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Gustave Malécot, 1911–1998: Population Genetics Founding Father

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IN November 1998 we lost one of the most important scientists of this century, Gustave Malécot. He was, in the best sense of the words, a great man. His contributions to science and mathematics began 60 years ago and continued until his death. His contributions to mathematical population genetics were arguably the most profound of any. If we will admit a fourth member to the "fathers" of population genetics, the others being Sewall Wright, R. A. Fisher, and J. B. S. Haldane, it would surely have to be Gustave Malécot. It seems safe to say that it was Malécot who first formulated models of population genetics as stochastic processes, in the sense of the term today, for example, as Markov chains. Moreover, Malécot's mathematics were elegant and exact. They were also often compact and abstract. Recognition of Malécot's achievements has at most times been slow, its spread a branching trickle that continues today. His achievements deserve fuller recognition.

The purpose of this article is to give a personal perspective of the person of Gustave Malécot and a conceptual account of his contributions to the field of population genetics. Some essential biographical information is given, but more important are some insights he himself gave into his early career. I was privileged to have him share these insights with me over the past 5 years. There are also some mathematical formulations necessary to put his work into its conceptual as well as historical context. The structure is mostly chronological. At times this account borrows heavily from an important Perspectives article written by NAGYLAKI (1989), who presented many details of Malécot's mathematics, especially the diffusion approximation approaches and other key conceptual issues. Other important accounts of Malécot's work and life include a recent interview with BOCQUET-APPEL (1996) and a series of articles by GILLOIS (1996a,b,c, and unpublished manuscript).

As was discussed in detail by Nagylaki, and as Malécot related directly to me, Malécot's doctoral dissertation, guided by George Darmois and completed in 1939, focused on Fisher's pioneering 1918 article on the phenotypic covariance of relatives. Prior to this, in 1935, Malécot completed his mathematics degree at the École Normale Superieure in Paris (NAGYLAKI 1989). Malécot told me how he had spent 2 years reading and mastering (no doubt in rigorous mathematical detail) Fisher's article, at the Institut Henri Poincaré, also in Paris. NAGYLAKI (1989) describes how Malécot's dissertation work made Fisher's connection of biometry with Mendelian inheritance more rigorous and general. Specifically, Malécot adopted a conditional expectation approach that foreshadowed his stochastic process approach to other problems. Although he respected the fundamental connections that Fisher had made, Malécot also related to me how he had "found some problems" with the mathematics of Fisher's theory.

What followed from Malécot's dissertation is, to my thinking, probably the first of several reasons that Malécot's work never received the rapid and widespread recognition it deserved. Although Malécot was not at all bitter about his career, he related to me on numerous occasions various aspects of the historical context to his earliest works. He explained how the leading Darwinians at the Université de Paris and the Sorbonne dominated the intellectual scene in Paris and in France generally at that time. Malécot said that many of the French Darwinians were also communists or even Stalinists. This is despite the fact that today it may seem that Darwinism and Stalinism are mutually exclusive, given the history of the role of Lamarckianism and social construction in the Soviet Union and China. As a result, the French Darwinists would invite from Russia only sympathetic scientists, not people such as N. I. Vavilov. More to the point, many of the Parisian Darwinians viewed Malécot's models as "anti-Darwinian" because the models were stochastic processes.

The Parisian Darwinians considered Fisher's work to be the complete and unarguable truth in reconciling Mendelian genetics and Darwin's theory. Since Malécot found in FISHER's (1918) article and later in his 1930 book, *The Genetical Theory of Natural Selection*, much that was mathematically wrong, he incurred the displeasure of these evolutionists. Malécot related how in some steps

of Fisher's work there was confusion of statistical sampling theory with stochastic process theory. Malécot benefitted from a longer tradition in France of the measure-theoretic approach to probability theory, the standard that is widely accepted today.

Publicly questioning Fisher did not help the acceptance of Malécot's work in France. Malécot related that on occasion Fisher visited Parisian universities and gave talks; Malécot asked him some critical questions, and Fisher answered politely that he simply disagreed, instead of the more usual cutting answers Fisher reputedly gave to other questioners. Malécot told me that Fisher always treated him and his work with high respect, and vice versa. In addition, Malécot published in French, and as a result the English-speaking were late in recognizing the importance of his work.

