

Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

Edited by James F. Crow and William F. Dove

GUSTAVE MALÉCOT AND THE TRANSITION FROM CLASSICAL TO MODERN POPULATION GENETICS

ABSTRACT

The contributions of Gustave Malécot to theoretical population genetics are described, discussed, and put into perspective relative to earlier and later work. In this context, certain aspects of the theory of inbreeding, the correlation between relatives, the evolution of finite panmictic populations, and (in more depth) spatial variation are reviewed. A brief biographical sketch of Malécot is also presented.

SELDOM does a doctoral dissertation substantially advance its field. Nevertheless, just such a rare dissertation, *Théorie mathématique de l'hérédité mendélienne généralisée*, was submitted fifty years ago, to the Faculty of Sciences of the University of Paris, by GUSTAVE MALÉCOT (1939a). Despite the breadth, depth, originality, power, and elegance of the contributions of this great French theoretical population geneticist, much of his work is known even now only to a small minority of researchers in his area. Therefore, it seems appropriate on this semicentennial to delineate and discuss MALÉCOT's contributions and to place them into perspective relative to earlier and later work, especially that of FISHER, WRIGHT, and KIMURA. It is also of interest to inquire why his contributions have not diffused more rapidly and widely.

MALÉCOT has written articles on the philosophy of science, on statistics, and on the theory of stochastic processes and its application to economics and physics. These will not be discussed here. About 45 of his papers fully or partly concern population genetics. They include brief research announcements; some items, such as lecture notes, whose aim is primarily didactic, but which often contain important new results and approaches; and long, detailed, powerful original papers. It is interesting to note, and an indication of MALÉCOT's intellectual independence and of the relative isolation in which he worked, that he is

This paper is dedicated to the memory of CHARLES W. COTTERMAN (1914–1989), one of the most lucid, rigorous, and original thinkers in mathematical genetics, who was always exceeding generous with his deep understanding and extensive unpublished research.

the sole author of every one of his papers in genetics.

MALÉCOT's work focuses on stochastic processes in population genetics. His doctoral research on the correlation between relatives (MALÉCOT 1939a) led him to the gradual discovery of one of the most basic and fruitful concepts in population genetics: *identity by descent* (MALÉCOT 1941, 1942, 1946, 1948). He used this idea to prove and interpret probabilistically WRIGHT's formulas for the genotypic frequencies under inbreeding (which he generalized to multiple alleles) and for the inbreeding coefficient of an individual with an arbitrary pedigree (MALÉCOT 1941, 1942, 1948), to derive the correlation between relatives for traits without epistasis (MALÉCOT 1948), to examine the evolution of finite panmictic populations (MALÉCOT 1946, 1948, 1951), and to investigate his original models for the genetic structure of populations distributed discretely or continuously in space (MALÉCOT 1948, 1949, 1950, 1951, 1965, 1967, 1975). Before molecular genetics might have motivated him, MALÉCOT (1946, 1948, 1951) introduced mutation by proposing that every allele mutates at the same rate and no mutant is identical by descent to any preexisting allele, and he employed this beautifully simple hypothesis in many of his studies. He deduced the asymptotic distribution of the gene frequency for pure random genetic drift (MALÉCOT 1944), the complete time-dependent diffusion approximation for the gene-frequency distribution with reversible mutation (MALÉCOT 1948), and the probability of ultimate fixation for selection without dominance (MALÉCOT 1952).

MALÉCOT's 1948 classic, *Les mathématiques de l'hérédité*, is one of the most original, elegant, concise, and

stimulating books every written on population genetics. His achievement is even more remarkable than it seems: MALÉCOT wrote a section of the book each week for a mathematical genetics course he was teaching at the Institute of Statistics of the University of Paris. For many readers, a slightly revised and extended English translation (MALÉCOT 1969) may provide the easiest entrée to MALÉCOT's oeuvre. The translation, however, contains some errors that do not appear in the original, both in the text and in the displays.

MALÉCOT's dissertation, his book, and some of his more didactic papers have been reprinted (with new typesetting) in *Probabilités et hérédité* (MALÉCOT 1966), which includes also a list of his publications complete to May 1, 1966. Unfortunately, financial exigencies have prevented the publication of a planned companion volume of his most important research papers. In particular, none of the papers cited above is reprinted in MALÉCOT (1966). FELSENSTEIN's (1981) superb bibliography is also useful.

After a brief biographical sketch, MALÉCOT's contributions will be described in more detail. This entails reviewing certain aspects of the theory of inbreeding, the correlation between relatives, the evolution of finite panmictic populations, and (in more depth) spatial variation. The final section comprises a broader discussion of the style and significance of his work and its relation to earlier and later research.

BIOGRAPHICAL SKETCH

GUSTAVE MALÉCOT was born in la Grand-Croix (Loire), near Saint-Étienne, on December 28, 1911. In 1932, after his secondary education at the Lycée de Saint-Étienne, he entered the École Normale Supérieure to study mathematics, with the intention of teaching it at the secondary level. At this "grande école," his professors included ÉMILE BOREL, ÉLIE CARTAN, GEORGES DARMOIS, and MAURICE FRÉCHET. He graduated in 1935 (Agrégé des sciences mathématiques), second in his class.

MALÉCOT then proceeded to the Institut Henri Poincaré of the University of Paris, where he had a research fellowship. His research was guided by DARMOIS, and in 1939 MALÉCOT received his Doctorat d'État for a thesis that elucidated, rigorized, systematized, and generalized FISHER's (1918) seminal but notoriously difficult reconciliation of biometry and Mendelian inheritance ("obscur et génial, comme tout ce qu'a écrit Sir Ronald" is MALÉCOT's description in a personal communication).

MALÉCOT taught mathematics first at the Lycée de Saint-Étienne (1940–1942) and then at the University of Montpellier (1942–1944), where he was maître de conférences. The work of WRIGHT (1921a, b, 1922a, 1931, 1933a, b) stimulated him to develop the concept of identity by descent (MALÉCOT 1941, 1942, 1946,



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1948) and to apply it to inbreeding (MALÉCOT 1941, 1942, 1948), the correlation between relatives (MALÉCOT 1948), and random mating in a finite population (MALÉCOT 1946, 1948, 1951). In graduate school, he had already studied the research of KOLMOGOROV, FRÉCHET, and DOEBLIN on Markov processes. Their probabilistic methods, together with the pertinent work of FISHER (1922, 1930a, b) and WRIGHT (1931, 1937, 1938a, 1939), inspired his powerful investigations of gene-frequency fluctuations in a finite population (MALÉCOT 1937, 1944, 1945, 1948, 1952).

In 1944, MALÉCOT became maître de conférences at the University of Lyon (Université Claude Bernard); from 1945 until his retirement in 1981, he was professor of applied mathematics there. At Lyon, he taught probability, mechanics, and mathematical economics. For many years, he lectured on population genetics at the Institute of Statistics of the University of Paris. Among those who have studied with MALÉCOT are GILLOIS, JACQUARD, LALOUEL, MARCHAND, PICARD, and SERANT. WRIGHT's island model (WRIGHT 1931) and treatment of isolation by distance (WRIGHT 1943a, b, 1946) and discussions with MAXIME LAMOTTE concerning geographical variation in the snail *Cepaea nemoralis* motivated MALÉCOT's extensive and important research on the genetic structure of populations with discrete or continuous spatial distributions (MALÉCOT 1948, 1949, 1950, 1951, 1965, 1967, 1975). He is still working on these problems.

MALÉCOT has received a number of honors for his work: Prix Montyon de l'Académie des Sciences, Officier des Palmes Académiques, Chevalier de la Légion d'Honneur (1962), and Officier de la Légion d'Honneur (1982).

CONTRIBUTIONS TO POPULATION GENETICS

This section comprises the description of MALÉCOT's research on identity by descent, inbreeding, the correlation between relatives, panmixia in finite populations, the balance between mutation and random

drift, the random drift of gene frequencies, and spatial variation. These subjects are discussed in the above order, rather than chronologically.

