

Western geneticists 'discover' Kimura

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Herman J. Muller won the Nobel prize for physiology or medicine in 1946 for his work on the effects of radiation on the production of mutations in animals. In 1951 he was probably the best-known geneticist in the world. He spoke widely for cultural and academic freedom, and the importance of science. The Committee for Cultural Freedom sponsored Muller's visits to India and Japan in April 1951. He spoke to large audiences in both countries. Muller's visit to Japan was a cultural event of high order, and well described by the English version of the *Annual Report of the National Institute of Genetics* for 1951 (No. 2, 1951, pp. 2, 3):

Among the large number of visitors was Prof. H. J. MULLER of Indiana University. Prof. MULLER spent a week from April 8 to 15 in Japan on his way back from India to the States. After an extremely busy two-and-half day program in Tokyo, being received in audience by the Emperor, attending a welcome party sponsored by the Japan Academy, delivering a public lecture to a large audience and visiting Tokyo University and the Sericulture Experiment Institution, he came to Misima on the 11th at about 10 o'clock in the morning. He heard reports of four geneticists from outside the Institute on recent outcomes of their studies. He next gave a lecture on recent advances in genetics to an audience which consisted of members of the Institute and many other biologists who had come to hear the well-known geneticist from all parts of Japan. He then went around the Institute and inspected the work of the members. In the evening he left Misima, and went to Atami, where he dined with the five senior members of the Institute [picture of Muller with Schull, Oguma (Director of the Institute), Komai, Tanaka, Kihara, and Sinotô]. He took a night train from Atami to Hiroshima with Drs. W. J. SHULL of A.B.C.C., KIHARA, and KOMAI. After inspecting the work in progress at the A.B.C.C. [Atomic Bomb Casualty Commission in Hiroshima] and giving a lecture at Hiroshima University, he stopped over at Kyoto on his way back, and gave another lecture in Kyoto University. On the whole, Dr. MULLER'S visit was highly beneficial not only to the Institute, but also to genetics and biology in Japan at large.

Most of Muller's time at the National Institute of Genetics (NIG) for discussion went to the director and department heads. But each research member had a chance to speak briefly with Muller.

Motoo Kimura found Muller's lecture difficult to understand. Muller spoke rapidly and Kimura's understanding of spoken English was weak. When Kimura had the brief chance to explain his work to Muller, he tried to tell Muller how he was going to help settle the argument between Sewall Wright and R. A. Fisher over random genetic drift using the Kolmogorov forward equation, used by physicists to model diffusion of gases and other phenomena. Kimura had just invented this possibility and he was very excited about the work, and hoped that Muller would respond with similar excitement.

Muller understood only that Kimura was trying to improve upon Wright and Fisher, and was immediately skeptical that this young Japanese geneticist could improve upon the greatest population geneticists in the world. Wright was also Muller's personal friend. Muller admired him beyond any other theoretical geneticist. Tanaka tried to help Muller to understand Kimura better, but with little success. Muller apparently completely forgot about this meeting with Kimura.

Four years later, however, Kimura was introduced again to Muller by James F. Crow at a meeting of geneticists at the Brookhaven National Laboratory. Crow described Kimura in glowing terms as the stunning theoretical population geneticist who had shortly before been praised by Sewall Wright in front of a large audience at the 1955 Cold Spring Harbor Symposium on Quantitative Biology. This time Muller was indeed impressed and began a friendship with Kimura that lasted until Muller's death in April 1967. Kimura always described Muller as the one who strongly encouraged him to direct his attention to molecular biology, and thus to the theory of neutral molecular evolution, which Kimura developed less than six months after Muller died. But in 1951 Muller was not at all impressed by Kimura.

Kimura's accomplishments by 1951

What Muller could not understand is how accomplished Kimura was at the time they met, nor how much promise he showed in mathematical population genetics. Although Kimura was in the Department of Cytology at NIG, in the previous year he had published not only three papers on chromosome substitution between species and recombination of chromosome segments under self-fertilization but also a paper on Sewall Wright's specialty, the effects of random fluctuations of selective rate on the distribution of gene frequencies in natural populations.

In addition, in 1950, Kimura published two papers, both in Japanese, summarizing mathematical genetics (eight pages) and mathematical population genetics (52 pages, all references in *NIG Annual Report # 1*). For about five years Kimura had voraciously read the technical papers in these fields, often laboriously copying the papers out by hand in full in his very many notebooks. He also kept other notebooks with his own ideas. He may have been self-educated in mathematical population genetics, but he was already very accomplished.