It was also in the late 1930s that Malécot became intensely interested in Wright's work, which also dealt with covariances and variances among relatives. Malécot freely and fully acknowledged that most of his work was inspired by Wright's work and creative genius. Malécot made these early ideas of Wright mathematically rigorous, again applying what are today widely accepted interpretations of probability theory. Malécot did improve on Wright's work. For example, Wright developed the inbreeding coefficient in terms of path coefficients and partial regression (or correlation) coefficients. Path coefficients are still used today but are limited as statistical measures, in part because they assume linearity of genetic effects (NAGYLAKI 1989). Malécot, in contrast, considered the probabilities that two genes are descended from various ancestral genes, using Mendel's laws of inheritance. Such probabilities Malécot originally termed "Les coefficients de parenté" (MALÉCOT 1941, 1942). Later, when he studied models that included mutation and focused on the population level, some but not all of his results were stated in terms of what became known as probabilities of identity by descent (GILLOIS 1996a). Malécot used other French names for these probabilities, and Crow first used the English term identity by descent (CROW 1954). Coefficients of consanguinity allowed what has become the preferred textbook method for teaching the calculation of inbreeding coefficients, through the chain-counting method, for example. Chains of genetic descent, often at the gametic rather than zygotic ploidy level, and probabilities of identity by descent became the center of much of Malécot's work that followed over the next six decades. Their immediate importance was that they allowed application to general pedigrees, rather than the special cases that Wright used to illustrate his method (see NAGYLAKI 1989).

Wright certainly knew of Malécot and his work, but it is less clear how well Wright understood the mathematical subtleties of Malécot's early work. More importantly, Wright apparently did not recognize much of the biological importance of Malécot's work. Perhaps it is fair to say that Wright was most interested in treating biological variables in terms of sample statistics, whereas Malécot was most interested in treating them as entities in stochastic processes. Malécot described himself as more of a mathematician than a geneticist. WRIGHT's (*e.g.*, 1978) later compilations contain numerous citations of Malécot. Malécot always spoke glowingly about Wright. Malécot thought that, in contrast, the pre-World War II Parisian Darwinians had a "very low opinion" of Wright. Malécot had also met Haldane more than once and knew his work, but because most of Haldane's models were deterministic, they generally did not spark Malécot's interest in the same way as did those of Wright.

After receiving his Doctorat d'État in 1939 for what must be viewed as a brilliant dissertation on Fisher's work, Malécot taught mathematics from 1940 to 1942 at the Lycée (secondary school) de Saint-Étienne. Then an important mentor, Émile Borel appointed Malécot to a position as maître de conférence (similar to a university lecturer) at the Université de Montpellier (1942 to 1944; NAGYLAKI 1989). In 1945 he joined the faculty of the Université de Lyon, where he became a professor of applied mathematics (1946), a position he held until his retirement in 1981. Lyon being in fairly close proximity to Paris, Malécot also frequently "lectured on population genetics at the Institute of Statistics..." at the Université de Paris (NAGYLAKI 1989). During the time immediately following his dissertation, Malécot developed many seminal models, often focusing on extending his probabilistic genealogical framework to the population level. It is fair to say that Malécot had been branded for his critical work on Fisher. All of his published papers during this time were written in French. In addition to his work related to Fisher's 1918 article, during this period Malécot published works on coefficients of consanguinity (MALÉCOT 1941, 1942, 1946), inbreeding (MALÉCOT 1941, 1942), random mating in finite populations (MALÉCOT 1946), and "drift" of gene frequencies (MALÉCOT 1937, 1944, 1945; NAGYLAKI 1989; GILLOIS, unpublished manuscript).