Identity by descent: Two homologous genes are identical by descent if and only if they are derived from the same gene or one is derived from the other (in both cases without mutation). This fundamental idea was discovered independently by COTTERMAN (1940) and MALÉCOT (1941, 1942, 1946, 1948); it had been foreshadowed by HALDANE and MOSHINSKY (1939). It is an essential ingredient of all of MALÉCOT's major contributions except those that deal directly with the random fluctuation of gene frequencies. COTTERMAN (1940, 1983) employed identity by descent to specify precisely the genetic relation between arbitrary relatives and to solve many interesting problems of particular importance in human genetics; KARLIN (1969), JACQUARD (1974), and CANNINGS and THOMPSON (1981) present extensions and other applications. Identity by descent lies at the heart of the powerful genealogical approach to population genetics (see DONNELLY and TAVARÉ 1987; HOPPE 1987; HUDSON and KAPLAN 1988; KAPLAN, DARDEN and HUDSON 1988; EWENS 1989; and references therein). Finally, extensions and variants of identity arguments have served vitally in many analyses of genome evolution (see OHTA 1985; NAGYLAKI 1988a; and references therein).

Inbreeding: This subsection covers MALÉCOT's definitions of the inbreeding coefficient and of the coefficient of consanguinity, his derivation of the genotypic frequencies under inbreeding, and his proof of WRIGHT's formula for the inbreeding coefficient of an individual with an arbitrary pedigree.

The inbreeding coefficient: The introduction of the inbreeding coefficient is only one of WRIGHT's (1921b, 1922a) many extremely important and highly creative contributions to population genetics. WRIGHT's definition, as the correlation between uniting gametes, however, involves irrelevant numerical values and (implicitly) gene frequencies, thereby disguising the basic facts that the inbreeding coefficient is a function only of ancestry, and is therefore the same for all (autosomal) loci and independent of gene frequencies. The definition of COTTERMAN (1940) and MALÉCOT (1941, 1942, 1946, 1948) exhibits these facts immediately and leads to a more concise, lucid, and rigorous theory of inbreeding. Therefore, it is the preferred approach for modern exposition and research. An individual is *autozygous* at a locus if and only if his two genes at that locus are identical by descent. The inbreeding coefficient, F , of an individual is the probability that he is autozygous.

A measure of the relatedness of two individuals is MALÉCOT's (1941, 1942, 1946, 1948) *coefficient of consanguinity*. The coefficient of consanguinity of individuals I and J , F_{IJ} , is the probability that a randomly

chosen gene from I and a homologous randomly chosen gene from J are identical by descent. Hence, if O is the offspring of I and J , then $F_{IJ} = F_O$, the inbreeding coefficient of O .

Genotypic frequencies: Consider an infinite population with discrete, nonoverlapping generations. Assume this population is initially in Hardy-Weinberg proportions and it practices pure inbreeding thereafter (*i.e.*, all other evolutionary forces are absent). If p_i and P_{ij} denote the respective frequencies of A_i alleles and ordered A_iA_j genotypes, then

$$P_{ii} = p_i^2 + Fp_i(1 - p_i), \quad (1a)$$

$$P_{ij} = (1 - F)p_ip_j, \quad i \neq j. \quad (1b)$$

This equation holds also for a finite population if the initial generation is sampled at random from an infinite population in Hardy-Weinberg proportions and the gene and genotypic frequencies are interpreted as expectations. The fundamental result (1), which encapsulates the biological significance of the inbreeding coefficient, was derived by WRIGHT (1921b, 1922b) for two alleles. COTTERMAN (1940) and MALÉCOT (1946) deduced (1) for two alleles by probabilistic arguments, which MALÉCOT (1948) soon extended to multiple alleles.

Pedigrees: WRIGHT (1922a) obtained his beautiful formula for the inbreeding coefficient of an individual with an arbitrary pedigree by examining special cases with his method of path coefficients (WRIGHT 1921a, b, 1934, 1968). Special cases, of course, cannot prove a general result. Furthermore, although WRIGHT recognized that the method of path coefficients requires linear determination of the dependent variables by the independent variables (*cf.* TUKEY 1954; MORAN 1961), he did not demonstrate this linearity in any of his genetic applications. COTTERMAN (1940) supported WRIGHT's formula by probabilistic reasoning. MALÉCOT (1941) noted the inadequacy of WRIGHT's analysis and established the formula by a subtle inductive argument. Consult BOUCHER (1988) for a more detailed and explicit proof.

The correlation between relatives: As noted above, MALÉCOT's (1939a) dissertation on the analysis of the phenotypic variance and the correlation between relatives was inspired by FISHER's (1918) classic treatment of these problems. MALÉCOT's concise, suggestive conditional-expectation arguments greatly simplified the calculation of the correlations, for which FISHER had used association tables. MALÉCOT (1938a, b, 1939b, c) reported his results in a series of short notes. In his elegant and seminal second investigation of this subject (MALÉCOT 1948), he used identity by descent. In both studies, he posited equilibrium, an arbitrary number of diallelic loci with independent assortment, and an additive, stochastically independent environmental contribution.

Random mating, inbreeding, and assortative mating will be discussed separately.

Random mating: Suppose first that the trait is determined without dominance or epistasis. WRIGHT (1922a) assumed further that the trait is not influenced by the environment and employed path coefficients to derive the formula $r_{IJ} = 2F_{IJ}$ for the correlation r_{IJ} between arbitrary relatives I and J whose coefficient of consanguinity is F_{IJ} . In his thesis, MALÉCOT (1939a) demonstrated how to calculate the correlation for any specified relationship. Later, he proved that $r_{IJ} = 2F_{IJ}h^2$, where h^2 is the heritability (MALÉCOT 1948).

FISHER (1918) included dominance and derived the correlation for the three closest ancestral relatives (*i.e.*, parent and offspring, grandparent and grandchild, and great grandparent and great grandchild), full siblings, uncle-niece, and single and double first cousins. (He showed as well that his results for the analysis of variance and the parental and sibling correlations hold for multiple alleles.) MALÉCOT (1939a) first evaluated the correlation for two classes of relatives: (i) those related only through one parent of one of them (*e.g.*, parent-offspring and uncle-niece) and (ii) those for which no parent of either individual is related to both parents of the other (*e.g.*, full siblings and double first cousins). A false assumption (MALÉCOT 1948, p. 21) unfortunately restricts the validity of his subsequent treatment to category (ii), which excludes, *inter alia*, the above examples of category (i). In any case, neither category includes relatives such as quadruple half-first cousins (TRUSTRUM 1961; VAN AARDE 1975). KEMPTHORNE (1955a, b, 1957, pp. 330–332) used identity by descent to derive the formula for arbitrary relatives.

The results described above do not, in fact, depend on the linkage map. If there is epistasis, this independence still holds for the decomposition of the variance (COCKERHAM 1954; KEMPTHORNE 1954, 1955a, b, 1957, pp. 413–419), but not for the correlation between relatives. FISHER (1918) generalized his formulae to two-factor epistasis, and MALÉCOT (1939a) indicated how to include three-factor epistasis. COCKERHAM (1954) extended FISHER's work to arbitrary relatives and arbitrary epistasis, but identity by descent was the crucial tool in KEMPTHORNE's (1954, 1955a, b, 1957, pp. 419–420) derivation of a concise and informative general formula. Identity by descent was equally vital in the incorporation of linkage (COCKERHAM 1956; SCHNELL 1963; VAN AARDE 1975).

Inbreeding: In the case of purely additive gene action, both WRIGHT (1922a) and MALÉCOT (1948) included inbreeding. MALÉCOT obtained the formula

$$r_{IJ} = 2F_{IJ}h^2 / [(1 + F_I h^2)(1 + F_J h^2)]^{1/2}, \quad (2)$$

where h^2 denotes the heritability with random mating and F_I and F_J designate the respective inbreeding

coefficients of individuals I and J . WRIGHT had derived (2) in the absence of an environmental effect ($h = 1$).

For a single locus, (2) is certainly correct. For two or more loci, however, all derivations of (2) tacitly assume that *allelic effects* at different loci are uncorrelated. But this is not obvious: as a rule, *genotypes* at different loci are mutually dependent under inbreeding. Although the equilibria of examples such as partial selfing (KIMURA 1963; NARAIN 1966; WEIR and COCKERHAM 1973) support the implicit conjecture, the general validity of (2) remains to be proved (or disproved).

