

Masatoshi Nei (1931 to 2023): Founder of molecular evolutionary genetics

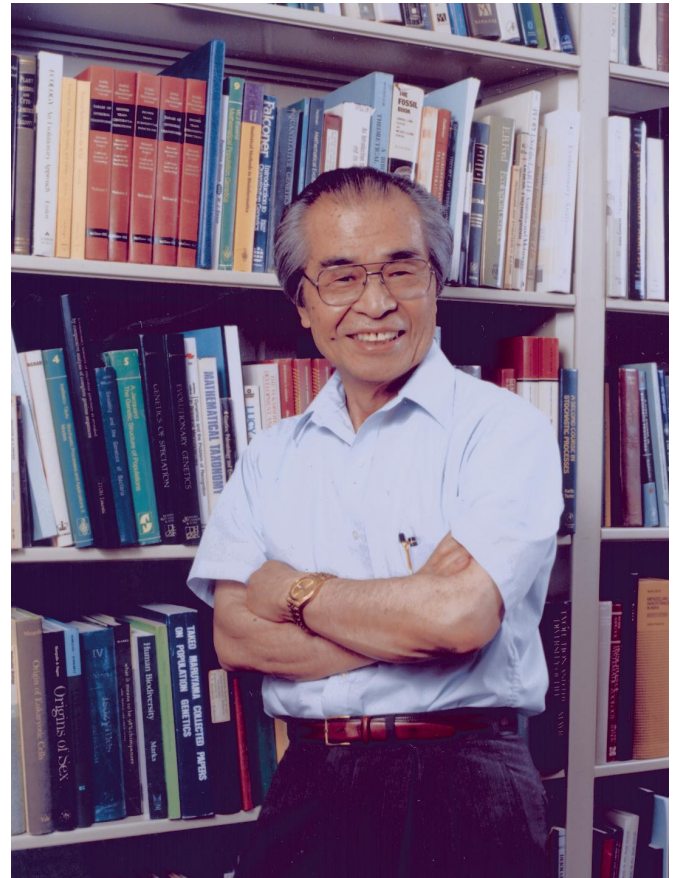
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The field of evolutionary biology lost a great one on May 18, 2023. Known for his mathematical rigor and tenacity in population genetic and phylogenetic analysis, no one has had a greater impact on the emergence of a formal field of molecular evolution than Masatoshi Nei. He developed the first methods for converting sequence divergence into evolutionarily meaningful measures. He helped lay the foundations for converting such measures into molecular phylogenies, developing logical and practical methods for analysis, e.g., the Molecular Evolutionary Genetics Analysis software package (1), which has made the lives of thousands of sequence gazers immeasurably simpler. Many of Masatoshi's ideas are outlined in seven books (2–8). With Walter Fitch, he worked tirelessly to establish the foundational journal *Molecular Biology and Evolution* (MBE), serving as managing editor for the first decade. They subsequently founded the international society with the eponymous name, whose annual meetings quickly grew from a few dozen to over 1,000 participants. He left behind a large legacy of collaborators, students, and postdoctoral fellows who comprise the leadership of today's field of molecular evolution.

Although he was a gentle man, Masatoshi was a somewhat intimidating figure to young investigators. Part of it was his formal attire and his embodiment of great achievement. But he also had a habit of closing his eyes when he spoke, leaving the recipient uncertain as to his level of boredom. He could have kept his left eye open, as he had lost functionality in it in 1946. After World War II, Japan was littered with unexploded military ordnance, and upon dissecting various remnants out of curiosity, a blasting cap blew up in Masatoshi's face. Given that he was also born color-blind set the bar for being a visionary. More than once, I saw him give talks almost entirely with his eyes closed (notably, string soloists often deliver beautiful performances in the same way, so the behavior is not unprecedented). An interesting statement in his memoirs is that “A famous man can give an ordinary talk” (9), but to whom he was referring is unclear.

The son of a poor farmer, Masatoshi grew up in a small town north of Miyazaki, Japan (~150 kilometer SE of Nagasaki), where he developed a curiosity about nature and a proclivity in mathematics. Recognition by his early teachers yielded scholarships that enabled him to become the first member of his family to go to college (graduating from Miyazaki University in 1953). During this period, he encountered the field of genetics, and after reading various papers by Fisher, Haldane, and Wright, became inspired by the idea that the mathematics that he enjoyed could be applied to actual biological problems.

Masatoshi then moved to Kyoto University, where he engaged in agricultural genetics work on rice and radishes. This was during the time of establishment of variance



Masatoshi Nei. Image credit: Penn State University, which is licensed under CC BY 4.0.

component analysis in quantitative genetics, and he developed methods for covariance analysis for quantitative traits. Unfortunately, he was a bit pre-empted by work by Oscar Kempthorne and Clark Cockerham in the United States [itself an interesting matter (10)]. He also started to question the practicality of applying quantitative-genetics analysis to natural populations experiencing enormous levels of year-to-year environmental variation. Methods to deal with these

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issues have subsequently been developed, and now agricultural genetics is heavily invested in the use of molecular markers, so in this modern era, Masatoshi might have stuck with the problem at hand.

