MATHEMATICS, COMPUTING, AND THE NEW BIOLOGY

Modern research calls on biologists to be fluent in analytical methods.

Max Delbruck, the physicist – turned – biologist who became a founding father of molecular biology, often told his students that "if you have to use statistics to interpret your experimental results, they can't be true."

That statement wasn't meant to denigrate the power of mathematics, former colleagues say; it was simply an attempt to provoke students into designing clear – cut experiments. Nevertheless, the remark shows how far biology has come since the mid-20th century, when Delbruck began grappling with the field's big questions. Researchers today are increasingly using statistics and other analytical tools not just to interpret their results but to arrive at them.

In an essay published last year in plos (Public Library of Science) Biology, **Joel E. Cohen,** a population biologist at the Rockefeller University, called mathematics "biology's next microscope." In the coming years, he wrote, mathematics will "reveal otherwise invisible words in all kinds of data" just as early microscopes first revealed the microbial and subcellular worlds. Further, Cohen asserts, the explosive pace of biological research will spawn new branches of mathematics just as physics stimulated the development of calculus.

"We've gotten so much better at using experimental tools to study complex systems," says **Charles F. Stevens,** an HHMI investigator at the Salk Institute for Biological Studies, "that now we need mathematical approaches to make a sense of it all."

"The old way of doing things was that you kept everything fixed, changed one variable, and then got the relationship between them," Stevens says. "But now the kinds f questions we're asking and the kinds of experimental abilities we posses are leading us to measure many things simultaneously, and we just have to have techniques for analyzing and thinking about the data."

CATALOGUING EVERYTHING IN THE CELL

To many, one of the boldest examples so far of the new biology has been the human genome project. **Gene Myers,** a computer scientist at the University of California, Berkely, was at the forefront of that effort. Five years ago, when myers was vice president of informatics research at Celera Genomics, his radical computing method for assembling DNA sequences catapulted the company to the front of the high – stakes race to read the three – billion – letter human genome sequence. Ultimately, Celera and its competitor – a government – sponsored consortium – joined forces and completed the genome sequence years ahead of schedule.

Now Myers has set even loftier goals: "Having produced the sequence of the genome, we'd like to understand what it actually says." Like the University of Washington's mathematician/geneticist Philip Green (see main article), he wants to know how the genome is regulated and how all of the molecules in cells interact. That going to take a lot of data crunching. "You're dealing with a system that's so large that the unaided human mind isn't going to see it," says Myers. "We're going to need the kind of help that computers are good at."

Consider his own efforts to use microscopes to track the moment – by – moment whereabouts of the hundred- or- so most important transcription factors (the proteins that turn networks of genes on and off) in the developing embryos of model organisms such as fruit flies or nematodes. "I want to see gene expression at the level of what's happening in each," says Myers. But he maintains that "at some point, our eyes aren't going to be able to look at all the images. We will be producing visual data at rates that require computation and interpretation by computers."

High – tech hardware alone won't be enough, however. Myers thinks that biologists have to do a better job of incorporating knowledge and approaches from other disciplines into their research. For example, "We're going to have to start thinking about the mathematical properties of these living systems from an industrial – engineering point of view – in terms of systems with feedbacks, failure modes, and redundancy."

FEMTOSECONDS TO MINTUES

J. Andrew McCammon, an HHMI investigator at the University of California, San Diego, is pushing mathematics to the extreme in his research on the infinitesimal and varied motions inside protein molecules – moments that can provide important clues about how proteins work and interact with other molecules, such as drug compounds. McCammon's group uses supercomputers to model, in extraordinary detail, the quivers, jiggles, twists, and bends that proteins undergo, as governed by the chemical and physical forces of each of the molecule's thousands of atoms. The time scales of these various motions range widely, moreover, from femtoseconds (quadrillionths of a second) to minutes.

Modeling protein movements at that level of detail takes a lot of computing power, says McCammon. "Just to get to the microsecond (millionth of a second) time scale in simulating a medium - sized protein requires on the order of a billion small steps in time, and each step might involve as many as a million separate calculations of forces between the pairs of atoms in the protein."

His team recently simulated 50 nanosecond (billionths of a second) of movements in a nerve – cell receptor as it binds to a neurotransmitter molecule. "The simulation model includes the receptor, a portion of the lipid bilayer it passes through, and water molecules on both sides of the bilayer, for a total of about 150,000 atoms," McCammon says. "To simulate the dynamics for about 50 nanoseconds, where we can begin to see the response of the receptor, requires about 500 processors on the DataStar supercomputer at the San Diego Supercomputer Center, running each processor for 200 hours."

Such intensely focused modeling may seem like much too much about much too little, but it can yield real – world payoffs for instance a new generation of drugs for treating HIV/AIDS. While inhibitors of one HIV's enzymes, called protease, have been effective anti-AIDS drugs, in recent year's protease inhibitor resistant HIV strains have emerged. Another of HIV's enzymes, integrase, structure was known, the enzyme hadn't been success- scrutinizing it a few years ago.

In modeling two nanoseconds' worth of integrase's movements, the team discovered that part of the protein chain moves in such a way that, for an instant, a "trench" opens up near the active site the part of the protein that catalyzes the stitching reaction. McCammon and his colleagues then designed compounds that they predicted would fit into the trench, there by jamming the enzyme so that it could no longer work. Scientists at Merck Research Laboratories have since confirmed this hypothesis by testing a number of the compounds as potential drugs to inhibit the HIV integrase, and clinical trails of one of them are expected to begin later this year.