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Mathematical Modeling and Cancer

Moving beyond the qualitative conclusions of earlier models in biology, mathematical models are beginning to make quantitative, testable predictions about real patients.

By Dana Mackenzie

When Renee Fister was three years old, she lost her younger brother, then 18 months old, to cancer. Growing up, she hoped to go to medical school so that she could fight the disease that claimed her brother. But along the way, she discovered that she didn't have the stomach for medicine—and that she liked mathematics a lot. She changed her plans, but reluctantly. "I thought I wouldn't be able to work on cancer any more," she says.

A generation ago, that might have been true. To mathematicians, biology seemed too nebulous, too hard to pin down with the precise laws and calculations that work so well in physics and engineering. Though mathematicians did have some success in genetics and population biology, a serious mathematical theory of cancer seemed like a figment of the imagination.

Now, though, mathematical models are popping up everywhere in cancer research. The approaches are as diverse as the disease they are grappling with. Fister, a mathematician at Murray State University in Kentucky, studies optimal-control models that promise to provide physicians the best timetables for drug treatments. Her colleague Carl Panetta, of the St. Jude Children's Research Hospital in Tennessee, uses systems of elementary differential equations—typically 30 or 40 at a time—to predict a patient's response to a given drug regimen. At the University of Washington, applied mathematicians James Murray and Kristin Swanson have developed a brain tumor model that is simple by comparison but uses complex three-dimensional brain anatomy to improve on the predictions of physicians about the spread of the tumors. Meanwhile, in Israel, Zvia Agur of the Institute for Medical Biomathematics is working on the ultimate biomathematical model: a "virtual cancer patient" for non-Hodgkin's lymphoma, which will take into account all the stages of a cancer cell's life cycle.

If these mathematical descriptions of cancer have any common denominator, it is a scrupulous attention to biological correctness. They are moving past the vague qualitative conclusions of older mathematical models in biology and making quantitative, testable predictions about real patients (or at least laboratory animals).

"I have worked in applications of mathematics to biology for nearly 30 years," says Murray, who was the founding director (in 1983) of the Centre for Mathematical Biology at Oxford University. "The whole tenor has changed in the last 10 years. At the Dundee meeting [of the Society for Mathematical Biology, held last summer], I was delighted to see that almost all of the talks were biologically oriented. The speakers were solving their equations quantitatively and saying what the answers predicted biologically. Having been brought up in Scotland, under the gloom of Calvinism, one shouldn't be optimistic about anything, but I am particularly optimistic about the future of mathematical biology."

Controlling the Uncontrollable

Fister and Panetta are both members of the younger generation of mathematical biologists, having received their doctorates in the 1990s. Panetta, like Fister, has been intrigued by cancer for as long as he has been a mathematician, and four years ago he jumped from an academic position at Pennsylvania State University in Erie to his present job at St. Jude. "It gives me a lot more chances to work with direct applications of math, plus I have access to all the data I need," he says.

Panetta's day-to-day work involves pharmacodynamics—a mouthful that he defines as the study of "how much of the drug is getting into the patient's cells and how fast it is getting cleared." To answer these questions, he uses a giant system of linear differential equations that model cell-to-cell and drug-to-cell interactions. Because they are linear, the systems can be solved exactly. But solving them is only half the job. The other half is parameter-fitting. Every patient reacts a little bit differently to a drug regimen, and the differences show up in the constant coefficients—the parameters—in the differential equations. The right parameters for each patient have to be teased out statistically from the data.

Panetta's differential equations model very well-established drugs like metha-trexate, which has been used to treat leukemia for 30 years. But he has also done more speculative work, such as an optimal-control approach to chemotherapy that he and Fister described in a 2003 paper in *SIAM Journal on Applied Mathematics* (Vol. 63, No. 6).

Fister and Panetta started with one simple differential equation:

$$\frac{dN}{dt} = rN\ln\left(\frac{\theta}{N}\right) - G\big(N, u(t)\big).$$

The variable N represents the tumor volume, the parameter r is a growth rate, and θ represents a maximum size for the tumor. The most interesting term is the last one: $G(N, u(t))$, which describes the interaction between the physician-prescribed treatment $u(t)$ and the tumor volume N. Because the nature of that interaction is very much up for debate, Fister and Panetta considered three possible versions. "One says that you kill the most cancer cells when the tumor is largest," Fister says. "The second, which was

based on Hodgkin's disease, says that the drug is most effective when the tumor is small but has the highest growth rate." The third incorporates a biologically realistic assumption—a saturation effect, which has the drug becoming less potent as fewer proteins are available for binding.