Instead, he became attracted to the idea of working with identifiable gene products, such as blood group markers and eventually allozymes, which emerged as molecular tools in the 1970s. Having already been appointed as an assistant professor at Kyoto University, under the recommendation of Motoo Kimura (founder of the neutral theory for molecular evolution), he obtained a Rockefeller Foundation fellowship to do postdoctoral work at the University of California, Davis, and North Carolina State University, Raleigh. Both places were major hubs of activity in the development of methods for analyzing quantitative traits, particularly in plant breeding, but he did not stay long. He returned to Kyoto in 1961, and in the following year, he moved to the National Institute of Radiological Sciences in Chiba, Japan, where he quickly established himself as a leading theoretical population geneticist. In 1963, he married Nobuko Hara, with whom he had two children, Maromi and Keitaro.

The lure of starting an independent research program in the United States was great, and just a few years later (1969), he joined the Department of Biology at Brown University, where his reputation continued to flourish. Jack Schull then recruited him to join and soon direct the new Center for Demographic and Population Genetics, University of Texas at Houston in 1972. Largely owing to his leadership, the CDPG quickly emerged as a world center for research in population genetics, with many other leaders of the field establishing their careers there. In 1990, Linda Maxson and Bob Selander recruited him to Pennsylvania State University to start a new Institute of Molecular Evolutionary Genetics. His lab there was a veritable United Nations of students and postdocs, and it was always great fun to visit them. He remained at Penn State for 25 years, until he suffered from a stroke and moved to a retirement community in New Jersey to be closer to his daughter. During this time, his former student and collaborator Sudhir Kumar arranged for him to have an honorary appointment at Temple University.

Many things will be written about Masatoshi's contributions to phylogenetic analysis (11, 12), but his early contributions to population-genetic theory cannot be overstated. Just a few will be mentioned here. Although his early papers were often single authored, he was also highly collaborative. With Wen-Hsiung Li, Arun Roychoudhury, Paul Fuerst, Takeo Maruyama, Ranajit Chakraborty, and others, he established the theory for the frequency distributions of deleterious alleles and the numbers of affected individuals. They also developed rigorous methods for estimating levels of heterozygosity and attaching proper levels of confidence support to them by accounting for sampling at the levels of nucleotide sites, individuals, and subpopulations (in ways that few of today's practitioners adhere to but should). The mathematics underlying this work is not easy, and the persistence of these individuals was a huge gift to the field.

Inspired by his early work on the distribution of human blood-group variants, Masatoshi also developed methods for quantifying levels of population subdivision using

allele-frequency information, e.g., for estimating Wright's famous F_{ST} index. He had very specific ideas on the ways in which population sampling should be dealt with, sometimes perhaps getting a bit too attached to his own favorite approach. For example, parallel methods were being developed by Clark Cockerham and Bruce Weir, using somewhat different approaches, but whereas the latter felt that populations should be treated as "random effects," Masatoshi advocated a "fixed-effects" approach, treating the observed populations as the only ones of interest. This led to a long string of point-counterpoint publications, all over whether the between-population measure of variation should involve weighting with $n-1$ vs. n (where n is the number of populations); for large n , there is not much difference in interpretation at all. Inspired by Masatoshi's work, I developed a similar method for estimating subdivision using nucleotide diversity estimates from mitochondrial DNA but had the misfortune of using a random-effects approach and then becoming assigned to MBE's senior editor Nei. Our exchange on this matter went on for months, with Masatoshi laboriously emphasizing why his view was correct in a cumulative volume of pages that exceeded our manuscript. He was a very meticulous editor, but eventually, he allowed us to publish our approach.

Masatoshi's work in population genetics was not simply focused on sampling statistics. He developed the first theory for the evolution of mating types, pointing out why a strong linkage between signaling and receptor loci is critical for the evolution of separate sexes. With Takeo Maruyama and Chung-I Wu, he developed one of the first quantitative models for the origin of reproductive isolation between incipient species and the distribution of time to achieve this. With Shozo Yokoyama, he worked out a theory for the consequences of fluctuating selection for the long-term distributions of allele frequencies, attempting to account for various aspects of ecology and demography in ways that no one had done before. With multiple colleagues, he contributed to our understanding of the evolution of duplicate genes, particularly in large multigene families.

What set Masatoshi apart from many of his contemporaries in molecular evolution was his dedication to developing statistically rigorous methods for data analyses. People like Motoo Kimura were extremely effective in developing the basic theory of molecular evolution. But Nei and colleagues were ultimately responsible for connecting the theory with data, telling us the limits to knowledge that can be acquired with finite sample sizes, etc. At the beginning of my career, when I was contemplating moving on from the field of ecology, I read his 1972 *American Naturalist* paper (13), outlining what would become known as "Nei's genetic distance," and was struck by its combination of elegance, simplicity, and connection to biology. Masatoshi felt that this paper launched his career, but his was not the only one.

I have only touched upon a fraction of the many contributions that Masatoshi made in the field of evolutionary biology, barely mentioning the foundational work that he and colleagues made to molecular phylogenetics in the last 25 years of his career. Toward the end of his life, he pushed ideas about mutation-driven evolution (4), but despite my

attempts to get a deeper understanding of what he was getting at, I never quite pulled this out of our conversations and was left feeling that I was missing out on something.

Not surprisingly, many honors came his way, including the Thomas Hunt Morgan Medal from the Genetics Society of America, the Kyoto Prize for basic sciences, and elected membership in the American Academy of Arts and Sciences, and

the United States National Academy of Sciences. At the end of his memoirs (9), commenting on the lasting contributions made by Darwin and Fisher, Masatoshi notes, "Ideally fame should be quantified with some measures. However, this does not matter now. The only thing that matters now is the fact that I worked hard and I enjoyed my life immensely. It was a wonderful life for me." And for us too.

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