During this period Malécot developed what he called "Les chaînes des kinship zygotique" (MALÉCOT 1942, 1973a), or zygotic kinship chains, which measured the probability that a certain chain of (diploid) ancestors occurred. This work was a quite complete and mathematically rigorous probability theory for pedigree analysis, based on the degrees of relatedness among individuals in a pedigree and their probabilities of occurring in the pedigree. This is a very important point, and it allowed Malécot to develop exact results when he turned his interest to the population level. Using these coefficients, he showed, for example, how to derive Wright's inbreeding coefficient, which he demonstrated was the sum of the different probabilities of the various zygotic kinship chains multiplied by the coefficient of consanguinities in the common ancestors. This was the basis for the chain-counting method used today. It is very

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interesting because, as discussed later, Malécot also developed a method that anticipated much of the now-popular coalescence probability theory by turning to an examination of "Les chaînes des kinship gametique." This change was important because at this time Malécot increasingly focused on population genetic processes, for many of which the pedigree is not fixed or known, but the frequencies (probabilities) of various types of mating types (*i.e.*, frequencies of matings based on the consanguinities) can be posited, and the analysis can be greatly simplified by considering sets of gametic genes rather than diploids. The method of gametic kinship chains was well developed in one of Malécot's papers in a fairly obscure French journal in 1973 (MALÉCOT 1973a), prior to Kingman's theory (*e.g.*, KINGMAN 1982). Malécot also continued extensions of his works on several other subjects. This is evident in good bibliographies of his articles from 1947 to 1970, for example, FELSENSTEIN (1981) and GILLOIS (unpublished manuscript).

In conversations, Malécot often expressed his admiration of Kolmogorov, who was largely responsible for the development of diffusion theory in the 1930s, including the forward equation for determining stationary distributions. Nonetheless, Malécot also realized that this approach, which is based on the first two moments, did not generally prove stationarity of the probability distribution (MALÉCOT 1945), and he deduced the forward equations by using a completely different approach (MALÉCOT 1948), as is described in detail by NAGYLAKI (1989). It should be noted that the problem goes away if the process is normally distributed. Malécot repeatedly rejected the normality assumption for population genetics, as it is clearly invalid if allele frequencies are near 0 or 1, and he emphasized the importance of "rare" alleles. He also rejected Fisher's approach using the arcsine square root transformation. Malécot did not use diffusion theory very much in his later work. Instead, particularly in his geographic models, he employed the Fourier and Laplace transforms.

The political situation of Malécot's science did not improve during the period from 1939 to 1948, but the important work he did was somewhat selectively compiled into his book, *Les Mathématiques de l'Hérédité*, published in 1948. The book was a landmark and became a classic text. It is somewhat difficult to penetrate, although much less so than his articles, and it was and remains a highly authoritative and definitive work that has influenced much of the theoretical population genetics field. Yet it did so over the following 5 decades in winding pathways through various leading theoreticians, paths too complicated to represent here. Recognition of the fundamental contributions represented in his book was not immediate nor quickly widespread. Malécot's book was made available to English readers in a translation by YERMANOS (1969). An introduction by Morton helped to widen its influence. I agree with Nagylaki that the translation contains numerous errors. I use parts of the translation in my graduate theoretical population genetics course, and I also found a number of errors that do not appear in Malécot's original text.

Malécot early on turned much of his attention to geographical genetics, which makes a great deal of sense in terms of genealogical approaches to population genetics. He had already considered a number of single population processes, such as the effects of unequal sex ratios on probabilities of identity by descent; these were among his first extensions from the pedigree to the population level. His earlier work on the inclusion of probabilities of individuals in pedigrees was logically extended to considerations of structured populations, which can be considered simply as groups that share genealogies. Patterns of migration among populations are analogous to pedigrees, whereas the degrees of relatedness and the sharing of gene genealogies among populations depends on spatial proximities. He worked on both discrete and continuous population models; both indicate shared genealogies and gene genealogies within groups of individuals owing to their spatial proximities, either because they are within the same discrete population or because they are proximal on a spatial continuum. Once again, Malécot freely admits he was inspired and provoked by the seminal works of WRIGHT (*e.g.*, 1931, 1943).