Muller, however, may perhaps be excused for this incident. Muller had just come from a meeting with the Emperor, he was on a very strenuous and tight schedule, he could not understand Kimura's English very well, and perhaps most important of all, he could not understand Kimura's attempt to tell him how complex diffusion equations could quantify more precisely the effects of random drift upon distribution of gene frequencies in populations. Nor could Kimura hand him a reprint on this subject—that was because Kimura had just discovered the approach he was trying to explain to Muller. Kimura had only shortly before discovered the forward and backward Kolmogorov diffusion equations in a book by K. Kunisawa, *Modern Probability Theory* (Kunisawa 1951). The implications of the Kolmogorov equations were very exciting to Kimura, but hard to explain to others.

Reactions of Japanese biologists to Kimura's population genetics

In 1951 population genetics did not exist in Japan, except for Kimura. Although he had some real support from Kihara and Komai, still the general reaction of biologists was

rather negative. On 12 October 1951 Kimura delivered a paper in Hiroshima for the annual meeting of the Genetics Society of Japan. He prepared three large handwritten pages presenting his ideas about random drift and the distribution of gene frequencies using the Kolmogorov forward equation applied to two loci (copies available in the Kimura Papers). Kimura mimeographed the pages and handed them out to the audience. The audience, however, still could not follow his work and Kimura recalled that the reaction was mostly negative—why try to turn biology into mathematics?

He gave essentially the same talk at a branch meeting of the Genetics Society of Japan near Tokyo on 18 November. The reaction of the audience came in the review of the meeting in the popular journal *Eden* (Heredity). In the edition of March 1952 the editorial stated that Kimura's talk had no biology in it, no organisms at all, just acrobatic mathematics. The distinguished biologists in the audience could understand the sleeping talk of *Drosophila* better than they could Kimura.

Kimura was upset by this negative reaction. His dream was to go to the USA and study mathematical population genetics with Sewall Wright. He received so little support for his work in Japan. Komai was also concerned about Kimura and his work. Komai was very familiar with Western interests in mathematical population genetics, and knew that Kimura would find a much deeper welcome there and also help in his studies. But how could Kimura come to the attention of Western population geneticists? The meeting with Muller had been a failure.

ABCC and Kimura

The October 1951 meeting of the Genetics Society of Japan in Hiroshima would have been a perfect occasion for the geneticists in the Atom Bomb Casualty Commission (ABCC) to hear and meet Kimura and to see first hand his exciting new work in theoretical population genetics. Except, of course, they did not speak or understand enough Japanese to follow what Kimura was saying or to read his handout. No Westerners at all came to this meeting (judging from the group picture).

In November, however, NIG published its first *Annual Report*, for 1950 (the annual report for any given year is actually published in the year following). Here were five summary papers by Kimura and citations of his other papers of 1950. The *Annual Report* was certainly sent to the ABCC but still the ABCC showed no recognition that Kimura's work existed.

Then, in the spring of 1952, Newton Morton came to ABCC. Morton had been a student of James F. Crow at the University of Wisconsin. Crow was familiar with all of classical population genetics, the work of Fisher, Haldane, Wright, Malécot, and virtually all others. He was an inspiring teacher. For his part, Morton was a brash and self-confident young man. While he was quick to criticize the shortcomings of others, there was little to criticize about Morton's quick mind and early accomplishments in population genetics.

In September and October of 1952 Morton attended three scientific meetings, mostly as a way of visiting places in Japan he had never yet seen. The second of these was the 24th annual meeting of the Genetics Society of Japan, held at Niigata University on the Sea of Japan coast almost directly north of Tokyo, during 8–10 October 1952. Morton recalls that it was probably Kihara who introduced him to Kimura. Though Kimura spoke rather slowly in English, Morton quickly discovered that he was an innovative theoretical population geneticist. Kimura had with him the newly published *Annual*

Report for 1951 (published on 5 October 1952), which included several more abstracts of his work on theoretical population genetics. Morton was genuinely surprised to find this talented population geneticist in Japan, and described him in our interview as 'brilliant and exceptional' and 'extraordinary'. Morton was the only Westerner attending the conference. He did not speak Japanese but his wife, a Japanese Hawaiian, helped to interpret, and of course many of the Japanese researchers spoke English. Morton and Kimura are both clearly visible in the group photograph reproduced in the proceedings of the conference.

