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Evolution of a finite population under gene conversion

(population genetics/recombination/meiotic drive/random drift/selection)

THOMAS NAGYLAKI

Department of Biophysics and Theoretical Biology, The University of Chicago, 920 East 58th Street, Chicago, Illinois 60637

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ABSTRACT **Evolution at a multiallelic locus under the joint action of gene conversion, mutation, selection, and random genetic drift is studied. Generations are discrete and nonoverlapping; the diploid, monoecious population mates at random. Under the assumption that all four evolutionary forces are weak, a diffusion approximation is established for the dynamics of the gene frequencies. For two alleles, the inclusion of gene conversion merely alters one of the two selection parameters of the thoroughly investigated diffusion process without conversion. Therefore, all results for this classical process, some of which are reviewed and extended here, are immediately applicable to the biologically more general problem. Small conversional disparities can dramatically affect the fixation probability (and hence the rate of gene substitution) and can greatly reduce the mean conditional fixation time of a new mutant. The mean absorption and fixation times are often sufficiently short to imply that biased gene conversion can be an important mechanism for the loss of genetic variability in and the genetic divergence of isolated populations.**

In a recent paper (1), data pertinent to the influence of gene conversion on the dynamics of allelic frequencies at a multiallelic locus were reviewed, and the evolution of a large population was investigated. It was shown that biased conversion often causes loss of genetic variability and contributes to the genetic divergence of isolated populations. If the effective population number is not much larger than the reciprocal of a typical disparity parameter (1), random genetic drift will significantly affect the evolution of the population. In this paper, we shall study the joint action of gene conversion, mutation, selection, and random drift at a multiallelic locus. *Sections 1, 2,* and *3* comprise the formulation of our problem, its approximation under the assumption that all four evolutionary forces are weak, and biological applications, respectively.

Generations are discrete and nonoverlapping; the diploid, monoecious population mates at random.

1. Formulation

There are n alleles; unless indicated otherwise, all sums run from 1 to n. The life cycle starts with N adults, among whom the genotype A_iA_j has frequency P_{ij}, $1 \le i \le j \le n$. The frequencies of ordered genotypes will also be useful and will always be indicated by a tilde:

$$\tilde{P}_{ij} = \frac{1}{2}(1 + \delta_{ij})P_{ij}, \qquad P_{ij} = (2 - \delta_{ij})\tilde{P}_{ij}, \qquad \tilde{P}_{ji} = \tilde{P}_{ij}, \quad [1a]$$

where δ_{ij} denotes the Kronecker delta. The frequency of A_i in adults reads

$$p_i = \sum_j \tilde{P}_{ij}. \quad [1b]$$

We exhibit the main features of the model in the following formal scheme.

$$\begin{array}{ccccccc} \text{Adults} & \xrightarrow{} & \text{Gametes} & \xrightarrow{} & \text{Zygotes} & \xrightarrow{} & \\ N,P_{ij} & \text{conversion} & \infty,p_i^* & \text{fertilization} & \infty,p_i^*p_j^* & \text{selection} & \\ \text{Adults} & \xrightarrow{} & \text{Adults} & \xrightarrow{} & \text{Adults.} & & \\ \infty,\tilde{P}_{ij}^{**} & \text{mutation} & \infty,\tilde{P}_{ij}^{***} & \text{regulation} & N,P'_{ij} & & \end{array}$$

The adults produce infinitely many gametes without fertility differences. To incorporate gene conversion, let c_{ij} designate the probability that a gamete chosen at random from an A_iA_j individual carries A_i. Consult ref. 1 for discussions of the parameters c_{ij} and the disparities b_{ij}, introduced below, and of the assumption that conversion in A_iA_j can produce only A_i and A_j. For the frequency of A_i in gametes, we have

$$p_i^* = 2\sum_j c_{ij}\tilde{P}_{ij}. \quad [2]$$

The gametes fuse at random to form zygotes, and viability selection follows, after which the ordered genotype A_iA_j has frequency

$$\tilde{P}_{ij}^{**} = w_{ij}p_i^*p_j^*/\bar{w}, \quad [3a]$$

where w_{ij} and

$$\bar{w} = \sum_{ij} w_{ij}p_i^*p_j^* \quad [3b]$$

represent the fitness of A_iA_j individuals and the mean fitness of the population.

