APPLIED MATHEMATICS

Models Aid Understanding, Help Control Parasites

With parasitic diseases affecting more than 1 billion of the world's people, you might think that specialists in the diseases would want every imaginable weapon at their side. But as recently as 15 years ago, they thought that one group of potential helpers, the mathematical modelers, had little to offer. They wanted news they could use: information on what part of a parasite's life cycle is most vulnerable to attack or on what interventions would work best at stopping the spread of infection. Instead, says one tropical medicine specialist, many of these older models were the products of "mathematicians playing around with mathematics, with very little relevance to biology." And it wasn't all a matter of archconservatism in the parasitology community. Some modelers simply weren't doing first-rate work. Says pioneer modeler Robert May of the University of Oxford, England, the worst work of the era was little more than "theorem proving." But no longer are the models considered largely irrelevant.

In the last few years, many modelers have been tying their models tightly to data from field studies, and that's begun to pay off. Take chemotherapy programs for parasites such as hookworms or the flukeworms that cause schistosomiasis. "Models contributed significantly" to the design of successful drug treatments for these conditions, says Adel Mahmoud, who chairs the Department of Medicine at Case Western Reserve University in Cleveland and is not himself a modeler. Indeed, tropical medicine specialist Kenneth Warren of the Long Island–based Picower Institute for Medical Research makes the global point: "Modeling," he says, "has been crucial to understanding the control of parasitic diseases."

Current models take several forms, although most fall into two broad categories: analytical and computer simulation. The definitions of the two blur at the edges, but compared to computer simulation models, analytical models tend to be relatively simple, usually sets of differential equations that keep track of a few important variables such as the number of infected individuals.

Analytical approaches to infection have a long history. Sir Ronald Ross, who won the Nobel Prize in 1902 for working out that mosquitoes transmit malaria, later built simple models to illuminate the transmission cycle of the disease. In the 1950s and '60s, George Macdonald extended Ross's models, and, says May, came to the important conclusion that "killing adult mosquitoes is much more efficient than killing larvae" in attempts to control malaria.


ANDREW HALL

Starting young. Children in Jakarta receive treatment for helminth infections.

The early promise of analytical modeling was not sustained, however. May notes that Ross and Macdonald's models were successful because they were closely tied to data acquired in the field. But models only distantly related to field data subsequently proliferated. Even some of Macdonald's later work went astray, May says, "because it wasn't in accord with common sense, and wasn't very good mathematically anyhow."

Analytical models revived. May and his Oxford colleague Roy Anderson are widely credited with the resurgence of interest in and appreciation for analytical models of infectious diseases. Their work "brought the results of models to non–mathematically inclined people," says Marilyn Scott, director of the Institute of Parasitology at McGill University in Montreal. The two Oxford workers began collaborating in the 1970s, when May was at Princeton University and Anderson was at Imperial College, London. Their goal was to try to determine the importance of parasites in regulating the abundance and distribution of populations, and to clarify the factors involved in controlling the pattern of parasitic infections. Because long-term data on parasite infections in animals were sparse, Anderson says, "we were inevitably drawn to the human literature, where there are long runs of data."

They have used the data to help build models—mostly consisting of sets of linked differential equations—that capture the dynamics of parasitic infections with as few parameters as possible (see Anderson article on p. 1884). These models indicate, for example, that the biting rate of the *Anopheles* mosquito that transmits the malaria parasite plays a crucial role in determining how the infection progresses. In schistosomiasis, the prevalence of infected snails is an important variable affecting human transmission, and it depends, in turn, on such parameters as the length of time snails are infected but not infectious.

Indeed, evolutionary biologist Simon Levin of Princeton University cites this work on building links between ecology and epidemiology as Anderson and May's major contribution. They pioneered "the analysis of disease systems within a population biology framework," says Levin, "so you could begin to address such questions as the evolution of resistance to treatment."

While doing this, their models focused attention on some long-known but little-appreciated facts. Chief among them is that "macroparasites"—the helminths or worms—are rarely, if ever, randomly distributed among their human hosts, as many earlier models had assumed. Typically, says May, "80% to 90% of all worms are in 10% of the people. That fact is crucial for understanding the overall dynamics and for designing public health measures."