What makes optimal control unique is another ingredient, the "objective functional," which expresses the desired goal of the therapy. Is it to minimize tumor size? Or is it to minimize the expense to the patient, which might be expressed as an integral of $u(t)$, the amount of drug given? Or should the goal be to maximize the patient's quality of life, which might be represented by a functional that penalizes high doses, possibly an integral of $u(t)^2$?

Or perhaps the therapy should aim for a combination of all the above.

Panetta and Fister found that each of these considerations has an important influence on the design of the optimal therapy. The tumor-size hypothesis implies that it is beneficial to delay treatment until the tumor is large, while the other two lead to recommendations for early treatment. The linear patient-cost model implies that "bang-bang controls" are best, in which the physician gives the patient either a maximum dose or no drugs at all. Based on the nonlinear patient-welfare model, the physician would phase the drugs in and out more gradually.

Although optimal-control theory has a long history in engineering, its application to cancer treatment is still very new. "Physicians have tried-and-true methods they've been using for a long time," says Panetta. "If you go to them with something new, they would say, 'Show me that it's better.' It will take more retrospective studies—but that's slowly happening."

Simplicity Is a Virtue

"Glioblastoma" is a word that you do not want to hear your doctor pronounce. One of the most aggressive brain tumors, it has a puzzling tendency to come back even after surgeons have removed the entire visible tumor. According to Kristin Swanson, "the mortality rate is essentially 100 percent. These tumors are considered uniformly fatal," with death usually coming within a year of diagnosis.

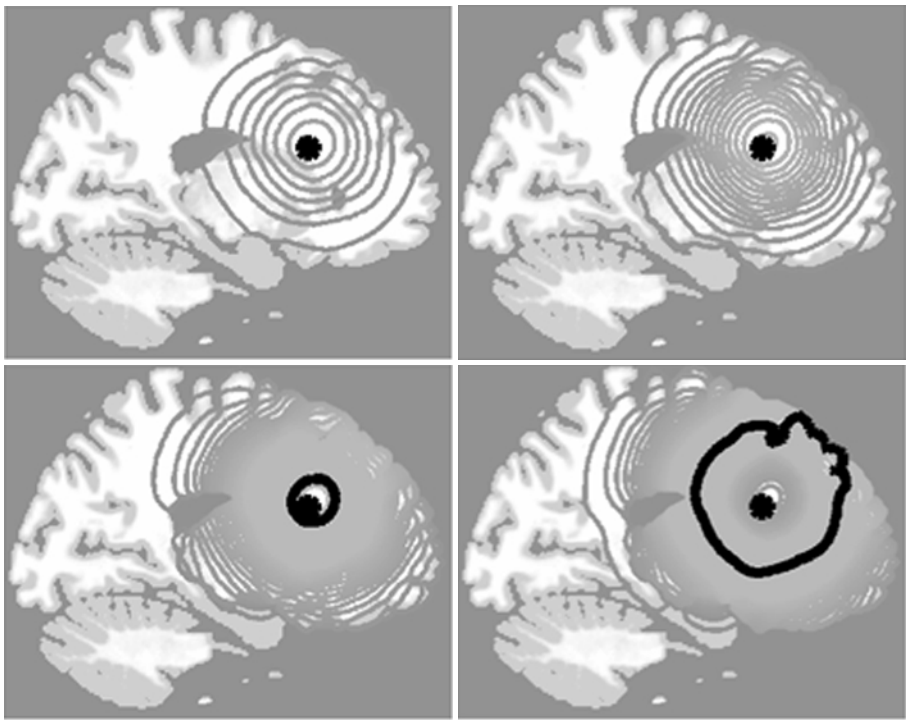
Given that neither surgery nor chemotherapy nor radiation can stop this disease, it would be foolish to expect mathematics to change the outlook. But what math can do—and what Murray's model, refined by several of his students and postdocs, has done—is give oncologists a much better understanding of the foe they are up against.

The model is dynamically quite simple, with only one equation, which describes the diffusion of cancer cells through brain tissue. "We'd make it more complicated, but so far we haven't had to," says Swanson. "We're still waiting for the simple model to be disproven." The model is plenty complex, though, when it comes to simulating the brain's anatomy. Swanson and Murray represent the brain as a $181 \times 217 \times 181$ grid, with each cube in the grid representing either gray or white matter; gliomas progress at different rates through the two types of tissue.