Assortative mating: FISHER (1918) was the first to treat assortative mating for a quantitative character. He posited stochastic independence of the environment, control of the character by many unlinked loci with contributions of the same order of magnitude, and the absence of epistasis. Using ingenious intuitive arguments, he evaluated approximately the genotypic variance at the equilibrium determined by assortative mating in terms of the initial, panmictic genotypic variance, and calculated the equilibrium correlation between sundry close relatives in terms of the marital correlation and the broad and narrow heritabilities.

MALÉCOT (1939a) proved for diallelic loci that FISHER's formulas for the variance and the parental and sibling correlations hold in the limit as the number of loci tends to infinity. FISHER's work had suggested that assortative mating increases the additive genetic variance, leaving the dominance variance approximately unaltered, and FISHER (1918) implicitly made this assumption in his study of the correlation between relatives. This result was also established by MALÉCOT (1939a).

This subject is difficult, and many challenging problems remain open (NAGYLAKI 1982a).

Random mating in a finite population: WRIGHT used path coefficients to deduce many basic properties of the evolution of a population under pure random genetic drift. Employing probabilities of identity instead of correlations as his dynamical variables, MALÉCOT derived equations equivalent to WRIGHT's and established some important new results. Although MALÉCOT's one-locus probabilities refer to identity by descent, he did not assume that they all vanish initially, as is conventional, but rather treated arbitrary initial conditions. Thus, his analyses differ only in interpretation from the later approach of KIMURA (1963), whose probabilities refer to identity in state. It is identity in state that is (at least in principle) measurable and, as far as probabilities of identity are concerned, more general. If the initial population is a random sample from an infinite population in Hardy-Weinberg proportions, then (1) and similar equations yield probabilities of identity in state in terms of probabilities of identity by descent.

MALÉCOT investigated evolution at a single locus in a monoecious population as well as at single autosomal and sex-linked loci and at a pair of autosomal loci in a dioecious population. In the important case of a single autosomal locus in a dioecious population, he studied also the effects of rapid population growth and arbitrary distribution of the number of progeny per individual.

Ideal population: Each of N monoecious individuals produces the same extremely large number of gametes, which fuse wholly at random (including self-fertilization); N randomly chosen zygotes survive to reproductive age. Thus, the rate of selfing is $1/N$. If at least one generation of panmixia precedes the initial generation, in which the heterozygosity is h_0 , then the expected heterozygosity in generation t ($=0, 1, 2, \dots$) reads (WRIGHT 1931; MALÉCOT 1946, 1948; KIMURA 1963)

$$h_t = h_0 \left(1 - \frac{1}{2N}\right)^t. \quad (3)$$

Therefore, the characteristic time for the loss of genetic variability is $2N$ generations. This is the first fundamental result of the theory of random genetic drift, and it motivated (in different directions!) the development of the evolutionary theories of both FISHER (1930b) and WRIGHT (1931, 1977, Ch. 13).

The distribution of the allelic numbers in any generation, conditioned on those in the previous generation, is multinomial. This is usually called the WRIGHT-FISHER model. On account of its simplicity, it is the reference model for random drift.

An autosomal locus in a dioecious population: MALÉCOT (1946, 1948) demonstrated that (3) approximates the expected heterozygosity in a panmictic population of N_1 males and N_2 females if the following five conditions hold: h_0 is replaced by k_0 , the probability that two genes chosen at random from distinct individuals in the initial generation are different alleles, N is replaced by the effective population number

$$N_e = \frac{4N_1N_2}{N_1 + N_2}, \quad (4)$$

$k_0 > 0$, $N_e \gg 1$, and $t \geq 1$. WRIGHT (1931) had shown only that replacing N by N_e approximates the asymptotic decay rate of the expected heterozygosity.

MALÉCOT (1946, 1948) proved also that if the population numbers N_1 and N_2 are deterministic functions of time, then some genetic variability is preserved (i.e., $h_t \not\rightarrow 0$ as $t \rightarrow \infty$) if and only if

$$\sum_{t=0}^{\infty} \frac{1}{N_e(t)} < \infty. \quad (5)$$

Thus, sufficiently rapid population growth preserves some genetic diversity. It is easy to show that the criterion (5) applies as well to ideal populations. This beautiful result has stimulated much work on the

more difficult problem of stochastically varying population number (see DONNELLY 1986; KLEBANER 1988; and references therein). Furthermore, if $N_e(t)$ is reinterpreted as the number of ancestors t generations in the past of a specified individual, then (5) is necessary but not sufficient for the preservation of some genetic heterogeneity in certain classes of regular inbreeding systems (ARZBERGER 1988).

In an ideal population, the number of successful gametes produced by a specified individual is binomially distributed. To take deviations from the binomial distribution into account, WRIGHT (1938b, 1939) devised the inbreeding effective population number. MALÉCOT (1951) derived an inbreeding effective population number for a dioecious population; his formula, a generalization of (4), closely approximates the exact one if the total population number is much greater than one (KIMURA and CROW 1963; CROW and KIMURA 1970, pp. 349–352; POLLAK 1977; CROW and DENNISTON 1988).

Sex-linked loci: Instead of (4), the effective population number is now (WRIGHT 1933a, MALÉCOT 1951, KIMURA 1963)

$$N_e = \frac{9N_1N_2}{2(N_1 + N_2)}. \quad (6)$$

Two loci: MALÉCOT (1951) derived the recursion relations for the two-locus probabilities of specified alleles (in the same gamete, in uniting gametes, or in randomly chosen gametes) in a dioecious population. Obvious averages of his variables and recursion relations yield those of KIMURA (1963); simple transformations establish agreement with WRIGHT's (1933b) recursions for correlations. Whereas WRIGHT and KIMURA investigated the equilibrium, MALÉCOT calculated the rate of convergence.

The balance between mutation and random drift: MALÉCOT (1946, 1948, 1951) introduced mutation by proposing that every allele mutates at rate u and no mutant is identical by descent to any preexisting allele. He proved for an ideal population (MALÉCOT 1946) and for autosomal (MALÉCOT 1946, 1948) and sex-linked (MALÉCOT 1951) loci in a dioecious population that the autozygosity converges as $t \rightarrow \infty$ to

$$\hat{F} \approx 1/(1 + 4N_e u), \quad (7)$$

where the approximation holds if the mutation rate $u \ll 1$, and the effective population number N_e is given in the three cases by the actual population number N , (4), and (6), respectively.

MALÉCOT's (1951) lucid discussion demonstrates that he considered the same elegant postulate for identity in state, but, lacking empirical motivation, did not pursue it. Similarly, WRIGHT (1948) mentioned this possibility only fleetingly. It was KIMURA and CROW (1964) who, with molecular genetics to support them, posited that each mutant is of a novel allelic

type—the model of infinitely many alleles—and began the investigation of the consequences of this hypothesis. Since the probabilities of the two kinds of identity differ only in their initial conditions, the first major result of this model is precisely (7), in which \hat{F} is now interpreted as the expected homozygosity. Thus, MALÉCOT's idea led to one of the most important and thoroughly analyzed models of molecular population genetics (EWENS 1979, 1989; KINGMAN 1980; KIMURA 1983; HOPPE 1987).

The random drift of gene frequencies: The probabilities of identity discussed in the last two subsections are functionals of the Markov chain that describes the evolution of the population. These probabilities yield some basic results quite easily, but the more difficult direct analysis of the Markov chain is more informative. This subsection concerns MALÉCOT's studies of the random fluctuation of the gene frequency at a diallelic autosomal locus in a finite population. Although he first formulated a general Poisson model for these fluctuations (MALÉCOT 1937), his subsequent papers treat various aspects of the Wright-Fisher model: the asymptotic probability distribution for pure random drift, the general stationary distribution, the (time-dependent) probability distribution for reversible mutation, and the fixation probability for genic selection (*i.e.*, selection without dominance).

