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Motoo Kimura (1924–1994)

Motoo Kimura, protagonist of the neutral theory of molecular evolution, died on November 13, 1994, on his 70th birthday anniversary. For the past two years, he had suffered from amyotrophic lateral sclerosis and was progressively weakening. Just before he died, his hands and arms were virtually numb, though he was mentally alert.

Kimura was born as the first son of a businessman in Okazaki, Japan. His father loved flowers and raised ornamental plants at home. Young Kimura was fascinated with their beauty and decided to become a botanist, which meant a plant taxonomist at that time. He collected and kept a large number of plant specimens folded between newspaper sheets. In school, however, he found himself talented in mathematics and wondered whether plant taxonomy was worth spending his entire life on. He then burned the whole collection of his precious specimens but still wanted to study plant cytogenetics, which was very popular in Japan in the 1940s because of the influence of the famous cytogeneticist, Professor Hitoshi Kihara.

In 1944, he entered Kyoto University to study cytogenetics, and after graduation from the university, he worked as a research assistant in the laboratory of Professor Kihara, where active research on cytogenetics was going on. Curiously, however, he gradually lost his interest in cytogenetics and started to study mathematical population genetics. This was primarily due to the influence of his cousin-in-law, Professor Matsui Tamura, a mathematical physicist working on quantum mechanics in the physics department of the same university. During and just after World War II, when Kimura was a university student, food was scarce, and almost every Sunday he visited Tamura's home to alleviate his hunger. In these Sunday visits, he discussed various topics in natural science with Tamura and learned the world of theoretical physics. He admired the rigorous mathematical approach used in physics and thought that biology should eventually be studied in mathematical terms as in the case of physics. While he was working in Kihara's laboratory, he then realized that there was an area of biology in which mathematics was already being used; it was theoretical population genetics. Once he found this area of biology, his determination to become a population geneticist never changed.

Obviously, he needed mathematical training to become a good population geneticist. However, he had a natural talent in mathematics, so he could study it by just reading mathematics textbooks. Therefore, his mathematics was largely self-taught, though he took several courses while he was a graduate student at the University of Wisconsin. I heard that when he was a research assistant in Kihara's laboratory, he spent most of his time reading mathematics or statistics books. Kihara was aware of Kimura's ability and determination, so he never complained about Kimura's devotion to his own study. Only his friends did. Kimura was an extraordinary person from this time. He was a man of determination and could endure enormous hardship to achieve his goal. At that time, Japanese libraries were very poor because of World War II, and only the main library of the University of Tokyo had a fairly good col-

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lection of new foreign journals and books. Kimura took several trips to the library to copy by hand recent papers including those of Sewall Wright. Tokyo is about 520 kilometers away from Kyoto, and it took him nearly one day to get there by trains.

In 1949, he obtained a research position in the newly established National Institute of Genetics in Mishima through Kihara's arrangement. He stayed there the rest of his life except for several years he spent abroad. When Kimura moved to Mishima, the building of the institute was a crude wooden structure previously used for the administration of a war time airplane factory. In his memoir, Kimura (1985, p. 467) later wrote, "Almost no scientific literature, let alone new foreign journals, was available, and we had to go either to Tokyo or to Kyoto if we wanted to read them. . . . I felt my life was lonely in Mishima, and I spent most of my time reading papers on mathematical population genetics and also studying mathematics and probability theory from newly published textbooks written in Japanese." Of course, this institute was later to become one of the most distinguished research institutes in Japan largely because of Kimura's reputation, and the institute is now housed in many modern buildings.

Kimura's research during his early days in Mishima was concentrated on the stochastic theory of population genetics. He was particularly interested in the debate between R. A. Fisher and Sewall Wright concerning the importance of random genetic drift in evolution. Fisher maintained that genetic drift is unimportant in natural populations because the population size is usually very large and that a more important factor would be fluctuation of selection coefficient. Kimura studied Fisher's suggestion, developing a mathematical model based on the heat conduction equation in physics, and clarified the relationship between the effects of genetic drift and random fluctuation of selection coefficient. He later wrote a paper on this subject, and the paper was lavishly praised by Wright and published in *Genetics* (Kimura 1954). This was the first of his papers to be published in western journals. During the first four years in Mishima, he also studied the complete process of pure random genetic drift in a finite population and a stepping stone model of migration. However, these studies were incomplete, and the final results were published only after he worked further on them in the United States.