Today, the English-language literature still attributes the discrete population models and the general idea of spatial variation primarily to the work of KIMURA and WEISS (1964) and WEISS and KIMURA (1965). Malécot had much to say about this because, although he certainly was not bitter, he was concerned, since he had developed the discrete population version in a series of articles in the 1940s and 1950s (MALÉCOT 1949, 1950), and the continuous space version was well developed by 1948. These works were written in French and published in journals not readily accessible to English-speaking scientists. In 1955 Malécot went to the Cold Spring Harbor Symposium on Quantitative Biology and gave copies of his articles to Kimura. He also said that, of those he met, only Oscar Kempthorne talked with him about his—Malécot's—work in detail. Kimura, apparently independently, had only conceived of the idea of discrete populations as published in his 1953 note, which scarcely mentioned correlations or spatial patterns and did not develop analytical results; or, to put it graciously, the note was "...mais sans formalisation" (Malécot interview with BOCQUET-APPEL 1996), a perception also evident in Malécot's published comments on Kimura's paper presented at the symposium (MALÉCOT 1955). Kimura's 1953 note was of minor importance in comparison with what Malécot had developed, and it was not until the above-cited articles of KIMURA and WEISS (1964) and WEISS and KIMURA (1965) that Kimura had popularized the concept of spatial isolation by distance among discrete populations. Malécot said that

Kimura sent him cards each year, repeatedly telling Malécot that he had not used his work because he did not read French, but Malécot decided not to correspond. Although WEISS and KIMURA (1965) did vaguely cite Malécot's book, Kimura could have done more to elevate recognition of the more fundamental contributions Malécot made.

Most of Malécot's work on migration models—both continuous and discrete—focused on "homogeneous" migration, where migration rates were the same for both directions within a dimension; otherwise they were nearly completely general. The articles were always mathematically rigorous. The advantage of the homogeneous migration assumption is that it allows the Fourier transform to be used to obtain analytic results, and Malécot used it extensively together with Laplace transforms in time. He rarely used diffusion approximation, a method put to good use by many others, most notably Kimura and Nagylaki (*e.g.*, NAGYLAKI 1978, 1986). Malécot often said that his own formulations of recursions for the probability theory were "exact," and this certainly seems to be true. Next, he used the Fourier transform and its inverse (using a modified version of the residue theorem and contour integrals in the complex plane—the Bromwich-Wagner approach). Naturally, such methods can involve approximations in the final inversion steps. Malécot's expositions were always crystal clear in pointing out the steps where approximations were made. He studied systems and models, of isolation by distance, for example, that existed in one, two, or three spatial dimensions. Apart from the homogeneity assumption, migration models were in essence completely generalized, as opposed to what I term the strict stepping-stone model of Kimura, which posited migration only among nearest-neighbor populations. Thus, Malécot created the probabilistic basis for geographical and spatial population genetics, although there have been many important developments by others in more recent decades (a number of these are discussed by NAGYLAKI 1989).

Malécot's models were exact and had sweeping generality. They were formulated in terms of probabilities, denoted by $\phi_n(x, w)$, that pairs of genes (x and w, each being random samples of size one) present at time period n are identical by descent. The variables x and w may represent samples from two individuals or two populations with locations in whatever dimension space defined by x and w. Malécot set k to be the rate of mutation and l_{zx} as the rates of migration from z to x. Much of Malécot's work on this problem begins with the following general recursion equation (*e.g.*, MALÉCOT 1973a):

$$\phi_n(x, w) = (1 - k)^2 \left\{ \sum_z \sum_u l_{zx} l_{wu} \phi_{n-1}(z, u) + \sum_z l_{zx} l_{wz} \frac{1 - \phi_{n-1}(z, z)}{2N} \right\}. \quad (1)$$

The second term, which was neglected in Kimura's approach, Malécot considered very important. Malécot used the Laplace transform to determine the temporal dynamics and stationarity conditions and the Fourier transform to determine the isolation by distance form. Similar equations (sans mutation) obtain for recursions of the pairwise coalescence probabilities (MALÉCOT 1973a).