Mathematical research in diffusion theory influenced population genetics only gradually. As described in more detail below, WRIGHT was unaware of KOLMOGOROV's (1931) pioneering paper, and WRIGHT, MALÉCOT, and KIMURA were all apparently unacquainted with KHINTCHINE's (1933) book. The work of these two great Russian mathematicians would have led these population geneticists to easier, more rigorous, and sometimes more general analyses. Thus, the mutually beneficial cross-fertilization between diffusion theory and population genetics did not start until FELLER published his seminal 1951 paper. But this probably still represents relatively rapid communication between fields.

A general Poisson model: FISHER (1922, 1930a, b) suggested that if an organism produces an exceedingly large number of progeny, of which only a small fraction survives, then (at least approximately) the number of surviving progeny should have a Poisson distribution, and he used this idea to examine the behavior of rare alleles. In his first publication, MALÉCOT (1937) extended FISHER's hypothesis to incorporate (random or nonrandom) mating, fertility differences among mating types, and viability differences among genotypes. Had he fixed the total number of offspring, his trivariate probability-generating function would have been of the same type as those of FELDMAN (1966), WATTERSON (1970), and ETHIER and NAGYLAKI (1980), who were all apparently unaware of MALÉCOT's model.

The asymptotic probability distribution for pure random drift: FISHER (1922, 1930a, b) and WRIGHT (1931) employed rough, intuitive methods to seek the distribution of the gene frequency (excluding absorption) in a large ideal population after a long time has elapsed.

In the first application of the diffusion approximation in population genetics, FISHER (1922) derived a partial differential equation for the gene-frequency distribution and deduced that as $t \rightarrow \infty$ this distribution becomes uniform and decays at the rate $1/(4N)$ per generation. However, comparison with a preliminary version of WRIGHT (1931) led FISHER (1930a, b) to discover an error in his 1922 derivation; the corrected asymptotic distribution is still uniform, but decays twice as fast, in agreement with (3). It must be noted that FISHER's analysis of the diffusion equation was still incomplete.

WRIGHT (1931) examined directly the Chapman-Kolmogorov equations (whose general validity for Markov chains was unknown to him) for steady decay at the rate (3) and observed that a uniform distribution satisfies them approximately. This does not suffice, however, to demonstrate that (3) gives the maximal eigenvalue of the Markov chain of gene frequencies.

Neither FISHER nor WRIGHT obtained the normalization of the uniform distribution and, as MALÉCOT (1944) pointed out, neither of them fully established convergence to this distribution. MALÉCOT (1944) appealed to the theory of Markov chains—the first time this was done explicitly in population genetics (SENETA 1974)—to show that for $t \gg N \gg 1$ and initial gene frequency p , the distribution of the gene frequency x ($0 < x < 1$) can be approximated by the probability density

$$\phi(p, x, t) \approx 6p(1-p)e^{-t/(2N)}. \quad (8)$$

This is precisely the leading term as $t \rightarrow \infty$ in KIMURA's (1955) complete solution of the Kolmogorov forward equation. Equation 8 approximates also the probability that the locus is still segregating in generation t .

The general stationary distribution: WRIGHT (1929) first presented without derivation a formula for the stationary distribution of the gene frequency under reversible mutation and genic selection. He showed later (WRIGHT 1931) that in the absence of selection his formula approximately satisfies the stationary CHAPMAN-KOLMOGOROV equations. Comparison with results of FISHER (1930b) for extremely low mutation rates revealed, however, that his selection factor was wrong. WRIGHT (1931) corrected his formula by enforcing constancy of the mean gene frequency. Subsequently, he obtained the stationary distribution for arbitrary selection by enforcing constancy of both the mean and the variance (WRIGHT 1937). Then he used the same method to derive the general formula

(WRIGHT 1938a)

$$\hat{\phi}(x) = \frac{C}{V(x)} \exp \left[2 \int^x \frac{M(y)}{V(y)} dy \right] \quad (9)$$

for the stationary distribution (in modern terminology) of a diffusion with drift and diffusion coefficients $M(x)$ and $V(x)$. (C is a normalization constant.)

In his classic 1931 paper, KOLMOGOROV showed that his forward equation yields the stationary result

$$\frac{1}{\hat{\phi}} \frac{d\hat{\phi}}{dx} = \frac{2M}{V} - \frac{1}{V} \frac{dV}{dx}, \quad (10)$$

from which (9) follows immediately. In 1935, he applied (10) to reversible mutation without selection, and about ten years later sent this biological paper (KOLMOGOROV 1935) to WRIGHT (1945). However, KOLMOGOROV did not cite his earlier paper, and therefore WRIGHT did not realize that KOLMOGOROV had proved both the forward equation and (9) in complete generality. The distributions in WRIGHT (1931, 1937, 1938a, 1945) follow easily and rigorously from the forward equation and (9).

MALÉCOT (1945) noted that invariance of the first two moments does not establish invariance of the probability distribution. By an original method (described below), he rederived the stationary case of the forward equation and from this easily deduced both the general formula (9) and its application to reversible mutation and arbitrary selection.

The probability distribution for reversible mutation: Reversible mutation without selection is the only process for which the time-dependent solution of the KOLMOGOROV forward equation was obtained before the extensive and systematic investigations of KIMURA (reviewed in KIMURA 1964; CROW and KIMURA 1970). This was accomplished independently by MALÉCOT (1948) and (slightly more explicitly) by GOLDBERG (1950). KIMURA calculated all the moments of the gene frequency, and from these he reconstructed GOLDBERG's solution (CROW and KIMURA 1956).

MALÉCOT's (1945, 1948) derivation of the KOLMOGOROV forward equation is of independent interest. Instead of following KOLMOGOROV (1931), he assumed that the drift and diffusion coefficients are polynomials and established a partial differential equation for the moment-generating function, from which he deduced the forward equation. Partial differential equations for the moment-generating function are often useful in the analysis of stochastic processes. MALÉCOT did not know that PALM (1943, pp. 56–66) had used them earlier in special cases. Independently of PALM and MALÉCOT, BARTLETT (1947, 1949) developed the method quite generally.

The fixation probability for genic selection: Fixation probabilities directly affect the rate of evolution and illuminate the fluctuation of gene frequencies. FISHER

(1922, 1930a, b) was the first to examine the fixation probability of a favorable mutation. HALDANE (1927) used FISHER's branching-process method to show that for a Poisson offspring distribution in an infinite population, if s designates the selective advantage of the heterozygote Aa over the homozygote aa and selection is weak (i.e., $0 \leq s \ll 1$), then the probability that the descendants of a single new mutant A are ultimately fixed (rather than lost) is $u \approx 2s$. For genic selection, by a rather complicated and indirect argument, FISHER (1930a, b) extended this result to a finite population of size N :

$$u \approx 2s/(1 - e^{-4Ns}), \quad (11)$$

provided $|s| \ll 1$ and $N \gg 1$. WRIGHT (1931) simplified FISHER's argument and confirmed (11).

Discussions with HALDANE prompted MALÉCOT (1952) to generalize (11) to an arbitrary initial frequency, p , of A . Invoking his derivation of the forward equation (MALÉCOT 1948), he showed easily that the moment-generating function

$$g(p, \xi, t) = E[e^{\xi X(t)} | X(0) = p] \quad (12)$$

of the gene frequency $X(t)$ satisfies the partial differential equation

$$\frac{\partial g}{\partial t} = \xi \left(s + \frac{\xi}{4N_e} \right) \left(\frac{\partial g}{\partial \xi} - \frac{\partial^2 g}{\partial \xi^2} \right), \quad (13)$$

in which N_e denotes the variance effective population number (CROW and DENNISTON 1988). Clearly, (13) implies that $g(p, -\sigma, t)$, where $\sigma = 4N_e s$, is constant. Appealing to (12) to evaluate $g(p, -\sigma, t)$ at $t = 0$ and as $t \rightarrow \infty$ demonstrates immediately that the fixation probability $u(p)$ satisfies

$$u(p)e^{-\sigma} + 1 - u(p) = e^{-\sigma p},$$

whence (MALÉCOT 1952)

$$u(p) = \frac{1 - e^{-\sigma p}}{1 - e^{-\sigma}}. \quad (14)$$

This approach does not extend readily to arbitrary dominance, and KIMURA (1957, 1962) used a more powerful method to deduce the general formula: he demonstrated that $u(p)$ satisfies the ordinary differential equation $Lu = 0$, where L represents the generator of the diffusion (the operator in the KOLMOGOROV backward equation), and solved for $u(p)$ with the appropriate boundary conditions. This method (for diffusions in one and two dimensions) goes back to KHINTCHINE (1933, pp. 32, 41); it was also treated by DARLING and SIEGERT (1953) and FELLER (1954).

