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Genetics

Evolution of a large population under gene conversion

(population genetics/recombination/selection/mutation/meiotic drive)

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ABSTRACT **The dynamics of allelic frequencies at a single multiallelic locus under gene conversion is studied. Generations are discrete and nonoverlapping; the diploid monoecious population mates at random; selection, mutation, and random drift are negligible. Analytical and numerical investigation indicates the following. (*i*) If gene conversion is biased within at least one pair of alleles, then the frequency of at least one allele must become arbitrarily small. (*ii*) If conversion is biased within every pair of alleles, then the frequency of at most one allele can fail to become arbitrarily small. Although allelic frequencies may become repeatedly small instead of remaining small, the biological ubiquity of small random perturbations (due, e.g., to random genetic drift) guarantees the ultimate loss of at least one allele in case *i* and of all alleles but one in case *ii*. The decay of genetic variability is often sufficiently rapid to imply that biased gene conversion can be an important mechanism for the genetic divergence of isolated populations.**

Gene conversion is the nonreciprocal transfer of information from one allele to another. It has been demonstrated in many species of fungi (for refs., see refs. 1 and 2) and in *Drosophila melanogaster* (ref. 3 and refs. cited therein), and experiments indicate its occurrence in *Zea mays* (ref. 4 and refs. cited therein). Conversion rates per locus per generation in fungi range from 0 to more than 0.5, most of them being between 0.002 and 0.10 (1, 5); in *D. melanogaster* and *Z. mays*, they appear to be much lower, about 10^{-5} (3, 4). In a large population, gene conversion alters allelic frequencies only if it is biased—i.e., when two alleles interact, one of them must be more likely to convert the other than *vice versa*. The disparity parameter that controls gene frequency change is the product of the conversion rate and a measure of conversional bias (1, 6). In fungi, the absolute values of the disparities are usually between 2×10^{-5} and 0.14, and the average of the mean absolute disparities from a number of studies is close to 0.01 (1); disparity parameters have not been measured in *Drosophila* and corn, but they cannot exceed the conversion rate of about 10^{-5}.

Whenever the disparities are appreciably greater than typical values of mutation rates (10^{-6} to 10^{-5}), as they are in most fungi, but apparently not in the much more limited and less detailed *Drosophila* and corn data, gene conversion may have considerable evolutionary importance. For gene conversion to significantly influence allelic frequencies, it is also necessary that neither the selection intensities nor the reciprocal of the effective population number greatly exceed the disparities.

Gutz and Leslie (6) and Lamb and Helmi (1) have studied the effect of gene conversion on the allelic frequency at a diallelic locus in a large population. Gutz and Leslie (6) showed that the characteristic time (in generations) for gene frequency change under pure conversion is the reciprocal of the disparity and investigated approximately the equilibrium gene frequency under the joint action of conversion and mutation. Lamb and Helmi (1) included selection in the approximate analysis of the equilibrium and presented extensive numerical calculations based on a theoretically exact model. The investigation of the influence of gene conversion on sequence homogeneity among repeated genes has also begun (2, 7–9).

In this paper, we shall examine the evolution of allelic frequencies at a single multiallelic locus under gene conversion. In *Section 1* we develop a formulation encompassing arbitrary patterns of selection, mutation, and gene conversion and briefly analyze the case of two alleles. We treat pure conversion in *Sections 2* and *3*: general results appear in *Section 2*; special cases and qualitative general conclusions are in *Section 3*. *Section 4* comprises a summary of our results, a discussion of their implications, and a consideration of the effect of incorporating mutation.

Generations are discrete and nonoverlapping; the diploid monoecious population mates at random and is sufficiently large to permit us to neglect random genetic drift. The joint action of gene conversion, selection, mutation, and random drift has been analyzed and will be reported in a subsequent publication (10).