Kimura's models (KIMURA and WEISS 1964; WEISS and KIMURA 1965) were always in terms of the correlation or covariance in gene frequencies. It is a little-recognized fact that these models require the assumption that the gene frequencies in the migrants are exactly those in the population from which they arose. This may be reasonable as long as there are large numbers of propagules relative to the population size after regulation (*i.e.*, after genetic drift) that migrate, but it is not reasonable where the reproductive adults (as in many animals) migrate. This limitation can be offset by including stochastic migration effects that were not included in correlation models until my own work on the spatial time series models known as "space-time autoregressive moving average," or STARMA (EPPERSON 1993, 1994).

There is a common misconception that Malécot's geographical genetics models differed from Kimura's, in that Malécot did not consider correlations or covariances in gene frequencies. In fact, he developed, with all mathematical rigor, models of the spatial distribution of covariances in articles as early as 1950 (MALÉCOT 1950). He often used expected values of indicator variables for the allele state of genes in haplotypes to move from probabilities of identity by descent to covariances in allele frequencies (*e.g.*, MALÉCOT 1971). He used the Fourier transform and similar tools as in the models in terms of probabilities of identity by descent. These models were exact, following precisely and deductively from the model assumptions. Indeed, there is a subtle problem with Kimura's approach, and for that matter with all studies that built upon that approach, including BODMER and CAVALLI-SFORZA (1968) and my own work on STARMA models. Specifically, the model ignores the probability of consanguinity among multiple immigrant genes from the same source population, and this adds a small effect to the covariance recursion equations, for example, the second term in Equation 2 below. Malécot chided that Kimura's model was one for "economics not genetics." It is clear that this effect is unimportant over short time periods, but less clear what effect it may have on the stationary state. However, the remarkable generality of STARMA models, beyond Kimura or Malécot's, gives them value that more than compensates for the approximation assumption, depending on the system being modeled. Moreover, estimation and other statistical procedures are much more straightforward with the STARMA approach.

Early on, Malécot distinguished two types of covari-

ances of gene frequencies and also considered coefficients of kinship, or consanguinity, based on his probability theory. These were the *a priori* expected values and the conditional or *a posteriori* expected values, as used in Bayes's theorem. He also sometimes used expected values of indicator variables to obtain the a priori and conditional covariances for the same types of migration models as represented in Equation 1. This caused considerable confusion in attempts to measure the covariances (particularly for geographic analysis of genetic variation, in humans, for example). As discussed in more detail below, Malécot was rarely interested in estimation, and this probably did not help his work become more widely known.

The recursion equation analogous to Equation 1 is as follows, in terms of the *a priori* expected values of higher moments, *i.e.*, the *a priori* covariances in gene frequencies between two sites (MALÉCOT 1971):

$$\sigma_n(x, w) = (1 - k)^2 \left\{ \left(1 - \frac{\delta(w - x)}{2N}\right) \sum_z \sum_u l_{xz} l_{wu} \, \sigma_{n-1}(z, u) + \delta(w - x) \frac{(C - C^2)}{2N} \right\} \qquad (2)$$

where C is the equilibrium gene frequency and δ is Kronecker's delta. This formulation is quite different from the recursions for the expected values conditioned on knowing all of the gene frequencies in the populations in the previous generation, which are not displayed here. Moreover, Malécot did not assume that the third and higher moments were zero, and thus his results did not depend on the assumption of a binomial or normal distribution. Again, he usually used Fourier and Laplace transforms (MALÉCOT 1972) to extract exact and approximate analytic solutions. He also produced equations and analytic results in terms of probabilities on nonidentity by descent and heterozygosity and inbreeding coefficients (MALÉCOT 1973a).

It is also commonly misperceived that Malécot's models were for selectively neutral loci and, therefore, were often of little interest to evolutionary and ecological genetics. In fact, in most of his articles Malécot first developed models concentrating on the genealogical relations and derived results for neutral nonmutating loci, but later in each article he would introduce the "recall coefficient," which pulls the system toward some equilibrium. The recall coefficient (k) could represent mutation (reversible or infinite alleles), migration from outside the system, some forms of selection, or combinations of these factors.