We signify the probability that A_i mutates to A_j by u_{ij} (by convention, $u_{ii} = 0$ for all i) and assume that the two genes at a locus mutate independently. Then, after mutation, the ordered genotypic frequencies become

$$\tilde{P}_{ij}^{***} = \sum_{kl} \tilde{P}_{kl}^{**}R_{ki}R_{lj}, \quad [4a]$$

where

$$R_{ki} = \left(1 - \sum_m u_{km}\right)\delta_{ki} + u_{ki}. \quad [4b]$$

Finally, random genetic drift operates through population regulation, which reduces the population number from infinity to N and changes the unordered genotypic frequencies to P'_{ij}. This means that, given $\mathbf{P}$, the allelic numbers NP'_{ij} $(1 \le i \le j \le n)$ are multinomially distributed with parameters P_{ij}^{***} and index N. In conjunction with [1]–[4], this defines a Markov chain for the basic vector $\mathbf{P}(t)$ $(t = 0, 1, 2, \ldots)$.

Biological considerations require the order of the deterministic effects posited above (1). Were we to insert random drift before the end of the life cycle, at least one of the other evolutionary forces would have to operate in a finite population, and this would require a much more complicated probabilistic

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treatment for those forces. The diffusion limit would most likely be the same as in *Section 2*, but this has not been proved.

Our model also applies to meiotic drive.

2. The diffusion limit

The intractability of the exact model formulated in *Section 1* compels us to seek approximations. The disparity parameters that control allelic frequency change due to gene conversion appear to be always much less than one, usually by at least two orders of magnitude (1). Mutation rates are generally between 10^{-6} and 10^{-4}; if we exclude lethality and sterility, most selection intensities do not exceed several percent (2). The effective population numbers (and even local population numbers) of natural populations usually exceed several hundred (3). Consequently, we lose very little biological generality by positing that all four evolutionary forces are weak.

We introduce the disparities b_{ij} and selection coefficients s_{ij} through

$$c_{ij} = \frac{1}{2}(1 + b_{ij}), \qquad w_{ij} = 1 + s_{ij}, \tag{5}$$

and assume that the disparity parameters, selection coefficients, and mutation rates are not much greater than the reciprocal of the population number, which is much larger than unity. Thus, we let $N \to \infty$ and suppose that

$$b_{ij} = \beta_{ij}/(2N), \qquad s_{ij} = \sigma_{ij}/(2N), \qquad u_{ij} = \mu_{ij}/(2N), \tag{6}$$

where β_{ij}, σ_{ij}, and μ_{ij} are fixed. These constants satisfy $\beta_{ij} = -\beta_{ji}$ (1), $\sigma_{ij} = \sigma_{ji}$, and $\mu_{ii} = 0$ for all i and j.

To derive the diffusion limit of the Markov chain $\{\mathbf{P}(t)\}$, we shall apply a theorem concerning the diffusion approximation of Markov chains with two time scales (4). For our purpose, the following statement suffices; consult refs. 4 and 5 for more detail and discussion.

For $N = 1, 2, \ldots$, let $\{\mathbf{Z}^N(t),\ t = 0, 1, \ldots\}$ be a time-homogeneous Markov chain in a metric space $\mathscr{C}_N$; suppose both $\mathbf{\Phi}_N\colon \mathscr{C}_N \to \mathscr{R}^m$ and $\mathbf{\Psi}_N\colon \mathscr{C}_N \to \mathscr{R}^l$ are continuous; define $\mathbf{X}^N(t) = \mathbf{\Phi}_N[\mathbf{Z}^N(t)]$ and $\mathbf{Y}^N(t) = \mathbf{\Psi}_N[\mathbf{Z}^N(t)]$ for each $t \geq 0$; and let $\varepsilon_N > 0$ and $\delta_N > 0$. Assume that $\lim_{N\to\infty} \delta_N = \delta_\infty$, $0 \leq \delta_\infty < \infty$, and $\lim_{N\to\infty} \varepsilon_N/\delta_N = 0$. All expectations, variances, and covariances refer to one-step transitions starting at $\mathbf{z}$. Set $\mathbf{x} = \mathbf{\Phi}_N(\mathbf{z})$ and $\mathbf{y} = \mathbf{\Psi}_N(\mathbf{z})$, and suppose that as $N \to \infty$