In 1953, Kimura received a fellowship to study in the United States and registered as a graduate student at Iowa State University. He originally intended to study under Wright at the University of Chicago. However, Wright was about to retire from Chicago and suggested that Kimura should study under the direction of J. L. Lush, who was active in the theoretical study of quantitative genetics. However, Kimura was dissatisfied with the research program at Iowa and later transferred to the University of Wisconsin to study under James Crow. In 1954, Wright also moved to Wisconsin after his retirement at Chicago, so that Kimura was finally able to study with Wright as well as with Crow. In June 1956, he received his Ph.D., majoring in genetics and minoring in mathematics.

In his 1985 memoir, Kimura wrote (p. 474), "Looking back, I think that the two years of study in Madison represents one of the most productive periods in my scientific career and served as a launching platform for my subsequent activity as a scientist." Indeed, he wrote a series of highly original papers during the two years and published them in high-profile journals such as *PNAS, Cold Spring Harbor Symposium Volume, Journal of Applied Probability,* and so forth. He rapidly became a world leader in the area of mathematical population genetics and was regarded as a successor to Fisher, Wright, and J. B. S. Haldane.

After returning to Japan, he continued to be productive but again had to work alone. His colleagues in Mishima did not seem to have appreciated his highly mathematical studies, though Professor Taku Komai, a noted evolutionist in Japan, always encouraged him to continue his mathematical work. In 1960, he published a textbook entitled *Outlines of Population Genetics* in Japanese. Probably it was the most advanced textbook on population genetics in the world at that time. Unfortunately, most population geneticists in Japan were experimentalists, and the number of readers who understood the entire book must have been very small. Nevertheless, this book stimulated a number of young geneticists to study mathematical population genetics. This book was also a forerunner of Crow and Kimura's (1970) more formal textbook, *An Introduction to Population Genetics Theory.*

It is well known that Kimura collaborated with Crow extensively, and this collaboration was very productive. They wrote many important papers such as "The Number of Alleles That Can Be Maintained in a Finite Population" (Kimura and Crow 1964), and so forth. However, most of his theoretical papers were single authored. As he established himself, he also collaborated with his younger colleagues, Takeo Maruyama, Tomoko Ohta, and Naoyuki Takahata. Because of the high level of research activity of Kimura and his collaborators, Mishima became a world center for theoretical population genetics in the 1970s. Since most of Kimura's mathematical papers have recently been reprinted by the University of Chicago Press with Takahata's editorial comments (Kimura 1994), I shall not discuss the work in detail.

Kimura's studies were not confined to theoretical population genetics; his contribution to the study of molecular evolution was also highly significant. He was the first to relate the rate of amino acid substitution to the probability of fixation of mutant alleles in populations (Kimura 1968*a*), the first to formulate the relationship between the rate of amino acid substitution and the level of average heterozygosity (Kimura 1968*b*), and the first to study the mean and variance of the time for a new mutant allele to be fixed in the population (Kimura and Ohta 1969). The latter time is, of course, the same as the time (coalescence time) of all genes in the population to converge to a single ancestral gene (Tajima 1983), a subject which has become popular in recent years. His two-parameter model of nucleotide substitution (Kimura 1980) is one of the most often used mathematical models in molecular evolution.

