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This Week's Citation Classic

Kimura M & Crow J F. The number of alleles that can be maintained in a finite population. *Genetics* **49**:725-38, 1964.

If the number of possible neutral alleles is so large that each mutant is of a type not currently represented in the population, the equilibrium homozygosity is $(1 + 4N_eu)^{-1}$ where u is the mutation rate and N_e the effective population number. Formulae are also given for the heterozygosity and segregation load when all heterozygotes are selectively advantageous. [The *SCI*® indicates that this paper has been cited over 150 times since 1964.]

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"This paper was written while Motoo Kimura was at the University of Wisconsin on leave from his regular position at the National Institute of Genetics in Japan. Earlier, he had been a graduate student with me at Wisconsin and we were continuing to work together.

"Kimura had been extremely successful, and still is, in applying diffusion methods to problems in population genetics. The Kolmogorov forward and backward equations offered solutions to a wide range of theoretical problems involving mutation, migration, and selection in the presence of random effects due to finite population size and fluctuating selection values.[1]

"By the early 1960s it was apparent that the gene had a nucleotide number of the order of 10^3, and that therefore the range of mutational possibility was enormous. This made possible the realistic, and greatly simplifying, assumption that each mutation was of a type not then existing in the population. The power of this assumption is that it permits Sewall Wright's inbreeding coefficient F to be given an absolute meaning; 1 — F, instead of measuring heterozygosity only relative to an unknown standard, measures the absolute heterozygosity.[2] This conceptualization of the problem also permitted a simple, three line derivation that requires no advanced mathematics.

"The equilibrium formula, $F = (1 + 4N_eu)^{-1}$, where F is the fraction of homozygous loci, N_e is the effective population number, and u is the mutation rate, was not really new. The same equation had been given by Malécot, but not, I believe, with the absolute meaning.[3]

"Most of the paper consisted of Kimura's solution to the much more difficult problem when selection as well as random drift is involved. But the paper is much more often cited for the elementary neutral formula mentioned in the previous paragraph than for the much more difficult later parts.

"Why has this paper been widely cited? I can only guess, but I think there are four reasons.

"The first is the simplicity of the key formula, and the absolute meaning that it gives to Wright's inbreeding coefficient.

"The second is that the paper was written at a time of considerable discussion of the genetic load created by selectively maintained polymorphisms. This controversy has largely disappeared.

"The third is that, very soon after the appearance of this paper, the electrophoretic work of Harris and of Lewontin and Hubby demonstrated the high level of enzyme polymorphism in natural populations; this provided data to which our formula could be applied.[4,5]

"The fourth reason is the neutral theory of polymorphism, for which this is the starting point of further mathematical analysis. Of course the development of the theory and discussions of the possibility of testing and actual distribution of allele frequencies has now gone much further."

1. **Kolmogorov A N.** Uber die analytischen Methoden in der Wahrscheinlichkeitsrechnung. *Math. Ann.* **104**:415-58, 1931.
2. **Wright** S. The genetical structure of populations. *Ann. Eugen.* **15**:323-54, 1951.
3. **Malécot** G. *Les mathématiques de l'hérédité.* Paris: Masson et Cie, 1948. 63 p.
4. **Harris H.** Enzyme polymorphisms in man. *Proc. Roy. Soc. London B* **164:**298-310. 1966.
5. **Lewontin R C & Hubby J L.** A molecular approach to the study of genie heterozygosity in natural populations of *Drosophila pseudoobscura. Genetics* **54**:595-609, 1966.