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

Michael Lynch

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 component analysis in quantitative genetics, and he developed methods for covariance analysis for quantitative traits. Unfortunately, he was a bit preempted 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...
issues have subsequently been developed, and now agricul-
tural 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 mole-
cular evolution), he obtained a Rockefeller Foundation fellow-
ship 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 popula-
tion 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 leader-
ship, 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
Maxon 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 contribu-
tions to phylogenetic analysis (11, 12), but his early contribu-
tions 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 hete-
rozgyosity 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 devel-
oped by Clark Cockerham and Bruce Weir, using somewhat
different approaches, but whereas the latter felt that popu-
lations 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 popula-
tions); for large $n$, there is not much difference in inter-
pretation 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 labori-
ously 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 pub-
ish 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 mod-
els 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 conse-
quences of fluctuating selection for the long-term distribu-
tions 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, particu-
larly in large multigene families.

What set Masatoshi apart from many of his contempo-
raries in molecular evolution was his dedication to develop-
oping 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 begin-
ing 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 contri-
butions 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.

7. M. Nei, N. Takahata Eds., *Current Topics of Molecular Evolution* (Institute of Molecular Evolutionary Genetics, Pennsylvania State University, 1993).