1. Formulation

Let p_j ($j = 1,2, \ldots,n$) denote the frequency of the allele A_j in zygotes in generation t ($= 0,1,2, \ldots$). We allow only viability selection, after which the frequency of the ordered genotype A_jA_k reads

$$P^*_{jk} = w_{jk}p_jp_k/\overline{w}, \qquad [1a]$$

where w_{jk} and

$$\overline{w} = \sum_{jk} w_{jk}p_jp_k \qquad [1b]$$

represent the viability of A_jA_k individuals and the mean viability of the population. We denote the probability that A_j mutates to A_k by u_{jk} (by convention, $u_{jj} = 0$ for all j) and assume that the two genes at a locus mutate independently. Then, after mutation, the genotypic frequencies are given by

$$P^{**}_{jk} = \sum_{lm} P^*_{lm}R_{lj}R_{mk}, \qquad [2a]$$

where

$$R_{jk} = \left(1 - \sum_l u_{jl}\right)\delta_{jk} + u_{jk}, \qquad [2b]$$

and δ_{jk} designates the Kronecker delta. Let c_{jk} denote the probability that a successful gamete from an A_jA_k individual carries A_j. These parameters enable us to incorporate arbitrary pat-

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terns and molecular mechanisms of gene conversion and yield

$$p_j' = 2\sum_k c_{jk}P_{jk}^{**} \qquad [3]$$

for the frequency of A_j in the zygotes of the next generation.

Our fundamental variables, the p_j, are confined to the simplex

$$p_j \geq 0, \qquad \sum_k p_k = 1, \qquad [4]$$

which is mapped into itself by the nonlinear transformation **1**, **2**, **3**. We discuss several aspects of this model in the remainder of this section.

While selection acts on the phenotype, which develops from the zygotic genotype, the germ cells mutate with no phenotypic effect. Gene conversion occurs during meiosis. Therefore, in any formal scheme, selection must precede and gene conversion should succeed mutation. This is precisely the order in our life cycle and in the numerical calculations of Lamb and Helmi (1).

Clearly, our model also applies to meiotic drive, as noted by Crow for the work of Gutz and Leslie (6).

For unbiased conversion, $c_{jk} = {}^1/_2$; A_j has a conversional advantage (disadvantage) with respect to A_k if $c_{jk} > {}^1/_2$ ($c_{jk} < {}^1/_2$). Hence, we introduce the disparity parameters b_{jk} through

$$c_{jk} = \frac{1}{2}(1 + b_{jk}). \qquad [5]$$

Since, by definition, $0 \leq c_{jk} \leq 1$ and $c_{kj} = 1 - c_{jk}$, **5** implies that the disparities satisfy $b_{kj} = -b_{jk}$ (which has $b_{jj} = 0$ as a special case) and $-1 \leq b_{jk} \leq 1$ for all j and k.

In writing **3**, we supposed that meiotic gene conversion in an A_iA_j heterozygote can produce only A_i and A_j. The assumption that gene conversion does not produce nonparental alleles is exact or accurate if the alleles differ from each other by any one of the following (11–14). (*i*) Single base substitutions at the same site. In this case, of course, the number of alleles cannot exceed four. (*ii*) Continuous nested deletions. As a special case, this formally includes insertions that all start or end at the same site. (*iii*) Continuous, nonnested, overlapping deletions. (*iv*) Any combination of substitutions, deletions, and insertions within short DNA segments (in fungi, much less than several hundred base pairs long).

For fungi, we let $Q_{jk,l:8\text{-}l}$ signify the probability that an A_jA_k genotype produces an l:8-l octad. (If tetrads are observed, simply double the numbers in the segregation ratios.) Then we have

$$c_{jk} = \frac{1}{8}\sum_{l=0}^{8} lQ_{jk,l:8\text{-}l}, \qquad [6]$$

whence **5** yields

$$b_{jk} = \sum_{l=0}^{8}\left(\frac{1}{4}l - 1\right)Q_{jk,l:8\text{-}l} \qquad [7]$$

$$= \frac{1}{2}\sum_{l=0,l\neq 4}^{8}\left(\frac{1}{4}l - 1\right)(Q_{jk,l:8\text{-}l} - Q_{jk,8\text{-}l:l}). \qquad [8]$$

Eq. **8** shows explicitly that the disparity b_{jk} is large only if both the conversion rate and the bias are large. For two alleles, **7** reduces to the parametrization of Lamb and Helmi (1).