$$\varepsilon_N^{-1}E[X_i^N(1) - x_i] = M_i(\mathbf{x},\mathbf{y}) + o(1), \tag{7a}$$

$$\varepsilon_N^{-1}\mathrm{Cov}[X_i^N(1), X_j^N(1)] = V_{ij}(\mathbf{x},\mathbf{y}) + o(1), \tag{7b}$$

$$\varepsilon_N^{-1}E[\{X_i^N(1) - E[X_i^N(1)]\}^4] = o(1), \tag{7c}$$

$$\delta_N^{-1}E[Y_k^N(1) - y_k] = c_k(\mathbf{x},\mathbf{y}) + o(1), \tag{7d}$$

$$\delta_N^{-1}\mathrm{Var}[Y_k^N(1)] = o(1) \tag{7e}$$

for $i,j = 1, \ldots, m$ and $k = 1, \ldots, l$. Assume further that $\mathbf{c}(\mathbf{x},\mathbf{0}) = \mathbf{0}$, and if $\delta_\infty = 0$, the zero solution of the differential equation

$$\frac{d}{dt}\mathbf{Y}(t,\mathbf{x}) = \mathbf{c}[\mathbf{x}, \mathbf{Y}(t,\mathbf{x})] \tag{7f}$$

is globally asymptotically stable; if $\delta_\infty > 0$, posit the same for the difference equation

$$\delta_\infty^{-1}[\mathbf{Y}(t+1, \mathbf{x}) - \mathbf{Y}(t,\mathbf{x})] = \mathbf{c}[\mathbf{x}, \mathbf{Y}(t,\mathbf{x})]. \tag{7g}$$

Then, provided some technical conditions are satisfied, $\mathbf{X}^N([\tau/\varepsilon_N])$ converges weakly to the diffusion $\mathbf{X}(\tau)$ with generator

$$L = \frac{1}{2}\sum_{i,j=1}^{m} V_{ij}(\mathbf{x},\mathbf{0})\frac{\partial^2}{\partial x_i \partial x_j} + \sum_{i=1}^{m} M_i(\mathbf{x},\mathbf{0})\frac{\partial}{\partial x_i}, \tag{8}$$

and $\mathbf{Y}^N([t_N/\delta_N]) \to 0$ in probability whenever $t_N \to \infty$.

We proceed to verify the conditions 7 for $\{\mathbf{P}(t)\}$. According to [6], all evolutionary forces operate on the slow time scale with $\varepsilon_N = 1/(2N)$. Then deviations of $\mathbf{P}$ from Hardy–Weinberg proportions are reduced on the time scale of a single generation; thus, $\delta_N = 1$. Therefore, it is natural to identify X_i^N and Y_{ij}^N with p_i and

$$Q_{ij} = P_{ij} - (2 - \delta_{ij})p_i p_j \tag{9}$$

$(1 \leq i \leq j \leq n)$, respectively. From [1]–[6], we obtain

$$p_i^{***} = p_i + \frac{1}{2N}\Bigg[\sum_k \beta_{ik}\tilde{P}_{ik} + p_i\sum_k \sigma_{ik}p_k - p_i\sum_{kl}\sigma_{kl}p_k p_l - p_i\sum_k \mu_{ik} + \sum_k p_k\mu_{ki}\Bigg] + O(N^{-2}), \tag{10a}$$

$$\tilde{P}_{ij}^{***} = p_i p_j + O(N^{-1}) \tag{10b}$$

as $N \to \infty$.

For [7a], we find from [10a]

$$2NE(p_i' - p_i) = 2N(p_i^{***} - p_i) = M_i(\mathbf{p},\mathbf{Q}) + O(N^{-1}), \tag{11a}$$

where

$$M_i(\mathbf{p},\mathbf{Q}) = \sum_k \beta_{ik}\tilde{P}_{ik} + p_i\sum_k \sigma_{ik}p_k - p_i\sum_{kl}\sigma_{kl}p_k p_l - p_i\sum_k \mu_{ik} + \sum_k p_k\mu_{ki}. \tag{11b}$$