Spatial variation: Since many, perhaps most, natural populations are distributed in space and mate at random only locally, it is important to study under what conditions the effects of population subdivision are negligible (NAGYLAKI 1980, 1983) and to seek quantities that, under suitable restrictions, are invar-

iant under population subdivision (NAGYLAKI 1982b and references therein). In the model of infinitely many neutral alleles, population subdivision produces interdeme differentiation and increases the mean homozygosity and the effective number of alleles (NAGYLAKI 1985, 1986). Only the investigation of particular migration patterns, however, can yield a detailed understanding of the stationary and transient patterns of genetic variability in spatially distributed populations.

MALÉCOT has devoted far more effort to this problem than to any other. His research has stimulated an extensive theoretical literature, much of which is discussed in this subsection. The rest of the literature on neutral models of spatial variation can be traced from the references. His results have been widely compared with data from natural populations (LAMOTTE 1951, 1959; CAVALLI-SFORZA and BODMER 1971; MORTON 1982; WIJSMAN and CAVALLI-SFORZA 1984; SLATKIN 1985).

After some general remarks about the sundry models for spatial variation, infinite and finite populations will be treated successively.

Models: The first idea was again WRIGHT's (1931): in his island model, infinitely many finite, panmictic colonies exchange migrants wholly at random, *i.e.*, with no spatial effect on dispersion. Much later, this model was formulated and analyzed for finitely many islands (MARUYAMA 1970a; MAYNARD SMITH 1970; NAGYLAKI 1983, 1986).

A more elaborate model is required to study the decrease of relationship with distance. WRIGHT's (1943a, b, 1946, 1951, 1969, pp. 295–324) model of isolation by distance in a spatially continuous population is a rough, intuitive scheme without detailed, explicit derivation of the fundamental equations from clearly specified assumptions. These equations depend only on the variance of the migration distribution (through the neighborhood size), whereas an exact discrete-time model must depend on the entire distribution (*cf.* MALÉCOT 1948, p. 61). This reduction occurs because WRIGHT treats a continuously distributed population as if it were a hierarchy of panmictic neighborhoods from which ancestors are drawn at random. It is also difficult to see why the demographic fluctuations discussed below would not occur in WRIGHT's scheme.

Like WRIGHT's, MALÉCOT's models are selectively neutral. Although his most recent papers concern continuous-time, birth-and-death migration models (MALÉCOT 1977, 1980, 1981), in the work described below he almost invariably posits discrete, nonoverlapping generations. To maximize biological interest and simplify the exposition, mutation to new alleles at rate u will be assumed. The theory is similar for the covariance of gene frequencies in a diallelic model with reversible mutation (MALÉCOT 1949, 1971; KIMURA

and WEISS 1964; WEISS and KIMURA 1965; FLEMING and SU 1974; NAGYLAKI 1978a); in this case, small fluctuations around a space-independent overdominant equilibrium can also be included (MALÉCOT 1948).

In most of his research on spatial variation, MALÉCOT postulates discrete distribution of the population into (finitely or infinitely many) panmictic colonies, often called demes. MALÉCOT (1949) first deduced the recursion relations for the covariances in the diallelic model under the reasonable approximation that all evolutionary forces (*i.e.*, mutation, migration, and random drift) are weak. Soon thereafter, he wrote the recursion relations satisfied by the probabilities of identity for the migration of nonselfing diploids (MALÉCOT 1950). If all the evolutionary forces are weak, these equations are close to the exact ones (SAWYER 1976; NAGYLAKI 1983). It was in his 1951 paper that MALÉCOT obtained the system to which he and others subsequently devoted so much attention. This system turns out to be exact for the following life cycle.

First, every one of the N_i monoecious, diploid adults in deme i produces the same very large number of gametes, which then disperse. Complete random union of gametes within each deme follows. Therefore, a proportion $1/N_i$ of the zygotes whose gametes both originated in deme i are produced by self-fertilization. Mutation is next, and finally population regulation returns the number of individuals in deme i to N_i . Let $f_{ij}(t)$ denote the probability that two distinct genes chosen at random from adults just before gametogenesis in generation t , one from colony i and one from colony j , are the same allele. Define m_{ij} as the probability that a gamete in deme i after dispersion was produced in deme j . After one generation, the probabilities of identity satisfy (MALÉCOT 1951, 1975; NAGYLAKI 1976a, 1980, 1983; SAWYER 1976)

$$f'_{ij} = v \left[\sum_{k,l} m_{ik} m_{jl} f_{kl} + \sum_k m_{ik} m_{jk} (2N_k)^{-1} (1 - f_{kk}) \right], \quad (15)$$

where $v = (1 - u)^2$ and the prime signifies the next generation. Actually, (15) holds if mutation occurs at any time between gametogenesis and regulation. Population regulation during this period would have no effect if it were sufficiently weak to leave very large numbers of gametes and zygotes. As SAWYER (1976) has noted, (15) also applies to a model with $2N_i$ haploid individuals in deme i .

If $0 \leq f_{ij}(0) \leq 1$ for every i and j , then $0 \leq f_{ij}(t) \leq 1$ for every i, j , and t . In addition, if $f_{ij}(0) = f_{ji}(0)$ for every i and j , then $f_{ij}(t) = f_{ji}(t)$ for every i, j , and t . Thus, biologically sensible initial conditions are preserved. If mutation is present ($u > 0$), then as $t \rightarrow \infty$, $f_{ij}(t) \rightarrow \hat{f}_{ij}$, the unique equilibrium of (15), at least as fast as v^t (NAGYLAKI 1980). Furthermore, some genetic variability is preserved: from (15) it follows that $\hat{f}_{ij} < 1$ for some i and j .

For the unbounded and circular stepping-stone models and for the island model with a finite number of islands, if mutation or random drift is weak, then the unique equilibrium of the gametic-dispersion model (15) is close to that of the exact diploid-migration model (SAWYER 1976; NAGYLAKI 1983). Consult NAGYLAKI (1983) for other results on this type of robustness.

Subdivision of a population into discrete colonies was proposed independently by KIMURA (1953). Although he presented no explicit formulation of his "stepping-stone" model for spatially homogeneous migration between nearest neighbors, it is clear that he focused directly on gene-frequency fluctuations, as he did in his subsequent collaborative analyses of the general homogeneous model (KIMURA and WEISS 1964; WEISS and KIMURA 1965).

In his more expository writings, MALÉCOT (1948, 1955, 1959, 1967) postulated continuous spatial distribution of the population. Independent reproduction and migration yield random fluctuations in the population density. Whereas in the above discrete model this difficulty can be obviated by population regulation, this has not been accomplished for any biologically reasonable continuous model (FELSENSTEIN 1975; KINGMAN 1977; SUDBURY 1977; SAWYER and FELSENSTEIN 1981). Furthermore, the lack of rigor in the formulation of the continuous model is reflected in the devastating fact that biologically sensible initial conditions in the continuous analog of (15) can lead (at least for low population densities) to probabilities of identity that are negative or greater than one (NAGYLAKI 1976a).

Despite these serious difficulties, it can be shown that the equilibrium probabilities of identity in the continuous analogs of the unbounded and circular stepping-stone models are between zero and one. Furthermore, approximating these equilibrium probabilities of identity for weak mutation in an infinite population (MALÉCOT 1948, 1955, 1959, 1967; NAGYLAKI 1974a, 1976b, 1978b) yields correct results (NAGYLAKI 1976a, SAWYER 1977a). Approximate formulas for the rate and pattern of convergence (as $t \rightarrow \infty$) in the special case of identity by descent without mutation (NAGYLAKI 1978b) are also correct (NAGYLAKI 1976a, SAWYER 1976).