Kimura explained his use of the Kolmogorov forward equation to address the question of random fluctuation of selection intensities. This particularly impressed Morton. Then Morton started to explain his work with Dr Crow about 'effective population size', N , often called 'population number' at that time. Effective population size was a central issue in Wright's conception of evolution in nature. Essentially, effective population size was a quantification of the breeding potential of the population, but more than that was a measure of how much random drift one might expect in the population. Smaller the N , greater the random drift. One of Wright's arguments against Fisher and Ford (1947) was that the effective population size was smaller than they had calculated, so the observed fluctuations in allele frequencies might be due to random drift.

Kimura also had recognized the importance of effective population size and had written a paper on this that appeared in the *Annual Report* for 1951. Morton was amazed that Kimura, completely self-taught, had some deeper insights on the question of effective size than Morton and Crow working together. And was it possible that Kimura was using more powerful mathematics than Wright himself to solve long-standing problems that had remained intractable to Wright and to all other Western population geneticists? At the same time Morton discovered that Kimura had no knowledge of Malécot, who had revolutionized the quantitative understanding of inbreeding. So Morton had something important to offer Kimura as well. This was a helpful interchange to both.

Morton wrote to Crow the following week:

Am also sending with the data the second annual report of the National Institute of Genetics. Pages 57–61 have interesting abstracts on effective number and random extinction. The first annual report has an article on variable selection coefficients—I don't have an extra copy, but you can probably obtain one. I met Dr. Kimura [Kimura actually had no doctorate at this time, though Morton naturally assumed he did] last week at a meeting of the Genetics Society of Japan and arranged to send him your papers, my thesis, Malécot (which is now back in print), and a copy of this letter. He is considerably interested in population number and with his mathematical background should be able to make more constructive comments than I can.
[Morton to Crow, 17 October 1952]

A few days later Morton wrote to Kimura (Morton to Kimura, 21 October 1952), following up on their meeting:

I am forwarding several manuscripts on population number and genetic drift, written in the following order:

Les mathématiques de l'hérédité	(Malécot)
Influence of population size on neutral genes	(Malécot)
Population number and genetic drift	(Morton)

Correspondence on population number [Crow has copies]
Effective population number (Crow)
Population number and genetic drift (Crow)

The titles of the papers of Morton and Crow immediately show that they were working very closely to problems on which Kimura had been making great progress by using the diffusion approach. Morton's letter was primarily an analysis of Malécot, Wright and Crow on population number, all by way of asking Kimura for his comments. Morton's letter ended: 'As you will observe, my mathematics is quite superficial, and I believe you may be able to settle some of these problems where I cannot. I will be very much interested in any comments you may have on these or other points touched on in the manuscripts.' Clearly Morton was deeply impressed by this young, self-trained Japanese population geneticist.

Once the astonishing discovery of the significance of Kimura's work on population genetics was understood at ABCC, things happened quickly. In early November Harold H. Plough, a well-known and highly respected geneticist then working for the Atomic Energy Commission (he had for many years been a professor at Amherst), visited ABCC in Hiroshima for three weeks to evaluate the ongoing gathering and analysis of data. On 11 November Plough went to NIG with Duncan McDonald, a geneticist with ABCC. I suspect that one important reason Komai and Kihara issued the invitation was to encourage Plough and McDonald to help Kimura get to the USA. Already alerted by Morton's very favourable impression of Kimura's work in population genetics, Plough and McDonald were impressed anew in meeting and talking with him. They understood that Kimura was self-taught in mathematics and population genetics, yet had accomplished so much. They also understood that there was no way for Kimura to further his education in this field in Japan.

McDonald decided to do all within his power to provide the opportunity for Kimura to go to the United States and study population genetics there, preferably with Sewall Wright. This certainly would be a dream come true for Kimura. On 3 December McDonald sent letters explaining Kimura's situation to both Jay L. Lush of Iowa State University and Sewall Wright:

In our work here in Japan, we meet most of the Japanese geneticists, either at meetings of the Genetics Society of Japan, or during visits to the various Universities. Amongst the younger geneticists, one, Moto KIMURA, stands out, would be exceptional anywhere. The enclosed series of reprints indicate the nature and calibre of his work, and the list of publications, the volume of his work, rather phenomenal for a man only 28 years old. I am not qualified to follow the details of his mathematical developments; but you will be able to do that from the reprints.