Another important event occurred in the mid-1960s when Malécot was invited by J. Neyman to give a lecture at the Fifth Berkeley Symposium on Mathematical Statistics and Probability. The symposium gave important exposure to his work in the United States, since he published his proceedings paper in English (MALÉCOT 1967). Malécot's nature was very generous, and he told me he used this opportunity to cite Kimura "generously." As another facet of his personality, Malécot was very gracious to any fair critic. For example, he repeatedly told me that FELSENSTEIN's (1975) famous criticism regarding singularity in the continuous case with two spatial dimensions was correct and welcomed. He added that "Felsenstein is a critical deep thinker."

An important step in Malécot's recognition, and indeed in the blossoming of the field of geographical genetics, came at a remarkable symposium on the genetic structure of populations held at the University of Honolulu in 1972, to which Malécot was invited by Morton. Wright was honorary president of the symposium. The authors of the collective papers published in the Proceedings (see reference to MALÉCOT 1973b) read like a Who's Who list. Malécot also recounted his meeting with Wright in a detailed account in a recent interview with BOCQUET-APPEL (1996). It must have been a pivotal and extremely interesting symposium. The symposium proceedings include not only the papers presented, but also transcripts of frank and detailed follow-up discussions—sometimes debates—among many powerful minds in the area of geographical genetics.

Malécot had a long-standing and important relationship with Morton. Malécot was rarely interested in pursuing estimation and other aspects of developing statistical methods of analysis of data, even though he had a keen interest in biology. Morton and his colleagues were leaders in developing a variety of statistical measures and estimation methods, squarely based on the predicted values generated by Malécot's stochastic models. Morton cited Malécot's work profusely, and appropriately so. As Morton and colleagues were for decades at the center of geographical analysis of genetic variation, particularly for human populations, this helped a great deal to spread recognition of Malécot's work on geographic and spatial stochastic processes. MORTON's methods (*e.g.*, 1973a,b, 1982) largely focused on Malécot's models that were explicitly in terms of the conditional kinship or conditional covariance of gene frequencies. The connection of estimators to stochastic process parameters is difficult, particularly in complex spatial-temporal processes. The distinction between prior and posterior probabilities must be made, and much of this boils down to knowledge of the grand mean of a system. Confusion about these difficult-to-penetrate and often subtle distinctions probably did not aid in what could have been greater or perhaps deeper appreciation of Malécot's models by the researchers and their readers who utilized Morton's methods. Moreover, Malécot did not always agree with all of Morton's estimators, and again this is understandable given the difficulties. Importantly, it seems likely that these difficulties probably encouraged the development of other statistical methods that were less connected with stochastic processes and that mostly did not cite Malécot's work. Here it should be noted

that inbreeding coefficients within populations and F statistics can be tied to Malécot's models.

Malécot's theory of geographical and spatial genetic variation had fully blossomed by 1973. He had just finished a series of three articles (MALÉCOT 1971, 1972, 1973a) in French. The first two are very important and focus on the coefficients de parenté and covariances in gene frequencies. The third article (MALÉCOT 1973a) is perhaps of even more remarkable proportions. Not only did it explicitly anticipate pairwise coalescence, it also compiled some of his most elegant mathematical developments, primarily using various combinations of the Fourier and Laplace transforms and inversion methods. He developed, for example, elegant analytic formulations of isolation by distance, in terms of probabilities of identity by descent, for general migration models in homogeneous systems with either one or two spatial dimensions. The article is written at a very accessible level, albeit in French. He also developed an equation relating the probabilities of identity by descent to the probabilities of pairwise coalescence events, *i.e.*, "les chaînes de kinship gametique," 20 years before the same formulation was developed in the coalescence literature (*e.g.*, SLATKIN 1993). Yet it is remarkable how little Malécot's work is cited in this literature. However, Malécot's precedence on some points does not reduce the importance of the extensive new work in this area. The original coalescence theory developed by KINGMAN (1982) had aspects that were completely new, and much of coalescence literature actually deals with development of statistical methods of estimation. Nonetheless, once again important developments produced by Malécot are in danger of not receiving timely, widespread recognition.