Appeal to ref. 4 (p. 31) and [10] yields

$$2N\,\mathrm{Cov}(p_i', p_j') = p_i^{***}(\delta_{ij} - p_j^{***}) + \tilde{P}_{ij}^{***} - p_i^{***}p_j^{***} = V_{ij}(\mathbf{p},\mathbf{Q}) + O(N^{-1}), \tag{12a}$$

where

$$V_{ij}(\mathbf{p},\mathbf{Q}) = p_i(\delta_{ij} - p_j). \tag{12b}$$

Exactly as in ref. 4 (p. 31), [7c] holds because

$$2NE\{[p_i' - E(p_i')]^4\} = O(N^{-1}). \tag{13}$$

From [9], [10], and [12a] we deduce

$$\begin{aligned} E(Q_{ij}' - Q_{ij}) &= E[(P_{ij}' - P_{ij}) - (2 - \delta_{ij})(p_i'p_j' - p_ip_j)] \\ &= P_{ij}^{***} - P_{ij} - (2 - \delta_{ij})[\mathrm{Cov}(p_i', p_j') + p_i^{***}p_j^{***} - p_ip_j] \\ &= -Q_{ij} + O(N^{-1}). \end{aligned} \tag{14}$$

We invoke [9] and two elementary inequalities in ref. 4 (p. 23) to establish [7e]:

$$\begin{aligned} \mathrm{Var}(Q_{ij}') &\leq 2[\mathrm{Var}(P_{ij}') + (2 - \delta_{ij})^2\mathrm{Var}(p_i'p_j')] \\ &\leq 2[\mathrm{Var}(P_{ij}') + 4(2)\{\mathrm{Var}(p_i') + \mathrm{Var}(p_j')\}] = O(N^{-1}). \end{aligned} \tag{15}$$

In view of [14], for [7g] we get the trivial difference equation $q_{ij}' = 0$, whence $q_{ij}(t) = 0$ for $t \geq 1$.

This concludes the verification of conditions 7. Therefore, in the diffusion time units of $2N$ generations, the population evolves arbitrarily close to the Hardy–Weinberg surface $\mathbf{Q} = \mathbf{0}$. More precisely, $Q_{ij}([2N\tau]) \to 0$ in probability as $N \to \infty$ with $\tau > 0$ fixed. Using [8], [11b], and [12b] leads to the generator

$$L = \frac{1}{2}\sum_{i,j=1}^{n-1} V_{ij}(\mathbf{p},\mathbf{0})\frac{\partial^2}{\partial p_i \partial p_j} + \sum_{i=1}^{n-1} M_i(\mathbf{p},\mathbf{0})\frac{\partial}{\partial p_i}, \tag{16a}$$

where

$$M_i(\mathbf{p},0) = p_i \sum_{k=1}^{n} \beta_{ik}p_k + p_i \sum_{k=1}^{n} \sigma_{ik}p_k - p_i \sum_{k,l=1}^{n} \sigma_{kl}p_kp_l - p_i \sum_{k=1}^{n} \mu_{ik} + \sum_{k=1}^{n} p_k\mu_{ki}, \quad [16b]$$

$$V_{ij}(\mathbf{p},0) = p_i(\delta_{ij} - p_j) \quad [16c]$$

for the limiting diffusion of $\mathbf{p}([2N\tau])$. It is essential to keep in mind that L in [16a] operates on functions of $(p_1, p_2, \ldots, p_{n-1})$; one must express p_n in the arguments of these functions as

$$p_n = 1 - \sum_{i=1}^{n-1} p_i.$$

The evolutionary effect of gene conversion is negligible if $N|b_{ij}| \ll 1$ for all i and j. The analyses in ref. 4 strongly suggest that the diffusion **16** applies to more general models than ours, provided we take into account biological features such as dioecy and nonbinomial variation in progeny number by replacing N everywhere in this section by the variance effective population number N_e.

3. Two alleles

For two alleles, [16] reduces to a diffusion on the unit interval $0 \le p = p_1 \le 1$:

$$L = \frac{1}{2}p(1-p)\frac{d^2}{dp^2} + M(p)\frac{d}{dp}, \quad [17a]$$

where

$$M(p) = p(1-p)(\alpha + \gamma p) + \nu - (\mu + \nu)p, \quad [17b]$$

$$\alpha = \beta_{12} + \sigma_{12} - \sigma_{22}, \qquad \gamma = \sigma_{11} - 2\sigma_{12} + \sigma_{22}, \quad [18]$$

$\mu = \mu_{12}$, and $\nu = \mu_{21}$. The generator **17** is identical with that of the classical diallelic diffusion for mutation and selection in a finite population, which has been extensively investigated (see refs. 6 and 7 for reviews). Gene conversion merely causes the appearance of β_{12} in α; in particular, if there is no dominance ($\gamma = 0$), conversion simply alters the selection intensity. In the remainder of this section, we shall review and extend a few properties of [17] that may be of particular biological interest for the evolutionary significance of gene conversion.