For two alleles, **1**, **2**, and **3** specify a smooth mapping of the unit interval into itself: $p = p_1$, $0 \leq p \leq 1$, $p' = f(p)$. A tedious direct calculation shows that if the biologically trivial condition $u_{12} + u_{21} < 1$ holds, then this mapping is monotone increasing ($df/dp > 0$), which establishes global nonoscillatory convergence. More explicitly, suppose that the initial value of p is p_0. If $f(p_0) < p_0$, there exists at least one equilibrium in $[0,p_0)$ and $p(t)$ converges without oscillation to the largest of these equilibria; if $f(p_0) > p_0$, there exists at least one equilibrium in $(p_0,1]$ and $p(t)$ converges without oscillation to the smallest of these equilibria. Hartl (15) proved these results by a different method in the absence of mutation, in which case the polymorphic equilibrium is unique; the local analysis had been carried out earlier (16, 17).

2. General results

Here, we examine pure gene conversion, for which **1**, **2**, and **3** lead to the gene frequency changes

$$\Delta p_j = p_j\sum_k b_{jk}p_k. \qquad [9]$$

The completely polymorphic equilibria $\hat{\mathbf{p}}$ ($\hat{p}_j > 0$ for all j) obviously satisfy

$$B\hat{\mathbf{p}} = \mathbf{0}. \qquad [10a]$$

Since B is skew-symmetric ($B^T = -B$), each of its eigenvalues is pure imaginary or zero. There are two cases.

(*i*) If the number of alleles, n, is odd, since the imaginary eigenvalues occur in complex conjugate pairs, zero must be an eigenvalue. Consequently, $\det B = 0$ and hence **10a** has nontrivial solutions; if all the components of one of these are nonzero and have the same sign, we can choose this sign to be positive and normalize $\hat{\mathbf{p}}$ so that

$$\sum_j \hat{p}_j = 1. \qquad [10b]$$

Generically (i.e., if B has rank $n - 1$), there exists at most one such solution.

(*ii*) If n is even, $\det B = 0$ only in biologically unimportant special cases, so **10a** generally has no nontrivial solution and then a completely polymorphic equilibrium does not exist.

It is fruitful to associate with each n-allelic conversion pattern an oriented graph (ref. 18, p. 10) with n points. The point j corresponds to the allele A_j; the points j and k are connected if and only if conversion between A_j and A_k is biased ($b_{jk} \neq 0$); if A_j has a conversional advantage with respect to A_k ($b_{jk} > 0$), the directed line that connects j and k points from k to j. (See Figs. 1, 3, and 4 for examples.) If the alleles can be divided into two or more disjoint sets such that conversion is biased only within each set, **9** easily reveals that these sets evolve independently of each other and the total gene frequency of each set is constant. Therefore, without loss of generality, we may restrict our attention to connected graphs (ref. 18, p. 13).

Next, we state and prove three principles that enable us to analyze directly many conversion patterns.

Principle 1. If A_j has a conversional advantage relative to every allele to which it is connected (i.e., A_j is a sink), then all those alleles are ultimately lost. In particular, if a sink A_j is connected to every other allele, then it is ultimately fixed.

Proof. From **9**, we have $\Delta p_j > 0$, which implies that $p_j(t)$ converges monotonically from below to some value $\tilde{p}_j$: $p_j \to \tilde{p}_j > p_j(0) > 0$. Hence, $\Delta p_j \to 0$, so that **9** yields $\Sigma_k b_{jk}p_k \to 0$. Let $I_j = \{k\colon b_{jk} \neq 0\}$; since $b_{jk} > 0$ for all k in I_j, we infer that $p_k \to 0$ for all k in I_j.

Principle 2. If A_j has a conversional disadvantage relative to every allele to which it is connected (i.e., A_j is a source), then A_j is lost or those alleles are lost (or possibly both). In particular, if a source A_j is connected to every other allele, then A_j is lost.

Proof. Now **9** yields $\Delta p_j < 0$, whence $p_j(t)$ converges monotonically from above to some frequency $\tilde{p}_j$, which implies that $\Delta p_j \to 0$. If $\tilde{p}_j \neq 0$, **9** gives $\Sigma_k b_{jk} p_k \to 0$. Since $b_{jk} < 0$ for all k in I_j, we conclude that $p_k \to 0$ for all k in I_j. If A_j is connected to every other allele, the fact that p_j is monotone decreasing implies that the total frequency of the other alleles, $1 - p_j$, is monotone increasing. Therefore, at least one of those alleles must survive, and hence A_j must be lost.