The pinnacle of Malécot's work on subdivided populations is his article in 1975 (MALÉCOT 1975), which is written in English. It is a beautifully conceived and ordered distillation of geographic and spatial stochastic models of migration. It uses much that is in earlier articles, but also uses some new approaches. Malécot, as mathematicians often strive to do, distilled his theory and proofs for a large variety of models into their kernels, with heightened elegance. The article focuses mostly on probabilities of identity by descent, but also covers heterozygosity and probabilities of gametic kinship chains, or what could be called pairwise coalescence probabilities. It is also highly abstract, dense, and difficult to penetrate.

Malécot did not publish a great deal after he became Emeritus Professor of the Université de Lyon. After 1982 there was only one scientific manuscript, a remarkable paper, an unpublished manuscript submitted to Theoretical Population Biology in 1989 (G. MALÉCOT and T. NAGYLAKI, personal communications). It deals essentially with n-coalescence, whereby each one of the n genes is located at a different site in a "continuous" case or in different populations, and this approach differs from KINGMAN's (1982). The two models represent extreme forms; each is useful. Malécot's apparently would allow only one sampled gene per population, whereas it is well known that Kingman's model assumes the n genes are from a single population. Coalescence has become a very popular topic; basically it involves superimposing a mutation model (usually the infinite sites mutation model) onto probabilities of coalescences. The work that Kingman developed is of remarkable importance, yet it is important to note that Kingman's n-coalescent appears to force restricting consideration to rather simple processes where all subsets of sample genes can be treated as stochastically equivalent, because of the inherent complexity of genealogies. One of the most complicated models studied precisely is the mixed-mating system model (FU 1997), in which two groups, selfs and outcrosses, of genes are followed. Some experimental studies have used coalescence theory, for example, to construct gene genealogies for geographically distributed data, but ignore the fact that coalescences among groups of genes depend on the spatial proximities of the sets of populations represented.

Throughout most of his life, Malécot published alone. He consistently developed his own central thesis and produced a highly personalized body of work. He fully knew the importance of his work, but he was also modest. His interest in publication was solely to contribute the important and fundamental results that stemmed from his central thesis. He was interested only in quality contributions that furthered our knowledge of how stochastic processes modeled and explained biology. Malécot was not interested in fame.

There is a final issue, that regarding data generated by modern molecular methods. Malécot was among the first to consider models in which mutations are always to novel alleles; this is the mutation model basis for the infinite alleles model or infinitely many alleles model (IAM; CROW 1989; GILLOIS, unpublished manuscript). This is remarkable, because 50 years ago few would agree it was ever a realistic model in biology. Another very important mutation model is the "infinite sites model" (ISM), which uses additional information in DNA sequence data, for example. Malécot's precedent-setting work on pairwise coalescence probabilities should be recognized, since many coalescence models either start out or end up equivalent to pairwise coalescence. Also, although the ISM may use additional information—if there is any—for DNA sequence data, the ISM is not required for some analyses of sequence data. Malécot's theory in terms of probabilities of identity by descent can utilize sequence data and the ISM, in which case they represent probabilities of no mutations at any site, *i.e.*, no segregating sites, along nonrecombining segments. In addition, it seems doubtful that models of geographic processes can incorporate all information on segregating sites because they are simply too complex, or if they are formulated, various additional approximations and assumptions must be made—not that

these should be discouraged, but they should not be presumed to be superior. Finally, it is questionable how often there is substantial additional information using the ISM rather than the IAM. I know of only two results on this matter. EWENS (1974) found the conditions under which the ISM *may* have more information than the IAM for a single population model of genetic drift and noted that for most species these conditions would not be met. Second, BARTON and WILSON (1995) showed that for the isolation by distance model for continuous populations, most of the information in the spatial pattern was between individuals (and their genes) who had very recent common ancestors (coalescences). It is unlikely that these differed by one and certainly not by more than one mutation, and hence probabilities of identity by descent should capture most of the spatial information.