The results, when presented as a computer animation, are sobering in the extreme. See illustration on facing page; readers can visit http://www.amath.washington.edu/~swanson/research.html for other examples of simulations. The typical glioma grows unsuspected for nearly 500 days before it becomes detectable by magnetic resonance imaging. (Until that time the cancer cells are not dense enough.) At 500 days, when a surgeon would typically find and remove a small tumor, the cancer cells have already spread through one whole temporal lobe of the patient's brain. No wonder surgery has little effect. "I like to use the iceberg analogy," Swanson says. "You see 10 percent above the surface, and there's 90 percent below the surface that you don't see."

Swanson and Murray can plug a patient's MRI scans into the model and predict where the cancer will invade next. This allows the doctors to plan their radiation therapy accordingly. The model also provides them with temporal information—how long the patient has to live. "What amazed me was how accurate the predictions of survival time were," Murray says.

In Murray's opinion, the model could benefit patients by convincing doctors not to attempt risky and hopeless surgery. "If we do surgery, the patient might lose mobility, or it might affect their sight or



Snapshots from a three-dimensional simulation showing the progression of a glioma. Top: At 425 (left) and 500 (right) days, the tumor is undetectable on magnetic resonance imaging; the contours indicate the distribution of the tumor predicted by the mathematical model. Bottom: At 575 (left) and 640 (right) days, a small portion of the tumor is detectable on MRI scans; the heavy black contour is the edge of detectability. The outer contours represent the "invisible" residual disease that is responsible for treatment failure and recurrence. Images courtesy of Kristin Swanson.

speech." says Murray. "The surgeons already know that, but most were not aware how far the infiltration [of a patient's brain by the tumor] has gone." Sometimes, he says, the best treatment may be no treatment at all. He cites the example of a patient who chose not to undergo surgery, and enjoyed nine more months of normal life. "I completely sympathize with her," Murray says.

. . . But So Is Complexity

At the other end of the spectrum, mathematically, lie the simulations developed by Zvia Agur. A biologist by training, she extols the value of simple models for providing insight, but argues that simplicity is not the way to go when you want clinically useful information. "Physicians are very busy people," she says. "They pay attention to models that give them something to use, not intellectual understanding."

One of Agur's models could help mitigate a side effect of chemotherapy, the destruction of blood platelets. Some doctors have had the idea of stimulating the body to produce its own platelets by injecting a naturally occurring protein called thrombopoietin (TPO). However, recombinant or synthetic TPO can provoke an immune reaction, because the body recognizes it as a foreign substance. Administering TPO is thus a delicate balancing act—injecting just enough to stimulate platelet production, without overdoing it and causing an immune reaction.

Unlike most cells in the body, the ones that manufacture platelets, called megakaryocytes, do not divide after reproducing their DNA. Some megakaryocytes, in effect, are more "mega" than others. Some are only little workshops, with twice the normal amount of DNA, while others are veritable factories, with 32 or 64 sets of DNA or even more. Not surprisingly, the workshops and the factories differ in their response to TPO. Accordingly, Agur's model includes ten variables representing the number of cells of each size, plus an eleventh variable representing the amount of TPO. She had to estimate more than 100 parameters, some of which had never been estimated before. She did this in two steps—first finding averages that work for the entire species, and then fine-tuning them for individual mice or monkeys.

Her results, published in the November issue of the *British Journal of Haematology*, were for the most part spectacular. In the mice, the predicted platelet levels almost perfectly matched the observed values for 11 days after injection. In four rhesus monkeys, the models gave good predictions for more than 30 days. But in the fifth monkey, who had an immune reaction against the TPO, the computer's output bore no resemblance to reality. "There are no miracles," Agur says. "Sometimes your model doesn't fit. Then you have to do good scientific thinking to find out why not."

Still, the results were promising enough that Agur is planning to start human trials with 10 to 100 patients. Best of all, she believes that she can improve on the currently recommended dosages of TPO. Her model predicted that she could get an equally strong platelet-building effect by giving one-tenth of the normal dose, but giving it four times as often. This would lessen the chance of an immune reaction. Experiments with mice and monkeys bore out the prediction—in her words, an "unprecedented" case of a new protocol suggested by theory being validated in the lab.

Although the medical community as a whole may still be suspicious of the value of mathematics, most of the cancer modelers have nothing but positive things to say about the support they have received from individual biologists. Murray says that the glioma model would never have gotten started without the instigation of Ellsworth Alvord, a pathologist at the University of Washington. Swanson, who has a joint appointment in pathology, adds, "When I started here as a postdoc, there was definitely some skepticism at first. But the transition to, 'Why don't you help me next?' was very exciting. The fact is that for gliomas, doctors are at wit's end when it comes to treatment options. They're willing to try anything that helps."

Dana Mackenzie writes from Santa Cruz, California.