Theoretically, for example, efficient disease control can be accomplished by targeting heavily infected individuals for drug treatment, since they are disproportionately responsible for disease transmission. That was an important insight because until recently, most drugs for parasitic infections had unpleasant side effects and were sometimes fatal themselves. So, the modeling work showed that most population members would not have to take the nasty drugs.

But because identifying "wormy" individuals can be costly, modelers took a slightly different tack, asking whether targeting the segment of the population with the greatest proportion of heavily infected people would also be effective. As Don Bundy, an Oxford colleague of May and Anderson, points out, in the developing world, school-age children often have the most severe parasitic worm infections, possibly because their personal hygiene isn't as good as that of adults' and because they've had less time to build immunity. Field observations indicated that selective treatment of children would indeed reduce the overall level of infection in a population. Models by Bundy and others have reinforced the effectiveness of that strategy and outlined the range of conditions under which it will work.

This theoretical work, combined with the availability of new, safe, broad-spectrum anthelmintic drugs, has had a direct practical outcome: a major international effort, the Partnership for Child Development, which was started in 1992 by the United Nations Development Program, the Rockefeller Foundation, and others, to combat helminth infections in school-age children in the developing world. The Partnership, with Bundy as coordinator, has enlisted four countries so far, and already tens of thousands of children in Ghana have gotten the first round of drug treatment.

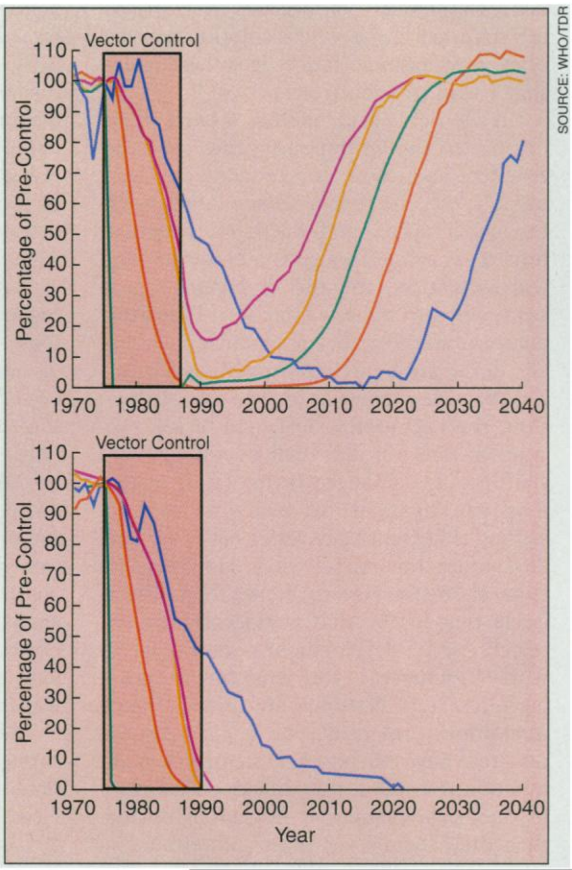
Enter the computers. But if mathematically accessible analytical models have, upon occasion, aided the design of parasite control strategies, their main goal has always been promoting an understanding of the dynamic behavior of parasitic infections. Says Bundy: "We're surprised and pleased when they also turn out to be predictive and have policy-making value." In contrast, computer simulation models try to incorporate many more of the variables influencing parasitic diseases. And they can be specifically designed to predict outcomes of control programs. "An analytical model grabs the basic characteristics of disease using simple mathematics," says Hans Remme, who coordinates applied field research for the World Health Organization's Tropical Disease Research program. "A simulation model tries to make predictions for operational decisions."

Remme speaks from experience: He helped develop the signature success story of simulation modeling. Called ONCHOSIM, this simulation helped participants in the Onchocerciasis Control Program (OCP) in West Africa decide how to bring that parasitic infection, better known as river blindness, under control—and thereby checked a scourge that has left some 340,000 people blind.