More remarkable still is that his mathematics is largely self-taught. He graduated from Kyoto University in botany, wrote his degree thesis on the nucleolus in plant cells. Although he took the full course in botany, he attended courses in the mathematics department, and continued his studies alone. Dr. Komai, under whose direction he works at the new National Institute of Genetics at Mishima writes: "He is quite unusual in mathematical ability. I can also assure you that his knowledge of cytology and genetics fairly compares with that of average professors of cytology or genetics in this country."

But now his development in mathematical genetics is limited by the fact that there is no-one in Japan to teach him. Obviously he should get either to the States or to England. [McDonald to Wright, 3 December 1952]

McDonald suggested that Wright take Kimura on as a graduate student and enclosed a set of Kimura's reprints, his curriculum vitae, and a list of his publications (28 at that time).

Plough, in a letter to Wright dated 8 January, reinforced McDonald's letter:

I met Mr. Kimura in the National Institute of Genetics at Mishima, Japan, and he impressed me as a very capable young Japanese whose English was good but slow. I saw a number of his papers and was much impressed by the variety and competence of the work he has done in the last six years. He appears to be extremely capable from a mathematical point of view, and yet most of his competence has been obtained from his own efforts.

I agree very heartily with the recommendations of Dr. McDonald and Dr. Komai that he should come to the United States for further study. I could think of no more fortunate opportunity for him than the University of Chicago where perhaps he might work with you.

Probably you have already written to Dr. McDonald concerning this possibility. If there is anything further I can do, I hope that you will let me know. [Plough to Wright, 8 January 1953]

Wright soon replied to McDonald:

I am very much impressed with Mr. Kimura's capacity for applying mathematics to problems of population genetics. His work is sound in all respects that I have had time to check.

We do not seem to have any scholarship that would meet his needs at the University of Chicago. I also doubt whether I would have much to teach him as far as the pure mathematics is concerned. I am primarily a biologist and have never assigned a thesis problem in purely mathematical genetics. For preparation for an attack on the problems in this field at a higher mathematical level than at present he should go to a department of mathematics. I should also add that I have ceased to take on new graduate students in any field of genetics as I am to retire in less than two years. I am scheduled to give my course in evolution (largely population genetics now) next spring for the last time.

The combination at Ames of a Statistics Department and of Dr. Lush's interest in the application to genetic problems make this an attractive place for Mr. Kimura to go if arrangements can be made. The Institute of Statistics of the University of North Carolina is another place in which advanced work in mathematical statistics is closely associated with genetic experiment. [Wright to McDonald, 20 January 1952]

Meanwhile Lush had responded quickly in late December to McDonald with a very positive letter.

This is in reply to your letter of December 3 about Mr. Moto Kimura. His reprints indicate a really remarkable ability. Dr. Kempthorne concurs with me in this. We would be glad to have him come and study with us, but I am afraid the financial help we could offer is not quite adequate to his requirements...

I think we could give him some rather useful and broadening information here. Dr. Kempthorne is especially qualified to explain and interpret the attitudes and published researches of such workers as R. A. Fisher and J. B. S. Haldane. I and Dr. Hazel and our associates are continually bearing down on the possibilities of applying these things to plant and animal populations and on the question of the importance of discrepancies between the mathematical model and the biological or

economic reality. We more nearly present the viewpoint of Sewall Wright, so far as there is any difference between that and the two English workers mentioned. We have rather too many graduate students to give him as much individual personal attention as he might wish, but this has some advantages in that these students learn lots by discussing their problems with each other and those who are here for a second or later year necessarily get much practice in explaining things to the ones who are just beginning. Dr. Kimura would get more up-to-date information on the latest developments in mathematical genetics if he could be with Dr. Sewall Wright and could receive much individual attention from him. However, Dr. Wright is involved in a good many things and for the most part I believe is able to give his students only a modest amount of attention outside of the regular lectures. The mathematical genetics which Dr. Kimura would get there would be more up-to-date and thorough than he would get here, but there would not be so many semi-amateurs arguing about it and trying to find illustrations and to understand just exactly what it means from a variety of plant and animal breeding viewpoints.