(i) Reversible mutation. If $\mu > 0$ and $\nu > 0$, the probability density of the frequency x of A_1 converges as $t \to \infty$ to (8, 9)

$$\hat{\phi}(x) = Bx^{2\nu-1}(1-x)^{2\mu-1}e^{x(\gamma x + 2\alpha)}, \quad [19]$$

where B denotes a normalization constant. Consult refs. 6 (pp. 442–445), 10 (pp. 363–365), and 11 (pp. 65–67) for discussions of the stationary distribution **19**.

(ii) No mutation. With negligible mutation ($\mu = \nu = 0$), we focus on the fixation probability, the mean absorption time, and the mean fixation time. Kimura (12, 13) treated fixation probabilities with arbitrary dominance [see also refs. 6 (pp. 423–428), 7 (pp. 146–148), 14, and 15]. Hereafter, we posit the absence of dominance ($\gamma = 0$); then the probability that A_1 is fixed reads (12, 13, 16)

$$\pi_1(p) = (1 - e^{-2\alpha p})/(1 - e^{-2\alpha}), \quad [20]$$

where p designates the initial frequency of A_1. If $|\alpha|p \ll 1$, [20] reduces to

$$\pi_1(p) \approx 2\alpha p/(1 - e^{-2\alpha}), \quad [21]$$

which is close to p, the fixation probability with pure random drift (12), if and only if $|\alpha| \ll 1$. In particular, with no selection and the heuristic insertion of the variance effective population number into [6] and of $p = 1/(2N)$ into [21], for a new mutant (A_1) we obtain

$$\pi_1[1/(2N)] \approx 2N_eN^{-1}b_{12}/(1 - e^{-4N_eb_{12}}) \quad [22]$$

$$\approx \begin{cases} 2N_eN^{-1}b_{12}, & e^{-4N_eb_{12}} \ll 1, \\ -2N_eN^{-1}b_{12}e^{-4N_eb_{12}}, & e^{-4N_eb_{12}} \gg 1. \end{cases} \quad [23]$$

This is much greater (less) than $1/(2N)$, the value without conversion, if $4N_eb_{12} \gg 1$ ($4N_eb_{12} \ll -1$). Thus, if $|b_{12}| \approx 0.01$, the mean absolute fungal disparity (1), gene conversion strongly influences the fixation probability in natural populations; it will often do so even if $|b_{12}| \approx 0.001$. Since we expect that new mutants frequently have a conversional disadvantage (17), the great lowering of the rate of gene substitution whenever $4N_eb_{12} \ll -1$ may have considerable biological significance.

The mean time to fixation or loss of A_1 is (18, 19)

$$\overline{T}(p) = 2N_e[\alpha(1 - e^{-2\alpha})]^{-1}[(e^{-2\alpha p} - e^{-2\alpha})I_1(p) + (1 - e^{-2\alpha p})I_2(p)] \quad [24a]$$

generations, where

$$I_1(p) = \int_0^p \frac{e^{2\alpha x} - 1}{x(1-x)}\,dx, \quad [24b]$$

$$I_2(p) = \int_p^1 \frac{1 - e^{2\alpha(x-1)}}{x(1-x)}\,dx. \quad [24c]$$

If $|\alpha| \ll 1$, the mean absorption time is close to Watterson's (20) result for pure random drift ($\alpha = 0$),

$$\overline{T}_d(p) = -4N_e[p\ln p + (1-p)\ln(1-p)]. \quad [25]$$

Therefore, we examine the behavior of rare alleles, $|\alpha|p \ll 1$, for $|\alpha| \gg 1$. If $\alpha > 0$, $2\alpha p\ln(2\alpha/p) \ll 1$, and $e^{-2\alpha}\ln(2\alpha/p) \ll 1$, [24] leads to the approximation

$$\overline{T}(p) \approx 4N_ep[\ln(2\alpha/p) + 1 + C], \quad [26]$$

where $C \approx 0.5772$ represents Euler's constant. If $\alpha < 0$ and $e^{2\alpha}\ln(-2\alpha/p) \ll 1$, [24] yields