Although the spatial distribution of a population obviously cannot be exactly continuous, in many cases the stepping-stone model surely overestimates the degree of clustering. Therefore, it would be highly desirable to formulate a biologically reasonable model for a population distributed with a finite, continuous density.

Diffusion approximation of the basic system (15) provides another route toward the derivation of a continuous model. This approach applies if all evolutionary forces are weak, and it leads to a partial

differential equation, which is more tractable than (15). Early work in this direction, initiated by MALÉCOT (1959, 1967, 1969) and continued by MARUYAMA (1971a), FLEMING and SU (1974), and NAGYLAKI (1974a, b) was heuristic, but in one spatial dimension more rigorous derivations have been presented (NAGYLAKI 1978a, 1986, 1988b). Unfortunately, the diffusion approximation fails in more than one dimension (FLEMING and SU 1974; NAGYLAKI 1974a, 1978a), essentially because the required scalings yield $N_i \rightarrow \infty$ only in one dimension (NAGYLAKI 1978a).

Organisms confined to a river, riverbank, seashore, mountain range, etc., do occupy essentially one-dimensional habitats, but most natural populations are distributed over two dimensions. Therefore, it would be important to develop a continuous-time, continuous-space model in two dimensions.

Infinite populations: Suppose there are demes of N individuals each at the points of the infinite integer lattice in d dimensions. Migration is homogeneous, i.e., the migration rates depend only on displacement, rather than on the initial and final positions separately (MALÉCOT 1949, 1950, 1951; KIMURA 1953). Probabilistic formulation and investigations of this stepping-stone model are extremely illuminating (SAWYER 1976, 1977b, 1979; RUSINEK 1982; SHIGA 1985; SHIGA and UCHIYAMA 1986), but, as in MALÉCOT's work, the emphasis here is on the probabilities of identity.

Consider first the *equilibrium* of (15). To express the results in simple form, first rotate coordinates so as to diagonalize the covariance matrix of the migration distribution m . Write the eigenvalues of this matrix as $\frac{1}{2} \sigma_i^2$ ($i = 1, \dots, d$), let w denote the separation (in the rotated coordinates) between the demes from which genes are sampled, and introduce the scaled coordinates $x_i = w_i/\sigma_i$ ($i = 1, \dots, d$). Finally, define

$$c = \prod_{i=1}^d \sigma_i, \quad (16a)$$

$$x = \left(\sum_{i=1}^d x_i^2 \right)^{1/2}, \quad \xi = 2\sqrt{u}x. \quad (16b)$$

The product Nc is essentially WRIGHT's (1946) neighborhood size. In natural populations, Nc always seems to exceed 30 and is usually at least about 300 (WRIGHT 1978, Ch. 2). The equilibrium probability of identity \hat{f} is spatially homogeneous, i.e., it depends on the coordinates of the two demes sampled only through their scaled separation x . Under some biologically trivial technical restrictions, $\hat{f}(x)$ can be approximated for weak mutation; consult NAGYLAKI (1976a) and, especially, SAWYER (1977a) for the most detailed and precise results. Although the exact value of $\hat{f}(x)$ depends on the entire migration distribution m , the approximations below depend on m only through the variances σ_i^2 .

In one dimension, the mean heterozygosity is given by

$$1 - \hat{f}(0) \sim 4Nc\sqrt{u} \quad (17a)$$

as $u \rightarrow 0$. (The notation means that the ratio of the two sides tends to one as $u \rightarrow 0$.) The probability of identity decays exponentially in space:

$$\hat{f}(\mathbf{x}) \sim e^{-\xi} \quad (17b)$$

as $u \rightarrow 0$ and $x \rightarrow \infty$ with ξ fixed. If $u \ll 1$ and $Nc \gg 1$ (and ξ is bounded above), the approximation

$$\hat{f}(\mathbf{x}) \approx \frac{e^{-\xi}}{1 + 4Nc\sqrt{u}} \quad (17c)$$

is adequate.

In two dimensions, the mean heterozygosity reads

$$1 - \hat{f}(0) \sim -4\pi Nc / \ln(2u) \quad (18a)$$

as $u \rightarrow 0$. As $u \rightarrow 0$ and $x \rightarrow \infty$ with ξ fixed,

$$\hat{f}(\mathbf{x}) \sim -\frac{2}{\ln(2u)} K_0(\xi), \quad (18b)$$

where K_0 designates the modified Bessel function of the second kind of order zero. If $\xi \gg 1$, (18b) becomes

$$\hat{f}(\mathbf{x}) \approx -\frac{1}{\ln(2u)} \sqrt{\frac{2\pi}{\xi}} e^{-\xi}, \quad (18c)$$

which decays more rapidly than the unidimensional result (17b). If $u \ll 1$ and $Nc \gg 1$ (and ξ is bounded below and above), the approximation

$$\hat{f}(\mathbf{x}) \approx \frac{2K_0(\xi)}{4\pi Nc - \ln(2u)} \quad (18d)$$

suffices.

The three-dimensional case may apply to some aquatic or subterranean organisms. There is no simple formula for the expected heterozygosity. If $u \ll 1$, $Nc \gg 1$, and ξ is bounded away from 0 and ∞ , then

$$\hat{f}(\mathbf{x}) \approx \frac{e^{-\xi}}{4\pi Ncx}. \quad (19)$$

This decreases faster than (18c) by a factor of \sqrt{x} .

In his very first paper on subdivided populations, MALÉCOT (1949) already presented an intuitive preliminary analysis of the unbounded, linear stepping-stone model; for symmetric nearest-neighbor migration, he obtained the rate of decay in (17c), but his approximation misses the 1 in the denominator. Next, he derived (17c) for symmetric nearest-neighbor migration and showed that the rate of decay is the same for arbitrary symmetric migration (MALÉCOT 1950). In his 1951 paper, MALÉCOT deduced (17c) in full generality. WEISS and KIMURA (1965) also obtained the numerator in (17c); as discussed in NAGYLAKI (1974a), their asymptotic analysis contains some er-

rors. See NAGYLAKI (1976a) and SAWYER (1977a) for proofs of (17) with error estimates.

The more difficult two-dimensional problem has a more complicated history. First, MALÉCOT (1948) established (18a) in the continuous model with isotropic Gaussian migration. Unfortunately, an error in the asymptotics of the stepping-stone model with symmetric nearest-neighbor migration led MALÉCOT (1950) to the pure exponential decay $e^{-\xi}$. Subsequently, he found the more rapid rate $e^{-\xi}/\sqrt{\xi}$ for isotropic Gaussian migration (MALÉCOT 1959). He misinterpreted this discrepancy, however, as an actual difference between the asymptotics of the discrete and continuous models. For symmetric nearest-neighbor migration, the mean heterozygosity (18a) can be extracted from the results of WEISS and KIMURA (1965). These authors also obtained the behavior $K_0(\xi)$ in (18b) for arbitrary symmetric migration, though not entirely correctly (*cf.* NAGYLAKI 1974a). It is fairly easy to prove (18a) in the most general case (NAGYLAKI 1976a; SAWYER 1977a), but a rigorous demonstration of the full result (18), with error estimates, is more delicate (SAWYER 1977a).

MALÉCOT did not examine the three-dimensional problem. WEISS and KIMURA (1965) and NAGYLAKI (1976b) investigated special cases; the general formula (19) is due to SAWYER (1977a).

The results are more accurate in one dimension than in two or more. For the same values of u and Nc , the mean heterozygosity increases with the number of dimensions. Note that the characteristic length of the decay of $\hat{f}(\mathbf{x})$ is greater than that of migration by the large factor $1/(2\sqrt{u}) \gtrsim 200$.

