Summer 1980

Biology By The Numbers: [Dr. Joel E. Cohen]

Fulvio Bardossi

Judith N. Schwartz

The whole development of science is a record of tearing down barriers between separate fields of knowledge and investigation.
ALFRED J. LOTKA, 1925

The replacement of typological thinking by population thinking is perhaps the greatest conceptual revolution that has taken place in biology.
ERNST MAYR, 1966

THE ROCKEFELLER UNIVERSITY
RESEARCH PROFILES
SUMMER 1981

Biology By The Numbers

How does an intellectual journey begin? For Joel E. Cohen, one of the first steps on the path was taken twenty-five years ago when, as a teenager in Battle Creek, Michigan, browsing the sale table of the local bookstore, he found a paperback edition of a book titled *Elements of Physical Biology*, by Alfred J. Lotta. As he flipped through its pages, he thought to himself, "Here's a guy who thinks the way I do. Mathematics might be a useful way to make some sense of life."

Today, Professor Cohen heads The Rockefeller University's laboratory of populations. Applied mathematician, biologist, public health specialist, ecologist, ethologist, he has been described by a colleague, world-renowned mathematician Mark Kac, as "a master of statistical methodology and a pioneer in the application of statistical and related mathematical techniques to a wide range of biological problems."

Population biology is the science concerned with the interactions of groups of living things. As Dr. Cohen explains: "Any ensemble of biological units, whether it's made up of molecules, organisms, or species, exhibits phenomena that frequently can't be deduced from the characteristics of an isolated unit of the ensemble. What I'm trying to do is develop concepts to help understand such phenomena by using mathematics. Just as an experimental biologist works with a microscope, mathematics is for me the essential instrument for making the unseen visible, for teasing apart things that couldn't otherwise be brought to light."

One of Dr. Cohen's major involvements as a population biologist is public health.

"I think of population biology as the science underlying public health in the same way that physiology and biochemistry underlie clinical medicine. In coping with the large-scale problems of the world, in places where there's a public health budget of maybe a dollar and a quarter per person, it's just not possible to have an internist available for everyone who gets sick. You have to have preventive approaches. That means interfering with the ecology of disease and that means understanding the ecology."

Malaria kills or sickens more people in the world than any other disease. Efforts are underway, at The Rockefeller and elsewhere, to develop a malaria vaccine and better antimalarial drugs. But the ecology—the dynamics—of malarial infection is still poorly understood. In Dr. Cohen's office there is a computer tape with eighty million numbers on it, the result of a study by the World Health Organization of several thousand people between 1971 and 1976 in an area of Nigeria where nearly everyone had malaria. With it, Dr. Cohen and Dr. Burton Singer, professor of mathematical statistics at Columbia University and an adjunct professor at Rockefeller, are studying the events in the time course of malarial infection. To understand these events and to detect patterns, they have invented sophisticated variations of a tool of statistical mathematics called Markov chains, a device for

Left to right, Dr. Nedelman, Dr. Cohen, and Visiting Professor John Hajnal, professor of statistics, London School of Economics and Political Science

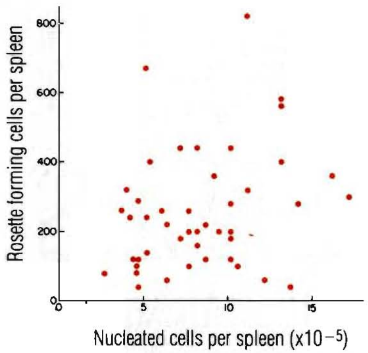


FIGURE 1. *Numbers of trinitrophenyl-specific rosette-forming cells in the spleens of mixed-breed fetal mice as a function of spleen size, measured by the number of nucleated cells in the spleen. Each point represents the results obtained for one spleen.*

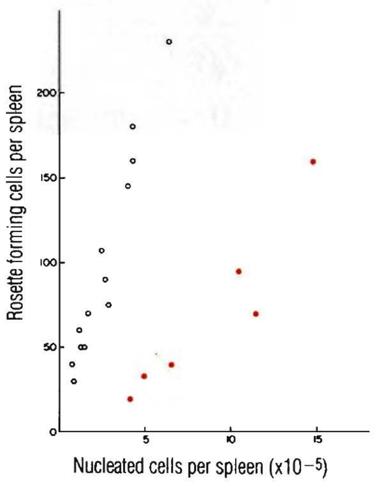


FIGURE 2. *Numbers of trinitrophenyl-specific rosette-forming cells in the spleens of individual fetal mice in two different (○, ●) inbred strains.*

describing future events on the basis of present information.