Principle 3. If there exists a unique, isolated completely polymorphic equilibrium $\hat{\mathbf{p}}$ and the initial gene frequency $\mathbf{p}(0) \neq \hat{\mathbf{p}}$, then $\mathbf{p}(t)$ converges to the boundary of the simplex **4**.

Proof. Consider the function

$$G(\mathbf{p}) = \sum_{j=1}^{n} (p_j - \hat{p}_j \ln p_j) \qquad [11]$$

in the entire positive orthant $p_j > 0$. This function is essentially the same as the conserved quantity in Volterra's (19) continuous-time model of multispecies interaction. An easy calculation reveals that $G(\mathbf{p})$ has an isolated global minimum at $\mathbf{p} = \hat{\mathbf{p}}$. Next, appeal to **11**; the elementary fact that $\ln x \leq x - 1$ for $x > 0$, with equality if and only if $x = 1$; **9**; and the skew-symmetry of B and **10a**:

$$\begin{aligned}\Delta G &= \sum_j [\Delta p_j - \hat{p}_j \ln (p_j'/p_j)] \\ &\geq \sum_j \left[\Delta p_j - \hat{p}_j \left(\frac{p_j'}{p_j} - 1\right)\right] \\ &= \sum_j \left(1 - \frac{\hat{p}_j}{p_j}\right) \Delta p_j \\ &= \sum_{jk} (b_{jk} p_j p_k - b_{jk} \hat{p}_j p_k) = 0. \qquad [12]\end{aligned}$$

Thus, $\Delta G \geq 0$; since $\hat{\mathbf{p}}$ is the unique completely polymorphic equilibrium, $\Delta G = 0$ in the interior of the simplex if and only if $\mathbf{p} = \hat{\mathbf{p}}$. Therefore, $\mathbf{p}(0) \neq \hat{\mathbf{p}}$ implies that there exists ε such that $\Delta G[\mathbf{p}(t)] \geq \varepsilon > 0$. Hence, $G[\mathbf{p}(t)] \to \infty$ as $t \to \infty$, which establishes convergence of $\mathbf{p}(t)$ to the boundary of **4**.

Remarks. Principle 3 means that $\mathbf{p}(t)$ permanently leaves every compact interior set of the simplex. A second alternative statement reads

$$\liminf_{t \to \infty} p_j(t) = 0 \qquad [13]$$

for some j. Notice that no allelic frequency need *remain* small: in many cases, as in Fig. 2 below, $\lim_{t\to\infty} p_j(t) \neq 0$ for any j. From principle 3 and the discussion at the beginning of this section of the existence of completely polymorphic equilibria, we can conclude that convergence to the boundary occurs for many conversion patterns if the number of alleles is odd.

Finally, observe that, in a continuous-time model, instead of Δp_j, the time derivative would appear on the left-hand side of **9**. Clearly, all results in this section except principle 3 would be unaltered. The latter would no longer hold, because G would be conserved. The constancy of G, however, is structurally unstable; i.e., it is destroyed by arbitrarily small changes in the model, some examples of which are the deviations from Hardy–Weinberg proportions associated with overlapping generations (20; ref. 21, pp. 79–92), demographic fluctuations, mutation, selection, and random drift. Therefore, the discrete-time model should be a much better guide to biological reality.

3. Special cases

In this section, we investigate special cases of the dynamics under pure gene conversion. For two alleles, **9** reduces to $\Delta p_1 = b_{12} p_1 p_2$, which shows that whichever allele has a conversional advantage is ultimately fixed (6). Therefore, we study loci with three, four, and five alleles; at the end of the section, we offer some general remarks. (All numerical calculations were carried out to 18 significant figures.) Let

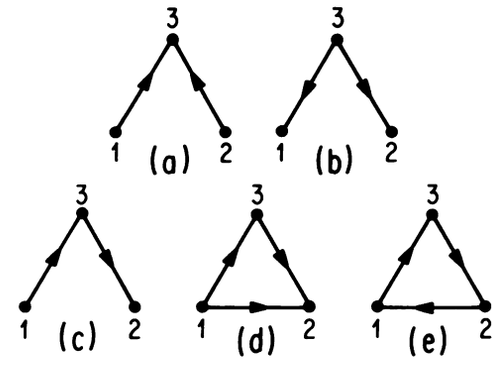

FIG. 1. The connected oriented graphs with three points.

$$T_m = \min\{t: p_k(t) < 10^{-m} \text{ for some } k\} \qquad [14]$$

designate the number of generations required for some gene frequency to become less than 10^{-m}. The times T_3 and T_{10} were used to characterize the rate of evolution; each run was stopped after T_{15} generations.