However, the most significant contribution is his proposal that most nucleotide substitutions that occur in the evolutionary process are the results of random fixation of neutral or nearly neutral mutations and that most molecular variation observed in the present population merely represents a phase of long-term molecular evolution (Kimura 1968*a*, 1968*b*). This view was so foreign to most evolutionists at that time that severe criticisms were raised against it. It was the time when neo-Darwinism had reached its height, and most evolutionists believed that gene substitution could not occur in large natural populations without the aid of natural selection. Some geneticists (e.g., Reed 1974) argued that since neutral theory requires identical fitness of the three or more genotypes at each polymorphic locus, its likelihood is vanishingly small. This argument, of course, missed the essential point of Kimura's hypothesis, because a pair of alleles are known to behave as though they are neutral if the selection coefficient of an allele relative to the other is less than the inverse of population size. However, there were other criticisms that were more substantive, and Kimura had to defend his theory from these criticisms. Since there were so many oppositions, the defense required his full energy. Fortunately, the neutral theory was testable, and it generated many experimental and theoretical works from both the neutralist and selectionist camps. In retrospect, about one decade from 1968 was one of the most exciting periods of research in the history of evolutionary biology, though it also polarized researchers. However, as DNA sequence data became available, it was clear that there is a large amount of genetic variation whose destiny is determined largely by random genetic drift. In 1983, he summarized the research on this subject in his book *The Neutral Theory of Molecular Evolution*. By this time, the neutral theory was largely accepted, so he was quite confident.

Historically, the idea that neutral mutations are prevalent was not new and had been conceived by a number of authors before Kimura, notably by the early post-Mendelian evolutionist Thomas Morgan (1932) with respect to morphological characters and by Kimura's contemporaries such as Freese (1962), Sueoka (1962), Robertson (1967), and Crow (1968) with respect to protein molecules. King and Jukes (1969) also independently wrote an influential paper with a title of "Non-Darwinian Evolution." However, it was largely Kimura who gave a theoretical foundation of neutral theory and convinced a large fraction of evolutionists of the tenability of the theory.

The controversy over the neutral theory was tainted with many misunderstandings, because most biologists were not well acquainted with the stochastic theory of population genetics on which the theory was based. Kimura was not always kind to explain the detail of his theory to biologists but rather often counterattacked them without the realization that this would deter the acceptance of the theory. He was critical of population geneticists who were not aware of the stochastic theory or of the latest developments in molecular biology. He was amazingly well acquainted with new developments of molecular biology, though he was primarily a theoretician. He also hated rhetorical arguments which were not based on facts or mathematical deduction. Among his close friends, however, he was a kind person. He helped many of his junior colleagues to study population genetics in the United States.

At any rate, it is unquestionable that he made a great contribution to the study of population genetics and evolution. He set out his goal at his early age and achieved it. Without his contribution, the study of molecular evolution might have been delayed considerably. He (and Richard Dickerson) established the rule that the rate of amino acid substitution is usually lower in a gene or parts of genes with an important function. Molecular biologists now often use this rule in their homology search, though they may not know how the rule was established. In the early 1970s, it was common for many evolutionists to argue that a high rate of amino acid or nucleotide substitution is an indication of positive Darwinian selection, and thus the gene or gene region with a high rate is biologically important. We now know that this occurs only in exceptional cases such as the antigen recognition site of major histocompatibility complex genes. It should be noted that the validity of neutral theory for amino acid substitutions is still being debated, but no one seems to doubt the importance of stochastic elements in molecular evolution any more.

For his contribution, Kimura was awarded many honors. A list of his prizes and awards include Genetics Society of Japan Prize, 1959; Weldon Prize, Oxford University, 1965; Japan Academy Prize, 1968; Japan Society of Human Genetics Prize, 1970; Foreign member, National Academy of Sciences of the U.S.A., 1973;

Japanese Order of Culture (Emperor's Medal), 1976; Chevalier de L'Ordre National du Mérite, 1986; Asahi Shimbun Prize, 1987; John J. Carty Award, National Academy of Sciences of the U.S.A., 1987; honorary member, Genetical Society of Great Britain, 1987; International Prize for Biology, 1988; Darwin Medal, Royal Society, 1992; foreign member, Royal Society, 1993. He also received honorary degrees from the Universities of Chicago and Wisconsin.

He was an atheist, and according to his wishes his memorial service was held at his home without affiliation with any religious groups. I heard that about 300 people gathered from various parts of Japan to pay their last tributes to him. He is undoubtedly the greatest evolutionist Japan has ever produced.

MASATOSHI NEI
Institute of Molecular Evolutionary Genetics
Department of Biology
Pennsylvania State University
University Park, Pennsylvania 16802

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