One important finding of the work to date is that infection caused by *Plasmodium falciparum,* the most lethal species of malaria parasite, not only does not confer resistance to another species, *Plasmodium malariae,* but may in fact increase the risk of infection with the latter. Such information can have a number of practical applications. "At the very least," says Dr. Cohen, "a firm grasp of the epidemiology is essential for evaluating the potential effectiveness of any proposed vaccine or drugs."

Dr. Jerry Nedelman, a postdoctoral fellow working with Drs. Cohen and Singer, is using the World Health Organization's data to get a better picture of the population dynamics of the mosquitoes that transmit malaria.

RAILS OF THOUGHT

Mathematics applied to biological research can provide what Dr. Cohen calls "rails of thought" along which experimenters and observers can carry the freight of particular empirical investigations. Mathematics, as Dr. Cohen sees it, can provide organizing concepts, experimental designs, and techniques of analysis, as well as a language for formal scientific theory. At Rockefeller, with its long tradition of interdisciplinary cross-pollination, it is not surprising that, in addition to his own projects, Dr. Cohen finds himself called upon by other laboratories to construct such rails. For example, during a chat with Professor Gerald M. Edelman, a Nobel laureate in immunology, Dr. Edelman mentioned that Peter D'Eustachio, then a graduate student of his, was having trouble understanding the variation in the numbers of specific antigen-binding cells in fetal mice. (Antigens are foreign molecules that challenge an organism's immune system. Certain immune cells that form during the development of a fetus have the capacity to bind to different antigens.)

"The first thing I was able to determine," says Dr. Cohen, "was that Peter's experiments were turning up more variation than should happen through pure randomness (Fig. 1). With a mathematical model, you can estimate what the probable amount of randomness should be in a given situation. Therefore, it seemed likely that there must be some other factor causing the waffle. He had been using mixed-breed mice, which made me think that the complication might be genetic. So we designed some new experiments using inbred mice. He got absolutely beautiful results (Fig. 2). We were able to demonstrate for the first time that the fraction of cells that bind to a specific antigen is constant, allowing for sampling variation. The process is governed by a specific gene that we discovered during the course of the research. Whether this finding will help cure some developmental anomaly some day it's too early to know, but the experiments did show that there is remarkable order in the control of cell population numbers. The system isn't sloppy."

Not long after, virologist Igor Tamm came to Dr. Cohen to discuss a problem concerning the origins of replication of the DNA molecule in mammalian cells. DNA—deoxyribonucleic acid—is the chemical material of the genes. Each time cells multiply, they make a copy of the DNA in the cell nucleus. How does this work?

"Replication doesn't begin at one end of the molecule and proceed like a zipper to the other end," explains Dr. Cohen. "That would take longer than we know the duration of the process to be. Dr. Tamm and Barbara Jasny, then a graduate student, wanted to find out whether there is any structural organization—some regularly defined distance between sites on the DNA molecule—where replication starts. Or are these sites random?

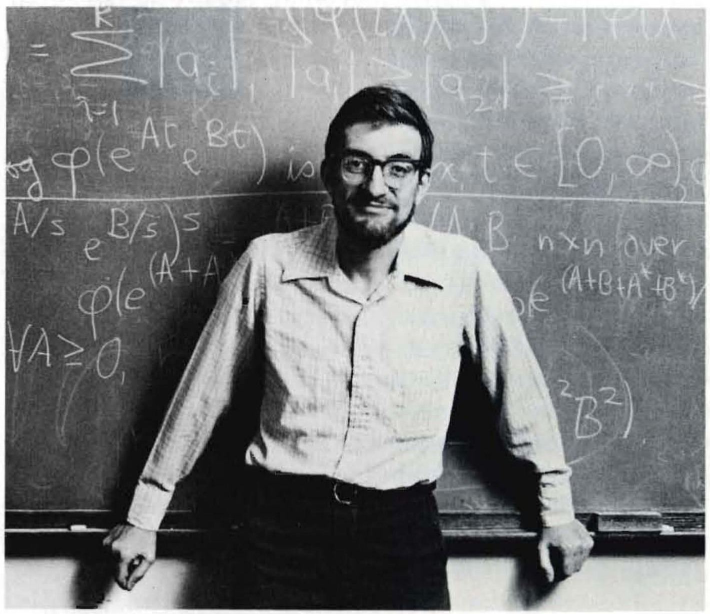
"Well, 'random' has no meaning by itself. As in the study with Dr. Edelman's student, randomness had to be given quantitative meaning. So I asked myself what would I expect if these sites of origin, thinking of them as dots, were sprinkled along a two-meter DNA molecule. Comparing mathematical predictions with information about actual sites that had been obtained by microscopic autoradiography methods, we were able to establish that the distances are not random in normal replication, but that the pattern in the positions of the sites can be altered by chemical agents or by viruses. Does this have a bearing on what happens in cancer cells? Again, we don't know yet."