Three Alleles. The three principles of *Section 2* yield a complete qualitative analysis for three alleles. All the distinct (i.e., nonisomorphic) connected oriented graphs with three points are exhibited in Fig. 1. For Fig. 1 *a–d*, principle 1 gives $p_3 \to 1$, $p_3 \to 0$, $p_3 \to 0$, and $p_2 \to 1$, respectively. Fig. 2.3b with the direction of motion reversed and figures 2.3b, 2.3c, and 2.3d, respectively, of ref. 21 (pp. 26–28) show sketches of the orbits. From **10**, we infer that for Fig. 1*e* there is always an internal equilibrium:

$$\hat{\mathbf{p}} = (b_{23}/d, b_{31}/d, b_{12}/d), \quad d = b_{12} + b_{23} + b_{31}. \qquad [15]$$

Hence, by principle 3, $\mathbf{p}(t)$ converges to the boundary of the simplex. The fixation states ($p_j = 1$) are obviously unstable; by **9**, as $p_1 \to 0$, $\Delta p_2 \to b_{23} p_2 (1 - p_2) > 0$, with analogous results for p_2 and p_3. We can conclude that in the limit $t \to \infty$, $\mathbf{p}(t)$ runs around the boundary of the triangle, as shown in Fig. 2. Akin

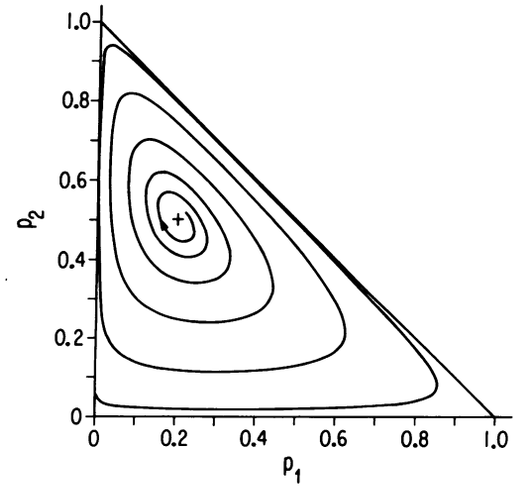

FIG. 2. A trajectory for pure gene conversion at a triallelic locus with $b_{12} = 0.3$, $b_{23} = 0.2$, and $b_{31} = 0.5$. The indicated unstable equilibrium is at (0.2, 0.5, 0.3).

and Hofbauer (22) have proved a similar theorem for a continuous-time model in game theory.

A local analysis in the neighborhood of **15** reveals some details of the dynamics of Fig. 1*e*. The eigenvalues are

$$\lambda = 1 \pm i\kappa = \rho e^{\pm i\theta}, \qquad [16a]$$

where $i = \sqrt{-1}$,

$$\kappa = (b_{12}b_{23}b_{31}/d)^{1/2}, \qquad [16b]$$

$$\rho = (1 + \kappa^2)^{1/2}, \qquad \theta = \tan^{-1}\kappa. \qquad [16c]$$

Close to $\hat{\mathbf{p}}$, the radius of the orbits is approximately proportional to ρ^t and the period is about $2\pi/\theta$. The data reviewed at the beginning of this paper indicate that $\kappa \ll 1$; in this case, $\rho^t \approx e^{\kappa^2 t/2}$, $2\pi/\theta \approx 2\pi/\kappa$, and the radius increases by a factor of about $\rho^{2\pi/\theta} \approx e^{\pi\kappa}$ per period. This suggests that the characteristic time to the boundary and the period are about $2/\kappa^2$ and $2\pi/\kappa$. Since $\kappa \to a\kappa$ if $b_{jk} \to ab_{jk}$, we can conclude that, for fixed relative values of the disparities, the typical convergence time and the period are inversely proportional to the square of the scale of disparity and to the scale itself, respectively. Finally, we note that the rate of evolution is maximized when κ is maximized, and for fixed d this occurs when $b_{12} = b_{23} = b_{31}$.

