frac{(N_h - N_1)(N_2 - N_h)(1 - q_1 - q_2)}{N_1 N_2 (q_1 + q_2) + N_h (1 - q_1 - q_2)}. \tag{65}$$

On the other hand,

$$\widetilde{N}_e^{(D)} = N_h + \frac{(N_h - N_1)(N_2 - N_h)}{N_1 N_2 (\gamma_1 + \gamma_2) + N_h} \tag{66}$$

holds by (47). The second equality in (29) can be shown by (51). The result of (28) can be seen quantitatively since $0.67 < \widetilde{N}_e^{(\mathrm{WF2})}/N_e^{(\mathrm{WF1})} < 0.68$ if $N_1 = 10$, $N_2 = 100$ and $q_1 = q_2 = 0.01$. □

References

Araki H, Tachida H (1997) Bottleneck effect on evolutionary rate in nearly neutral mutation model. Genetics 147:907–914

Cannings C (1974) The latent roots of certain Markov chains arising in genetics: a new approach. I. Haploid models. Adv Appl Prob 6:260–290

Chia AB, Pollak E (1974) The inbreeding effective number and the effective number of alleles in a population that varies in size. Theor Popul Biol 6:149–172

Crow JF (1954) Breeding structure of population. II. Effective population number. In : Kempthorne O (ed) Statistics and mathematics in biology. Hafner, New York, pp 543–556

Donnelly P (1986) A genealogical approach to variable-population-size models in population genetics. J Appl Probab 23:283–296

Ewens WJ (1982) The concept of the effective population size. Theor Popul Biol 21:373–378

Gillespie JH (1998) Population genetics—a concise guide. The Johns Hopkins University Press, Baltimore

Gillespie JH (2000) The neutral theory in an infinite population. Gene 261:11–18

Heyde CC, Seneta E (1975) The genetic balance between random sampling and random population size. J Math Biol 1:317–320

Iizuka M (1987) Weak convergence of a sequence of stochastic difference equations to a stochastic ordinary differential equation. J Math Biol 25:643–652

Iizuka M (2001) The effective size of fluctuating populations. Theor Popul Biol 59:281–286

Iizuka M, Matsuda H (1982) Weak convergence of discrete time non-Markovian processes related to selection models in population genetics. J Math Biol 15:107–127

Iizuka M, Tachida H, Matsuda H (2002) A neutral model with fluctuating population size and its effective size. Genetics 161:381–388

Jagers P, Sagitov S (2004) Convergence to the coalescent in a populations of substantially varying size. J Appl Probab 41:368–378

Kaj I, Krone MS (2003) The coalescent process in a population with stochastically varying size. J Appl Probab 40:33–48

Karlin S (1968) Rates of approach to homozygosity for finite stochastic models with variable population size. Am Nat 102:443–455

Kimura M (1968) Evolutionary rate at the molecular level. Nature 217:624–626

Klebaner FC (1988) Conditions for fixation of an allele in the density-dependent Wright–Fisher model. J Appl Probab 25:247–256

Nei M, Maruyama T, Chakraborty R (1975) The bottleneck effect and genetic variability in populations. Evolution 29:1–10

Ohta T (1973) Slightly deleterious mutant substitutions in evolution. Nature 246:96–98

Ohta T (1992) The nearly neutral theory of molecular evolution. Annu Rev Ecol Syst 23:263–286

Sano A, Shimizu A, Iizuka M (2004) Coalescent process with fluctuating population size and its effective size. Theor Popul Biol 65:39–48

Seneta E (1974) A note on the balance between random sampling and population size. Genetics 77:607–610

Sjödin P, Kaj I, Krone S, Lascoux M, Nordborg M (2005) On the meaning and existence of an effective population size. Genetics 169:1061–1070

Tachida H (2000) DNA evolution under weak selection. Gene 261:3–9

Tavaré S (1984) Line-of-descent and genealogical processes, and their applications in population genetics models. Theor Popul Biol 26:119–164

Wright S (1938) Size of population and breeding structure in relation to evolution. Science 87:430–431