FOOD WEBS AND NICHE SPACE

One of the most basic biological interactions is that members of some populations eat members of others. A major concern of ecologists is how the food chain works. Three years ago, Princeton University Press published *Food Webs and Niche Space* by Dr. Cohen in its Monographs in Population Biology series. The book distilled ten years of effort toward creating the beginnings of a theoretical framework for "teasing apart" the tangle of predator-prey relations in nature.

Food webs are diagrammatic representations of who eats whom in a particular community of species. The term niche space describes the composite of all the environmental factors within the niche that affect an organism—everything from the temperature or altitude at which it lives to how fast it moves. Dr. Cohen studied data on thirty-one food webs from more than twenty reports made over a period of fifty years, applying the branch of mathematics called combinatorics—the theory of the structure of discrete objects.

Dr. Cohen



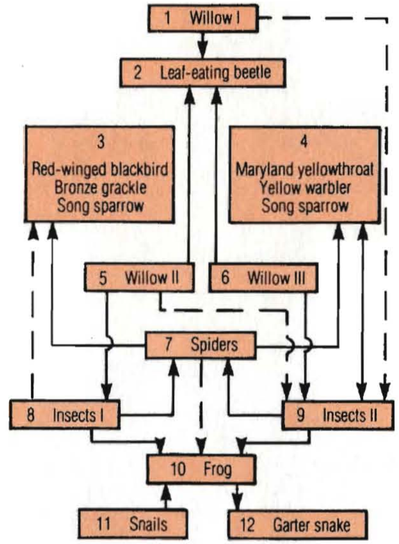
Among the things he learned is that food webs in real life appear to fall into a small subset of theoretically *possible* food webs. What organisms eat seems to depend often, if not always, on only one dimension—one characteristic—of the niche space. He illustrated this by mapping, with something called an interval graph, the line along which the feeding habits of various species overlapped in a Canadian willow forest. He also found, in the communities he studied, that there seems to be a constant ratio between the number of kinds of prey and the number of kinds of predators.

What is the significance of such findings? Are they useful in predicting what might happen if the species balance in an environment is disturbed?

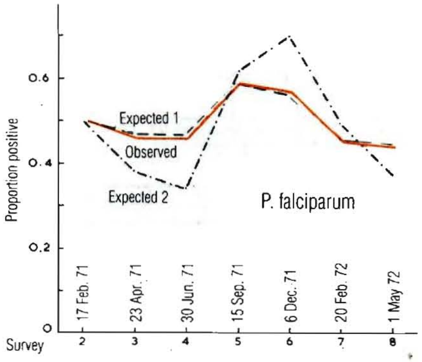
As Dr. Cohen admits: "This is only a beginning. For the moment, the study has provoked more questions than answers, but I have been astonished by the number of people writing papers in response to it, and shooting at parts of it. I sit and watch the fur fly. One thing I think the work does suggest is that life may be simpler than we had reason to suspect previously."

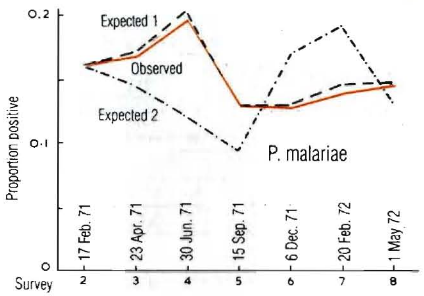
A reviewer, writing in *American Scientist,* hailed the book as an "exploration of new territory" and "a methodological tour de force" in which, "while introducing a new technique to biology, Cohen introduces to mathematics a new empirical connection."