The work of WRIGHT (1943a, 1951, 1969) suggests that in the absence of mutation one- and two-dimensional populations tend to genetic homogeneity. Indeed, perhaps the most interesting qualitative property of the stepping-stone model is that as $u \rightarrow 0$, $\hat{f}(\mathbf{x}) \rightarrow 1$ for $d = 1, 2$, but $\hat{f}(\mathbf{x}) \rightarrow 0$ for $d \geq 3$ (WEISS and KIMURA 1965; NAGYLAKI 1976a; SAWYER 1976). Since the population is infinite, the ultimate loss of genetic variability in one or two dimensions is a consequence of spatial structure. The underlying distinction between $d = 1, 2$ and $d \geq 3$ is recurrence of the associated migration random walk (SAWYER 1976).

If $u = 0$, in a finite population ultimately the descendants of one of the genes initially present are *fixed* with probability one. In the stepping-stone model, the interpretation of $\hat{f}(\mathbf{x}) \equiv 1$ is more subtle (SAWYER 1976): the descendants of any particular initial gene ultimately become *extinct* with probability one. Apparently, every bounded region is eventually occupied by single dynasties (*i.e.*, the descendants of a single initial gene) for increasingly long periods of time, and the periods of transition between dynasties become too rare to produce $\hat{f}(\mathbf{x}) < 1$.

The equilibrium results are biologically important

only if *convergence* occurs on an evolutionarily reasonable time scale. Convergence will be treated here only in one or two dimensions; SAWYER's (1976) theorems are very general and could be applied in three or more dimensions. For long times, the asymptotic behavior depends on the recurrent potential $\psi(\mathbf{x})$ of the associated random walk (NAGYLAKI 1976a; SAWYER 1976; SPITZER 1976, Chs. 2, 7). This complicated functional of the migration distribution satisfies $\psi(\mathbf{0}) = 0$ and

$$\psi(\mathbf{x}) \sim x, \quad d = 1, \quad (20a)$$

$$\psi(\mathbf{x}) \sim \frac{\ln x}{\pi}, \quad d = 2, \quad (20b)$$

as $x \rightarrow \infty$ (NAGYLAKI 1976a; SAWYER 1976; SPITZER 1976, pp. 124, 345).

Let $f_t(\mathbf{y}, \mathbf{z})$ represent the probability of identity for genes sampled from demes at \mathbf{y} and \mathbf{z} (in the rotated and scaled coordinates) in generation t . The probability of nonidentity

$$h_t(\mathbf{y}, \mathbf{z}) = 1 - f_t(\mathbf{y}, \mathbf{z}) \quad (21)$$

yields the mean heterozygosity at \mathbf{y} if $\mathbf{y} = \mathbf{z}$. The separation between the demes is $\mathbf{x} = \mathbf{y} - \mathbf{z}$. The results are much simpler for $u = 0$ than for $u > 0$.

If there is no mutation ($u = 0$), it suffices to impose the exceedingly mild decay condition

$$\lim_{r \rightarrow \infty} \sup_{\mathbf{x}=\mathbf{r}} f_0(\mathbf{y}, \mathbf{z}) = 0 \quad (22)$$

on the initial probability of identity. Notice that for identity by descent, $f_0(\mathbf{y}, \mathbf{z}) = 0$, so (22) holds trivially. Then

$$h_t(\mathbf{y}, \mathbf{z}) \sim [1 + (2Nc)^{-1}\psi(\mathbf{x})]h_t(\mathbf{0}, \mathbf{0}) \quad (23a)$$

as $t \rightarrow \infty$ with \mathbf{y} and \mathbf{z} fixed, and the expected heterozygosity

$$h_t(\mathbf{0}, \mathbf{0}) \sim 2Nc \sqrt{\frac{2}{\pi t}}, \quad d = 1, \quad (23b)$$

$$h_t(\mathbf{0}, \mathbf{0}) \sim \frac{4\pi Nc}{\ln t}, \quad d = 2, \quad (23c)$$

as $t \rightarrow \infty$.

If mutation is present ($u > 0$), assume initial spatial homogeneity:

$$f_0(\mathbf{y}, \mathbf{z}) = f_0(\mathbf{x}, \mathbf{0}) \quad (24)$$

for every \mathbf{y} and \mathbf{z} . Then $f_t(\mathbf{y}, \mathbf{z}) = f_t(\mathbf{x}, \mathbf{0})$ for every \mathbf{y}, \mathbf{z} , and t , and one can set

$$\hat{f}(\mathbf{x}) - f_t(\mathbf{y}, \mathbf{z}) = v'\phi_t(\mathbf{x}). \quad (25)$$

Instead of (22), now impose the stronger but still weak decay condition, $f_0(\mathbf{x}, \mathbf{0}) = O(x^{-2-\eta})$ as $x \rightarrow \infty$, for some $\eta > 0$. Both hypotheses hold trivially for identity by descent. Finally, suppose that $t\phi_t(\mathbf{x})$ is monotone de-

creasing in t for sufficiently large t , for every \mathbf{x} . Then

$$\phi_t(\mathbf{x}) \sim [1 + (2Nc)^{-1}\psi(\mathbf{x})]\phi_t(\mathbf{0}) \quad (26a)$$

as $t \rightarrow \infty$ with \mathbf{x} fixed, and

$$\phi_t(\mathbf{0}) \sim ANc \sqrt{\frac{2}{\pi t^3}}, \quad d = 1, \quad (26b)$$

$$\phi_t(\mathbf{0}) \sim \frac{4\pi ANc}{t(\ln t)^2}, \quad d = 2, \quad (26c)$$

as $t \rightarrow \infty$, where the constant A is given by

$$A = -\phi_0(\mathbf{0}) + \frac{1}{c} \sum_{\mathbf{x}} \phi_0(\mathbf{x})[2Nc + \psi(\mathbf{x})]. \quad (26d)$$

For identity by descent,

$$A = \frac{v}{1-v} \sim \frac{1}{2u} \quad (26e)$$

as $u \rightarrow 0$.

In one dimension, the diffusion limit exists, and under the simplifying assumption (24), it leads to an explicit solution for $\phi_t(\mathbf{x})$ for every \mathbf{x} and t (NAGYLAKI 1974a, 1978b, 1986). Approximating this solution as $t \rightarrow \infty$ yields (23a, b) and, without the monotonicity assumption on $t\phi_t(\mathbf{x})$, (26a, b); in the diffusion limit, $\psi(\mathbf{x}) = x$ exactly and (26d) is replaced by an integral (NAGYLAKI 1974a, 1978b, 1986).

MALÉCOT confined himself to identity by descent in one dimension. He used generating functions and a Tauberian theorem to deduce (20a) and (23a, b) (MALÉCOT 1975); in later, unpublished research, he obtained (26a, b) with his methods (G. MALÉCOT, personal communication).

Equations 20 to 26 were derived in NAGYLAKI (1976a). For $u = 0$, however, the assumptions in NAGYLAKI (1976a) are stronger than the very weak ones—due to SAWYER (1976)—presented here. For $u > 0$ and identity by descent, (26) follows from SAWYER (1976). His outstanding paper contains powerful methods, interesting ideas, and other important results.

The most important biological conclusion from these results is that in the absence of mutation, the rate of loss of genetic variability in two dimensions is negligibly slow: (23c) shows that even if Nc were only 10, after 10^{500} generations the mean heterozygosity would still be about 0.11! If there is mutation, the rate of convergence to equilibrium is much faster; convergence is faster in one dimension than in two.

If $u = 0$, subject to (22), the results are spatially homogeneous and independent of the initial condition f_0 ; if $u > 0$, they depend on f_0 only through the constant A .

Under the assumptions made here, the spatial dependence is the same for $u = 0$ and $u > 0$. In the usual biological situation $Nc \gg 1$, so $\psi(x) \ll 2Nc$ unless $d = 1$ and x is at least of the same order as Nc . Therefore,

(23a) and (26a) reveal that the spatial dependence is sometimes negligible if $d = 1$ and often negligible if $d = 2$.

If part of the habitat is bounded, spatial homogeneity is lost and the analysis becomes much more difficult. The boundary may be either a barrier impenetrable to migration, or a point or line of contact with a region of extremely high population density or dispersal rate (a density-mobility boundary). For a semi-infinite linear habitat with either type of boundary, a complete analysis of the equilibrium has been obtained in the diffusion approximation (NAGYLAKI and BARCILON 1988).