When the OCP was launched in 1975, it tried to stem the spread of the disease with a pesticide that kills the larvae of the black fly vector that transmits the parasite from one human to another. Since larviciding is expensive, program managers wanted to continue only as long as necessary to be reasonably sure that the reservoir of the long-lived parasite in human hosts was too small to lead to a resurgence of the disease when the black fly population recovered.

To address this question, Remme and collaborators from Erasmus University in the Netherlands wrote a microsimulation model in which they created an entire West African community in a computer. Every person in this hypothetical community was represented, each with his or her own risk of being infected with a new worm. A single computer run follows the population from years before the start of a control measure to years after its completion. At each time step, events occur that are governed by probability distributions: A person is bitten by a fly or not; if bitten, an infectious larva is transmitted or not; if the larva is transmitted, it is male or female; and so on. Hundreds or thousands of computer runs are necessary to build up a realistic picture of the possible outcomes of control measures.

For example, the modelers were asked to simulate the effects of larvicide treatment for different lengths of time. ONCHOSIM indicated that 13 years of applications would leave an unacceptably high chance of the disease returning, but 14 years was enough to drive that likelihood below 1%. Based partly on that analysis, the OCP stopped the application in the central part of the treatment area after 14 years. So far, the predictions have been borne out; black flies captured there remain free of the parasite.



A shade of difference. By analyzing such indicators of onchocerciasis prevalence as the numbers of female worms *(pink lines)* and the number of cases of river blindness *(blue)*, the ONCHOSIM model concluded that 14 years of vector control would do the job.

Skeptics remain. But despite successes like these, modelers have yet to win over all their critics. Take Stephen L. Hoffman, a malaria specialist at the Naval Medical Research Institute in Bethesda, Maryland. Although he says he is excited about the potential for models to contribute insights, Hoffman is troubled about the lack of validation of the models: "Generally, they are based on limited data, and it doesn't seem that anyone goes forward to demonstrate that the models conform to reality."

Bryan Grenfell, a modeler from Cambridge University, England concedes that many critics believe that, but maintains that "the criticisms are often of [specific] models, not modeling." He even suggests that models may be more interesting when wrong, permitting refinement of the hypothesis represented by the model.

This sort of debate is exacerbated by the fact that, even among the practitioners of the two forms of modeling, there's some rivalry. Model makers face a constant tension between simple, generalizable models on the one hand and complex models that try to mimic the real world on the other. Grenfell, a proponent of the analytical approach, agrees that ONCHOSIM seems to have worked well. But, he says, "you're not quite sure why. It's like driving in a car and not being sure how it works." Because the model contains so many parameters—more than 70—that must be estimated, "you don't know exactly what is driving the dynamics," he says. In contrast with simple analytical models, "you can explore explicitly the consequences of your assumptions."

Remme counters that many of the parameters are not critical to ONCHOSIM's dynamics but are included to help create output that is realistic enough to convince the model's many clients, from medical professionals to village leaders, that it is in fact true to life. He adds that analytical models have their own weaknesses: They "don't usually address the time dimension, such as the longevity of the parasite," he says, and that can undermine their usefulness, as such information is needed to design control strategies.

The infighting among the cognoscenti is a sign of a vital field, one competing for attention and funding. Viewed as irrelevant by most parasitic disease specialists a few decades ago, mathematical modeling has helped many of these specialists relate the disease they see in individuals to the pattern of infection they find in populations. Increasingly, say public health experts, modeling is doing more than proving theorems: It's helping.

–Billy Goodman

Billy Goodman is a free-lance writer based in Montclair, New Jersey.

Additional Readings

R. M. Anderson and R.M. May, *Infectious Diseases of Humans: Dynamics and Control* (Oxford University Press, Oxford, 1991).

M. Scott and G. Smith, Eds., *Parasitic and Infectious Diseases: Epidemiology and Ecology* (Academic Press, San Diego, 1994).

J. H. F. Remme, E.S. Alley, A. P. Plaisier, "Estimation and prediction in tropical disease control: the example of onchocerciasis" in *Epidemic Models: Their Structure and Relation to Data*, D. Mollison, Ed. (Cambridge Univ. Press, Cambridge, in press).