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SHORT PAPER

On the gene conversion model as a mechanism for maintenance of homogeneity in systems with multiple genomes

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SUMMARY

The gene conversion model reported by Birky & Skavaril (1976) has been analytically studied by using the theory of diffusion models of Kimura (1964) in population genetics. It has been shown that the fate of new mutations in systems with multiple genomes may be satisfactorily treated by the diffusion model.

Birky & Skavaril (1976) presented an interesting gene conversion model for the explanation of high homogeneity in a cell in systems with multiple genomes such as mitochondrial DNA or repetitive DNA in chromosome. In this model, members of multiple gene family undergo repeated rounds of mating, recombination and gene conversion, resulting in high homogeneity. They have shown, through extensive simulation studies, that this model provides a reasonably efficient mechanism for eliminating new mutations and giving high homogeneity.

Fortunately there is a convenient analogy between this kind of homogenizing process and random sampling of gametes at reproduction in finite Mendelian populations (Hood, 1975; Tartof, 1975). In fact, I have shown that the process of gene fixation by unequal crossover in a multigene family investigated by Smith (1974) may be treated analytically by using the theory of gene frequency change in population genetics (Ohta, 1976). In this note, I shall show that the gene conversion model can be similarly analysed and that the theory gives a good fit to the observed values of the simulation studies by Birky & Skavaril (1976).

The fate of new mutations in mitochondrial DNA in a cell has been studied by these authors. The time until loss of a new mutant from the cell is analogous to the time until extinction of a mutant gene in a finite population, theoretically analysed by Kimura & Ohta (1969*a*, *b*). What one needs, in order to apply Kimura and Ohta's theory, is to evaluate the mean and the variance of mutant frequency change per unit time.

Following Birky & Skavaril (1976), I shall designate the wild and mutant allele by R and S respectively. Let n be the number of genophores and x be the frequency of the mutant in a cell. By random mating of genophore, the heterozygous (RS or SR) mating occurs with probability $2x(1-x)$. Birky and Skavaril assumed, in their simulation study, that the heteroduplex is formed from the heterozygous mating and that the gene conversion occurs, resulting in four equally probable consequences: RS, SR, RR and SS. Under this process, the mean change ($M_{\Delta x}$) of mutant frequency (x) is zero. In one round of mating, every one of the n genophores is involved as $n/2$ pairs and each pair contributes *exactly* two gametes to the next round. Then the variance of change of x per *one mating round* becomes $x(1-x)/2n$, which is exactly the same as that per one generation of random sampling of gametes in a finite population with effective size $N_e = n$ (e.g. Crow & Kimura 1970). Note here that the effective population size is twice the actual number of genophore pairs because of equal contribution of gametes from each pair.

Kimura & Ohta (1969*a*, *b*) obtained the mean and variance of the time until extinction of mutant genes excluding the case of fixation. Based on the above analogy, one can directly apply their formulas by replacing N_e with n. Thus, the time until extinction of a mutant in terms of *the number of mating rounds* becomes

$$t_0(p) = -4n\left(\frac{p}{1-p}\right)\log_e p, \tag{1}$$

where p is the initial frequency and is equal to $1/n$ for a single mutant, therefore in this case

$$\bar{t}_0 \approx 4\log_e n. \tag{2}$$

The variance of the time until extinction of a single mutant becomes, again by replacing N_e with n in Kimura and Ohta's formula,

$$\begin{aligned} V(t_0) &= \overline{t_0^2} - \bar{t}_0^2 \\ &\approx 16\{2n - (\log_e n)^2\}. \end{aligned} \tag{3}$$

Let us compare Birky and Sakvaril's result with the present prediction. In their simulation, two cases, $n = 50$ and 100, were done, the theoretical average time until extinction becomes $\bar{t}_0 = 15{\cdot}65$ and $18{\cdot}42$ from formula (2) for these two cases. The two points, $\bar{t}_0 = 15{\cdot}65$ of their fig. 2*a* and $t_0 = 18{\cdot}42$ of fig. 2*b*, give 80–90 % of homoplastic cells of simulation experiments. This is a reasonable figure since $\bar{t}_0$ is the average time until extinction of the mutant and is much influenced by rare cases in which the mutant takes a long time to be lost, in other words, the distribution of the time to extinction is very skewed (see table 3 of Kimura & Ohta, 1969*b*).

It should also be noted that in the present case the probability of fixation of the mutant in a cell is equivalent to that of the selectively neutral case in finite populations and is equal to the initial frequency. Thus it is just expected that Birky and Skavaril observed a couple of cases in which the mutant gene spreads in the cell in their simulations.

The rectification of repetitive DNA sequences in chromosomes by means of gene conversion may also be treated similarly, by using the proper time scale corresponding to the mating round. Although the gene conversion model of Birky and Skavaril is different from the conventional model of unequal crossing-over (e.g. Smith 1974), essentially the same mathematical treatment is applicable. For further theoretical analyses on the model of unequal crossing-over, see Ohta (1976) and Perelson & Bell (1977).

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REFERENCES

BIRKY, C. W. JR. & SKAVARIL, R. V. (1976). Maintenance of genetic homogeneity in systems with multiple genomes. *Genetical Research* **27**, 249–265.

CROW, J. F. & KIMURA, M. (1970). *An Introduction to Population Genetics Theory*. New York, London: Harper and Row.

HOOD, L. (1975). The organization, expression, and evolution of antibody genes and other multigene families. *Annual Review of Genetics* **9**, 305–353.

KIMURA, M. (1964). Diffusion models in poulation genetics. *Journal of Applied Probability* **1**, 177–232.

KIMURA, M. & OHTA, T. (1969*a*). The average number of generations until fixation of a mutant gene in a finite population. *Genetics* **61**, 763–771.

KIMURA, M. & OHTA, T. (1969*b*). The average number of generations until extinction of an individual mutant gene in a finite population. *Genetics* **63**, 701–709.

Ohta, T. (1976). A simple model for treating the evolution of multigene families. *Nature* **263**, 74–76.

Perelson, A. S. & Bell, G. I. (1977). Mathematical models for the evolution of multigene families by unequal corssing over. *Nature* **265**, 304–310.

Smith, G. P. (1974). Unequal crossover and the evolution of multigene familes. *Cold Spring Harbor Symposia on Quantitative Biology* **38**, 507–513.

Tartof, K. D. (1975). Redundant genes. *Annual Review of Genetics* **9**, 355–385.