Four Alleles. The 34 connected oriented graphs appear among the four-point digraphs in ref. 18 (pp. 227–230). Principles 1 and 2 inform us that the frequency of at least one allele converges to zero in 30 of these graphs. We display the other four graphs (graphs 16, 32, 35, and 45 of ref. 18) in Fig. 3. Since there is generically no equilibrium with four alleles, principle 3 does not apply, and hence the graphs in Fig. 4 were studied numerically. Convergence to the boundary occurred in all cases. For all four graphs, there are conversion patterns that lead as $t \to \infty$ to an orbit along the four edges of the simplex corresponding to the boundary of the square (and in the same direction). The following types of dynamics also occur; the term "cycle" refers to the recurrence of edges but not necessarily to that of points on those edges. Fig. 3*a*: a pair of diagonally opposite alleles disappears, and the ultimate frequencies of the remaining alleles depend on $\mathbf{p}(0)$. Fig. 3*b*: (*i*) $p_1 \to 0$ and $p_3 \to 0$, and the final state depends on $\mathbf{p}(0)$; (*ii*) $p_4 \to 0$, leaving a 132 edge cycle. Fig. 3*c*: (*i*) $p_2 \to 0$, leaving a 143 edge cycle; (*ii*) $p_4 \to 0$, leaving a 123 edge cycle. Fig. 3*d*: (*i*) $p_4 \to 0$, leaving a 123 edge cycle; (*ii*) $p_1 \to 0$, leaving a 234 edge cycle. Even if we include the dynamics obtained by relabeling, the list may not be exhaustive.

Five Alleles. There are 582 oriented graphs with five points, though some of these are unconnected (23). Consequently, we confine ourselves to the biologically generic case: biased conversion within every pair of alleles, represented by complete oriented graphs, or tournaments (ref. 18, pp. 16, 205). We display the 12 five-point tournaments in Fig. 4 (C. Cotterman, personal communication). By principles 1 and 2, in Fig. 4 *a–f*, at least one allele is lost. Fig. 4 *g–l*, however, have neither sources nor sinks. Define

$$\beta_1 = b_{25}b_{34} - b_{35}b_{24} + b_{45}b_{23}, \qquad [17a]$$

$$\beta_2 = -b_{15}b_{34} + b_{35}b_{14} - b_{45}b_{13}, \qquad [17b]$$

$$\beta_3 = b_{15}b_{24} - b_{25}b_{14} + b_{45}b_{12}, \qquad [17c]$$

$$\beta_4 = -b_{15}b_{23} + b_{25}b_{13} - b_{35}b_{12}, \qquad [17d]$$

$$\beta_5 = b_{14}b_{23} - b_{24}b_{13} + b_{34}b_{12}. \qquad [17e]$$

For any conversion pattern with five alleles, in the generic case that B has rank 4, there exists a completely polymorphic equilibrium if and only if all five β_j are nonzero and have the same sign, and then this equilibrium is unique and is given by (24)

$$\hat{p}_j = \beta_j \Big/ \sum_k \beta_k. \qquad [17f]$$

Whenever this criterion is satisfied, principle 3 implies convergence to the boundary.

Fig. 4 *g–l* were investigated numerically both in the presence and in the absence of a completely polymorphic equilibrium. Convergence to the boundary occurred in all cases. With an internal equilibrium, no gene frequency converged to zero and the ultimate pattern observed was either a five-edge cycle or an irregular trajectory on which sometimes only one or two allelic frequencies were small. Without an internal equilibrium, one or two alleles were lost in every run, leaving a four- or a three-edge cycle, respectively.

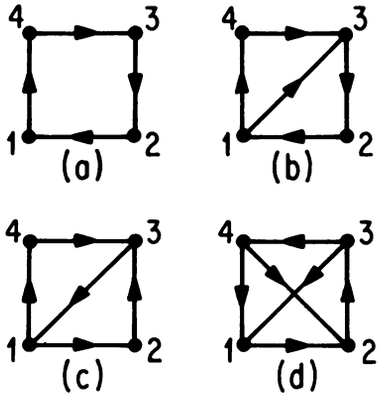

FIG. 3. The connected four-point oriented graphs with neither sources nor sinks.