SAWYER (1978) has studied migration models in a (topological) tree, which may describe some populations in river systems. SAWYER and FELSENSTEIN (1983) have investigated the important case of hierarchically clustered population.

Finite populations: If σ^2 is the typical variance for migration, then (16), (17), and (18) show that the habitat can be treated as infinite only if its typical linear dimension greatly exceeds $\sigma/(2\sqrt{u})$.

MALÉCOT (1951) was the first to formulate and analyze a model for a subdivided finite population. In his *circular stepping-stone model*, n demes, each of which comprises N individuals, form a closed loop; migration is homogeneous. This arrangement might be a mathematical idealization of an atoll; demes around a mountain, lake, or shore of an island; or colonies of amphibians or shallow-water organisms in a large, deep lake or around an island.

MALÉCOT (1951) derived an explicit formula for the probability of identity at equilibrium and deduced from it the limiting cases of panmixia and the unbounded, linear stepping-stone model (see also MALÉCOT 1965, 1975). Much later, MARUYAMA (1969, 1970a, b, c) rederived MALÉCOT's solution. Although theoretically useful (NAGYLAKI 1983), MALÉCOT's solution (a sum of n terms) is too complicated to yield much direct biological insight; for this, approximations are necessary. Approximation of the discrete-time, continuous-space model (NAGYLAKI 1974b) agrees with the more rigorous diffusion approximation (NAGYLAKI 1986), and this simple solution enables one to examine the expected heterozygosity, genetic diversity, and interdeme differentiation of gene frequencies at equilibrium (NAGYLAKI 1986).

MARUYAMA was the first to investigate the rate and pattern of convergence of the circular stepping-stone model. Positing symmetric nearest-neighbor migration and spatial homogeneity, he obtained the exact characteristic equation and found approximations for the eigenvalues and eigenvectors for both strong and weak migration (MARUYAMA 1970d). He confirmed his approximations for the maximal eigenvalue and eigenvector by a diffusion analysis (MARUYAMA 1971a, 1972a). Approximations for all the eigenvalues

and eigenvectors can be derived in the discrete-time, continuous-space model (NAGYLAKI 1974b); these agree with the diffusion limit and enable one to deduce the probability of identity for any spatially homogeneous initial condition (NAGYLAKI 1974b, 1986). MALÉCOT (1975) derived the approximations for the maximal eigenvalue directly from the general discrete model. By Theorem 2.4 and Remark 2.9 of BOUCHER and NAGYLAKI (1988), the assumption of spatial homogeneity does not affect the ultimate rate and pattern of convergence.

To study the effects of dimensionality, MARUYAMA (1969) introduced the model of an abstract *torus*, in which the colonies occupy the product space of d circles. Although he solved this model at equilibrium (MARUYAMA 1969, 1970c, d), his very complicated formula is useful only numerically. MARUYAMA (1972b) has also calculated the asymptotic rate of convergence in some numerical examples. MALÉCOT (1975) deduced the equilibrium solution in a more concise form and obtained some analytic approximations for the rate of convergence.

If the colonies are along a finite *line segment* (MARUYAMA 1970a, b, c, e), the loss of spatial homogeneity greatly increases the difficulty of the analysis. Therefore, even for the equilibrium with symmetric nearest-neighbor migration, MARUYAMA (1970a, b, c) was able to find only rough approximations. For both strong and weak symmetric migration, he obtained also approximations for the maximal eigenvalue and eigenvector (MARUYAMA 1970e, 1971a, 1972a). In the diffusion approximation, FLEMING and SU (1974) deduced explicit formulae for the equilibrium and for all the eigenvalues and eigenvectors.

Only rough approximations are available for a *rectangular habitat* (MARUYAMA 1970a, c, 1971b, 1972b). The general strong-migration limit applies, however, to all finite populations (NAGYLAKI 1980, 1983).

SAWYER and FELSENSTEIN (1983) have studied finite *hierarchically clustered populations*.

DISCUSSION

In this paper, an attempt was made to demonstrate that GUSTAVE MALÉCOT has contributed important and fruitful ideas, methods, models, and results that have permanently transformed theoretical population genetics. By 1948, he had rederived and extended in a lucid, convincing manner many of the classical results of FISHER and WRIGHT, thereby initiating the modern era in population genetics. The first major line of work in modern population genetics was MALÉCOT's formulation and analysis of the stepping-stone model. It was KIMURA who originated and greatly advanced many of the other important lines of modern research.

Why, then, is much of MALÉCOT's work known even now only to a small minority of population geneticists?

First, MALÉCOT usually wrote in French, whereas since FISHER, HALDANE, and WRIGHT, the predominant language of theoretical population genetics has been English. It was not until 1967 that he published a paper in English from which most of his work can be traced. Second, many of his important papers are in journals, such as the *Annals of the University of Lyon*, that are not widely distributed. Third, in most of his papers, MALÉCOT needed and used more mathematics than many population geneticists find palatable. His masterly 1948 book is his most frequently cited work not only because it was translated in 1969, but also because it is more elementary than his major papers.

But do these superficial observations suffice? A fourth point is that MALÉCOT is a theorist's theorist: although he was occasionally stimulated by data, his main interest clearly lay in the development of the theory itself. The desire to develop the theory as an intellectual subdiscipline consistent with known, reasonably idealized biological reality is frequently misperceived as mathematical motivation. It is inevitable and desirable that most theoretical effort should be centered on applications to specific evolutionary problems, to human genetics, and to animal and plant breeding. However, the physical analogy of quantum mechanics and field theory versus their applications to solid state, nuclear, and elementary particle physics demonstrates that symbiotic coevolution of theory and applications is optimal.

Fifth, much of MALÉCOT's research was stimulated by that of WRIGHT. Perhaps partly because of the immensity of WRIGHT's creative accomplishment and the importance and influence of his work (PROVINE 1986), the necessity of MALÉCOT's reformulations and reanalyses is frequently unrecognized. As shown above (and many other examples could be adduced), WRIGHT's formulations were not always clear or complete, his derivations often had logical gaps, and his approximations were sometimes unjustified. These observations refer not to WRIGHT's lack of rigor in the sense of the pure mathematician, for this type of rigor is usually absent even in less original scientific work, but rather to the fact that to a qualified, careful, critical reader who evaluates WRIGHT's work without appeal to external information, his analyses are often unconvincing and the validity of his results sometimes seems uncertain. It is eloquent testimony to both WRIGHT's deep intuition and his remarkable patience with checking special cases numerically (until the middle 1970s on an electromechanical calculator!) that his results, at least when properly restricted and interpreted, are almost invariably correct.

Finally, in modern population genetics, a mathematical model is usually studied as an independent, well-posed entity (*i.e.*, one with acceptable solutions, neither overdetermined nor underdetermined), based on clearly stated biological assumptions, whose analy-

sis may be guided but not replaced by extrinsic biological considerations. (The *interpretation* of the results should, of course, be biological and, as far as possible, intuitive.) Close reading of WRIGHT's work and extensive personal communication with him reveal that he rarely worked in this modern spirit. The first population geneticist to do so consistently was MALÉCOT.

WRIGHT, FISHER, and HALDANE drove many rough trails into the forest. MALÉCOT cleared, widened, and greatly extended some of these trails, significantly facilitating our exploration of the interior. Thus, his rôle in the transition from classical to modern population genetics is a crucial one, and much contemporary theoretical population genetics can be traced back to him, just as he and COTTERMAN taught us to trace the ancestry of genes.

GUSTAVE MALÉCOT's intellectual independence, enthusiasm, and generosity of spirit have been manifest in our extensive correspondence. I am much indebted to him not only for the assistance he thus provided, but also for inspiring my research with his own. I am very grateful to STEWART ETHIER, WARREN EWENS, MOTOO KIMURA, JERRE LEVY, STANLEY SAWYER, STEPHEN STIGLER, and SANDY ZABELL for perceptive comments on the manuscript. I thank MICHEL GILLOIS and ALBERT JACQUARD for useful information and MARC LAVENANT for help with translation. It is a pleasure to thank MITZI NAKATSUKA for careful, beautiful, and rapid typing. This work was supported by National Science Foundation grant BSR-8512844.

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