Malécot's students included Gillois, Jacquard, Lalouel, Marchand, Picard, and Serant (NAGYLAKI 1989). They have made various important advances in theoretical populations, physical anthropology, and other subjects. Very recently, the youngest generation of French population geneticists had the opportunity to meet Malécot, when he gave a featured lecture at the 1998 annual Réunion du Groupé de Biologie et Génétique des Populations, in Lille, France. He received a standing ovation.

Perhaps the best insight I can give into Gustave Malécot's character comes from my own experience. I had studied Malécot's work for many years and viewed him as a great mathematician and someone who always "does things right." Although his articles are difficult to penetrate, they are almost always not only exact, but also amazingly free of errors and typos. A little more than 5 years ago, I wrote to him and sent him some of my publications. I had been "recommended" to him in the proper manner of his era, by Michel Gillois, a former student of Malécot, whom I met in 1993. The work of mine that I sent to him was twofold: theoretical approaches (STARMA) that I had developed and papers on experimental studies of population genetic surveys, both of which stimulated his interest.

We met for the first time the next summer (1994) at his house in a small village in southern France. The directions were complicated. When I knew I was within a few hundred meters of his home, but still could not find it, I stopped and asked some neighbors where Professor Malécot's house was. They claimed that there was no professor in the small village. After several rounds, the neighbor finally exclaimed "Oh, Malécot, that is the old guy who rides the bike." His village did not even know they had an eminent mathematician in their midst. This was typical of his personal modesty. When I reached his home, he was standing in the rain, waiting, much to my chagrin. I hoped that he had not been waiting there during the storm of 1-centimeter hail 10 minutes earlier.

Later that day when I left, he walked along to direct my driving along the muddy roads that by this time also served as creeks. Malécot was amazingly robust. He was a warm and caring person. We talked all that day, mostly in English. I was astonished that, whatever population genetics issue came up, he immediately would find such and such equation that might be in one of his papers from 50 years earlier scattered in piles on his tables. It was a blessing to have known him, and I am extremely honored to have worked with him. The work we were doing together was destined to be the highlight of my professional life. He was a great man, in the truest sense, and an inspiration.

After this meeting we traded ideas via letters, and within the next year Malécot invited me to coauthor a book as well as some technical papers. The development of our book was primarily in the form of letters that we exchanged frequently over the following years. The letters were mostly dense mathematical formulations. We were nearly finished collating the materials when he died. I will finish the book on my own with him as coauthor. Malécot's era and my "publish or perish" era are quite different. He repeatedly rebuked me, "Why are you in such a hurry [to finish the book]—we have our whole lives in front of us." I traveled to France every year to spend time with Gustave and to further our collaboration. He was a beloved friend and mentor. I felt closer than ever to him during my stay with him last summer. He was as healthy as ever, and I am told he was taking bike rides of up to 50 kilometers.

Gustave Malécot was born December 28, 1911, and grew up in L'Horme, a small village near St. Étienne in the departmente de la Loire, the son of a Protestant "ingenieur en chef des mines." In 1938 he married Suzanne Eyraud, who passed away in 1983; he remarried in 1986, to Emilienne LaSalle. He enjoyed skiing, hiking, and bicycling, which he continued throughout his life. Undoubtedly this contributed to his physical robustness. In the years I knew him, he and Emilienne greatly enjoyed visiting their large family. His intellectual activities are evident. He had since childhood an interest in flora, geology, and natural history, and he developed an early specialization in mathematics. He did not believe in determinism, and his personal philosophy was humanist.

Gustave Malécot died suddenly, and it is comforting to know that he probably suffered as little as possible. His wife Emilienne told me that he had been outside capturing the day's last rays of sun, as he was wont to do. He went inside to his work desk, no doubt working on population genetics theory. A short time later Emilienne found him. In addition to Emilienne, Gustave Malécot is survived by 4 children (Christian, Bernard, Jean Luc, and Isabelle) and 13 grandchildren.

Malécot's work never received a fraction of its deserved recognition. Nonetheless, he has received a number of awards: 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; NAGYLAKI 1989), all of which honor his memory.

If we do not admit Gustave Malécot as a fourth founding father of population genetics, he must be its first-born.

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