$$\overline{T}(p) \approx 4N_ep[-\ln(-2\alpha p) + 1 - C]. \quad [27]$$

The mean time **26** exceeds $\overline{T}_d(p)$, which exceeds [27], because the fixation probability is an increasing function of α (see [20]) and we expect for a rare mutant the mean time to fixation to exceed the mean time to loss. In fact, [21] reveals that $\pi_1(p)$ is exponentially small for $\alpha \ll -1$, which explains why [27] agrees with the approximate mean conditional extinction time (21).

For a new mutant in the absence of selection, we heuristically substitute $p = 1/(2N)$ into [26] and [27] to obtain Kimura's (19) formulae: if $b_{12} > 0$,

$$\overline{T}[1/(2N)] \approx 2N_eN^{-1}[\ln(8N_eNb_{12}) + 1 + C]; \quad [28]$$

if $b_{12} < 0$,

$$\overline{T}[1/(2N)] \approx 2N_eN^{-1}[-\ln(-2N_eb_{12}/N) + 1 - C]. \quad [29]$$

Thus, on an evolutionary time scale, the mean absorption time for a new mutant is extremely short and, hence, the decay of genetic variability can be very rapid. This happens because, in view of [23] and the fact that $|b_{12}| \ll 1$, a new mutant is much more likely to be lost than fixed. Our formula **29** is identical with the approximation of Kimura and Ohta (22) for the mean conditional extinction time.

Finally, we investigate the mean conditional fixation time. In generations, this reads (23)

$$\overline{T}^*(p) = \frac{2N_e}{\alpha(1 - e^{-2\alpha})}\left[\left(\frac{e^{-2\alpha p} - e^{-2\alpha}}{1 - e^{-2\alpha p}}\right)J_1(p) + J_2(p)\right], \quad [30a]$$

in which

$$J_1(p) = \int_0^p \frac{(1 - e^{-2\alpha x})(e^{2\alpha x} - 1)}{x(1 - x)}\,dx, \quad [30b]$$

$$J_2(p) = \int_p^1 \frac{(1 - e^{-2\alpha x})(1 - e^{2\alpha(x-1)})}{x(1 - x)}\,dx. \quad [30c]$$

If $|\alpha| \ll 1$, $\overline{T}^*$ is near the value for pure random drift (23),

$$\overline{T}_d^*(p) = -4N_e p^{-1}(1 - p)\ln(1 - p) \to 4N_e \quad [31]$$

as $p \to 0$. Hence, we study the mean fixation time for rare alleles, $|\alpha|p \ll 1$, for $|\alpha| \gg 1$. Since [30] is independent of the sign of α (ref. 7, p. 151; ref. 24), we take $\alpha > 0$ without loss of generality. Thus, in the following formulae α and b_{12} refer to the absolute values of these parameters. We express J_1 and J_2 in terms of exponential integrals and use the asymptotic expansions of these functions (25):

$$\overline{T}^*(p) =$$

$$4N_e\alpha^{-1}\left[\ln(2\alpha) + C - (2\alpha)^{-1} - \frac{1}{2}\alpha p + O(\alpha^{-2}, \alpha^2 p^2)\right] \quad [32]$$

as $\alpha \to \infty$ and $\alpha p \to 0$.

For a new mutant, of most interest is the ratio

$$r = \lim_{p\to 0} \overline{T}^*(p)/\overline{T}_d^*(p) = \alpha^{-1}[\ln(2\alpha) + C - (2\alpha)^{-1} + O(\alpha^{-2})]. \quad [33]$$

In the absence of selection, $\alpha = 2N_e b_{12}$. If the absolute value of the disparity has the typical fungal value $b_{12} = 0.01$ and $N_e = 250$, 10^3, 10^4, 10^5, and 10^6, then $r \approx 0.556$, 0.212, 0.0328, 4.44×10^{-3}, and 5.59×10^{-4}. Thus, conversional bias in either direction will often greatly depress the mean fixation time below its approximate value for pure random drift, $4N_e$ generations. We conclude that gene conversion can be an important mechanism for the genetic divergence of isolated populations.

Note Added in Proof. The biological discussion in ref. 26 is pertinent to the subject of this paper.

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