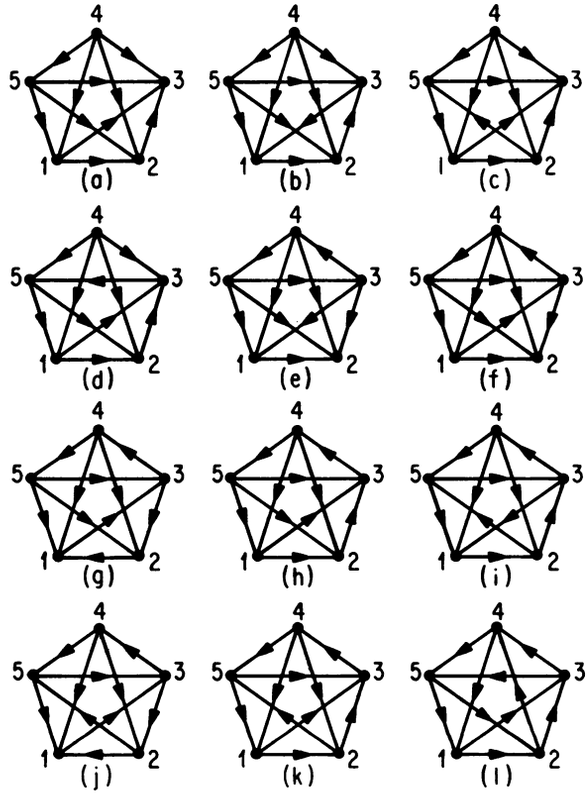

FIG. 4. The five-point tournaments.

General Remarks. Our analyses and extensive numerical calculations indicate the following: (*i*) If conversion is biased within at least one pair of alleles, then the frequency of at least one allele must become arbitrarily small. (*ii*) If conversion is biased within every pair of alleles, then the frequency of at most one allele can fail to become arbitrarily small. More succinctly, **13** holds for at least one j for every connected oriented graph and fails for at most one j for every tournament.

Since the numerical results indicate that the approach to the boundary of **4** is considerably faster if at least one allelic frequency converges to zero, we focus now on those situations in which this does not happen. In these cases, the computation suggests that the scaling properties discussed below **16** hold for more than three alleles: in particular, the characteristic convergence time to the boundary appears to be roughly proportional to the square of the reciprocal of the typical disparity. The convergence times are very similar for three, four, and five alleles; T_{10} (see **14**) seems to be about two or three times T_3. For disparities around 0.1, 2,000 generations is a typical rough value of T_3.

4. Discussion

The analytical and numerical results reported here indicate that, in the absence of mutation and selection, biased gene conversion at a single multiallelic locus decreases genetic variability. If conversion is biased within every pair of alleles, ultimately only one allele survives. Which alleles are lost often depends on random genetic drift and other stochastic perturbations that may affect gene frequencies. If b represents a typical disparity parameter, in a large population the frequency of some allele is reduced to about 10^{-3} in *roughly* $20/b^2$ generations, and sometimes much faster; the (deterministic) characteristic time to 10^{-10} is at most a few times greater. The loss of alleles by this mechanism is of evolutionary importance if b is not much less than the mean absolute fungal value of 0.01, the typical selection intensity at the locus under consideration, and the reciprocal of the effective population number. In many cases, the first condition may be weakened to about 10^{-3}, and if an allele has a conversional advantage or disadvantage with respect to every other allele, even to about 10^{-5}. Since we expect that new mutants frequently have a conversional disadvantage (2), and their frequency is low, usually their elimination should be particularly rapid.

Since random factors often influence which alleles are lost, biased conversion must frequently contribute to the genetic divergence of isolated populations.

If every allele mutates to every other allele ($u_{jk} > 0$ for all j and k, $j \neq k$), all alleles must remain in the population. For neutral alleles, **1**, **2**, **3**, and **5** yield

$$p_j^* = \left(1 - \sum_k u_{jk}\right) p_j + \sum_k p_k u_{kj}, \qquad [18a]$$

$$p_j' = p_j^{**} + p_j^{**} \sum_k b_{jk} p_k. \qquad [18b]$$

Numerical analysis of **18** indicates that for sufficiently weak mutation the trajectories still tend toward the boundary of the simplex **4** but no longer converge to it. In particular, whenever the pure-conversion frequencies converge to a trajectory along some or all of the edges of **4**, the introduction of mutation leads to an orbit close to this trajectory. The computations support the structural stability of our model, a point discussed at the end of *Section 2*.

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