"Mathematics," says Dr. Cohen, "is a great field for intellectual punsters who like to take something from one place, adapt it, and put it in another. For example, the interval graphs I used in the food web study were invented simultaneously by a European mathematician as a purely theoretical construct and by Seymour Benzer, a molecular biologist, who used it to study the fine structure of genes. I got the idea to use them in a dream I had after hearing a lecture about Benzer's work. The exponential distribution methods I used with Barbara Jasny and Dr. Tamm were adapted from my senior thesis at college on the distribution of the abundance of species. The contingency tables that helped Peter D'Eustachio were suggested by a study I had done on the effects of birth order on mortality rates in pre-industrial Europe."



The food web graph of the willow forest, Canada. The arrows are directed from the kind of organism eaten to the kind of organism that eats. The dashed arrows are tentative.





*Fractions of populations observed to be infected with malaria (*falciparum *above,* malariae *below) compared with predicted fractions, according to two different models.*

RESEARCH PROFILES is published four times a year by The Rockefeller University. It is written and edited by Fulvio Bardossi and Judith N. Schwartz. This is issue Number 5, Summer 1981. Inquiries should be addressed to the University's Public Information Office, 1230 York Avenue, New York 10021 or phone (212) 360-1261. Photographs, Ingbert Grüttner.

In like manner, Dr. Singer has been adapting some of the concepts associated with uncertainty principles in physics and electrical engineering in collaboration with Professor Vincent P. Dole, head of the University's laboratory of the biology of addictive diseases. Dr. Dole, developer of methadone maintenance for the treatment of heroin addiction, and Dr. Singer find that there is a trade-off between the scope and precision of a medical follow-up study. They are supplying what has been missing until now—a quantification of that trade-off.

EARTHWORMS AND LOGARITHMS

Joel Cohen's view of mathematics as a way to "make sense of life" began early. "Like most kids," he says, "I was interested in living things. Then one day I read about an experiment in which it was shown that the amount an earthworm turns its head in the direction of a light is directly proportional to the logarithm of the intensity of the light. I had just learned about logarithms in school. I was amazed that this simple organism was behaving in a mathematically lawful way, and that it knew logarithms without school! It seemed to me I had better learn some math."

He learned too much to suit the principal of Battle Creek Central High, who found it inappropriate for students to "go their own way" ahead of the class. It seemed eminently appropriate, however, to Dr. Cohen's father, a rabbi turned political scientist, and to his mathematician-sociologist mother. They encouraged him to get a scholarship to a private boarding school where his self-propulsions would be accepted.

At the new school he was pointed to good texts and allowed to struggle. He was also allowed to indulge his passion for writing, fired at the age of eleven when a local newspaper accepted a piece of his for publication; and he discovered French. After reading Abraham Moles' *Information Theory and Esthetic Perception,* he wrote the author in Paris requesting permission to do the English translation, enclosing as sample his version of the first chapter. The request was granted. He then wrote to the University of Illinois Press, which subsequently published it. Neither author nor publisher knew their translator was a sixteen-year-old.

As college time approached, a high school counselor told him about Harvard. He looked through the catalog, saw a lot of names familiar to him from his reading, and decided it might be right for him. Harvard agreed, and the National Merit Scholarship Corporation awarded him a full scholarship. He majored in math, took all the science he could, tried his hand at newspaper writing, and became editorial chairman of the Harvard *Crimson.*

At graduation, Harvard awarded him a Frederick Sheldon Traveling Fellowship, with which, for the next fourteen months, he explored the world. He studied tropical ecology in Latin America, primate behavior in Japan and East Africa, family planning in Taiwan, and economic development in India. He counted game in the foothills of the Himalayas, trapped rats for an ecologist in Calcutta, sorted archeological implements with Mary Leakey in Tanzania, and acquired a sea urchin spine, still in his hand, while investigating the coral reefs of the Red Sea. He went to the Max Planck Institute for Psychiatry in Munich, sat in on Jean Piaget's classes in child development in Geneva, and learned about communication in electric eels at the Institute of Animal Physiology in Cambridge.

"I saw a lot," he remembers, "but mostly what I saw is that the world is very poor and most people are sick. Two-thirds of the people in the world have worms. That's only a statistic until you see people who don't have enough to eat and most of what they do eat goes to feed their worms. In India, you step over bodies in the street. If they don't move for several days, they get carted away. It made a deep impression."

He returned to Harvard, completed a Ph.D. in applied mathematics and another in public health, and served on the Harvard faculty for four years before coming to The Rockefeller.

In September, Dr. Cohen will take a sabbatical leave at the Center for Advanced Study in the Behavioral Sciences in Stanford, California. In his words: "I'm interested in population biology and epidemiology and social structure and behavior because I think that these things must be understood if we are ever to assure the health of populations." □