Rarely if ever do we get a letter recommending a man in higher terms and fortified with evidence of scholarship which are any better than those you submitted. I hope that Dr. Kimura does, in some way, get the opportunity which his talents seem to justify for him. [Lush to McDonald, 30 December 1952]

Assuming from Lush's letter that Kimura would be able to work with either Lush or Wright, McDonald moved quickly to get the necessary clearances. During these occupation years, study in the United States for a Japanese citizen required a document from the US Army guaranteeing that the student could speak English sufficiently well for academic communication.

McDonald was confident about Kimura's abilities to become fluent in English, but knew that his understanding of rapidly spoken English was questionable. So McDonald arranged for Kimura to come to visit ABCC for a week of discussions in English, to be followed by a meeting with the officer who would sign the necessary document for foreign study after evaluating a conversation with Kimura. Morton wrote to offer Kimura a place to stay:

I hope that we will be seeing you shortly. My wife and I would be delighted to have you stay with us, or there are bachelor accommodations if you prefer them.

I just received a letter from Dr. Crow referring to a number of points in his papers and in my last letter to him. Without copies of these I have difficulty following his comments. Could you bring the material on population number with you if you come? Incidentally, there is a good possibility that I will be returning to Wisconsin during the summer, so we may perhaps be neighbors. I know Dr. Crow would be very much interested in meeting you if you go to Ames. Meanwhile, we at ABCC have many genetics problems we would like to discuss. We are looking forward to your visit if you are able to come. [Morton to Kimura, 12 January 1953]

Kimura went to ABCC, stayed with the Mortons, and had a fine week of discussion about population genetics. Morton recalls reading Malécot's monograph with Kimura, who did not at the time read French (though later Kimura translated this monograph into English to satisfy his French requirement while a graduate student at the University of Wisconsin!). Morton would translate the French into English, but found it difficult to explain the equations quickly. But that was no problem, because Kimura had already absorbed the equations while Morton was translating, and Kimura was always ready for Morton to translate more text. Also on this visit, Kimura passed his language proficiency test with the American officer at a meeting delicately scheduled by McDonald.

Komai was very supportive of Kimura's desire to study in the United States, and Director Oguma wrote to Iowa State on January 27, 'I hereby certify that Motoo Kimura, a member of the staff of this Institute, will continue to receive his present salary of 12,450 yen a month, in full, during his stay on leave in the United States.' (The salary amounted to less than \$35 per month, but was considered good pay in postwar Japan at that time.) Kimura's father had to provide this guarantee: 'I hereby assure that I shall provide my son, Motoo Kimura, with all expenses, which might be necessary for his recovery, in case of illness or any other emergency, during his stay in the United States. . . . Itsusaku Kimura.' On 17 February 1953 Kimura was formally accepted, with a foreign fellowship, into the Graduate College of Iowa State College. McDonald, concerned that the foreign fellowship would be insufficient, requested a Cramer Fellowship from Dartmouth College for Kimura. The \$1000 Cramer award (following receipt of a letter from Kimura outlining his study and research plans) and a travel grant from the Fulbright Foundation, combined with the fellowship, enabled Kimura to have financial security for his first year in the US. Kimura went from being virtually unknown to Western geneticists to acceptance in graduate school in the US in about four months.

Kimura has described the voyage:

In the summer 1953, as one of the Fulbright grantees, I left Yokohama for Seattle on board *Hikawa-Maru*, the sole passenger boat left in Japan after the war. The voyage which took 2 weeks was a most memorable event in my life. Pleasant and enjoyable days on the boat, playing deck golf every day, being served excellent meals, taking naps in the afternoon, with comfortable vibration constantly coming from the engine seemed to have a salutary effect; from this time on, my chronic stomach trouble, which had annoyed me for years and which might have been caused by nervous tension, disappeared. This made my life in the United States and thereafter much happier. During the voyage, I wrote a manuscript reporting my solution of the stochastic process of gene frequency change under random fluctuation of the selection coefficient around the neutral point [published as Kimura 1954].

As he arrived in Seattle harbour, Kimura began sketches and brief commentary in a small sketch book, which he filled during his first year, and then replaced with a camera. This sketch book is an extraordinary record of his first impressions of the United States, as he started a new and exciting phase of his life.

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