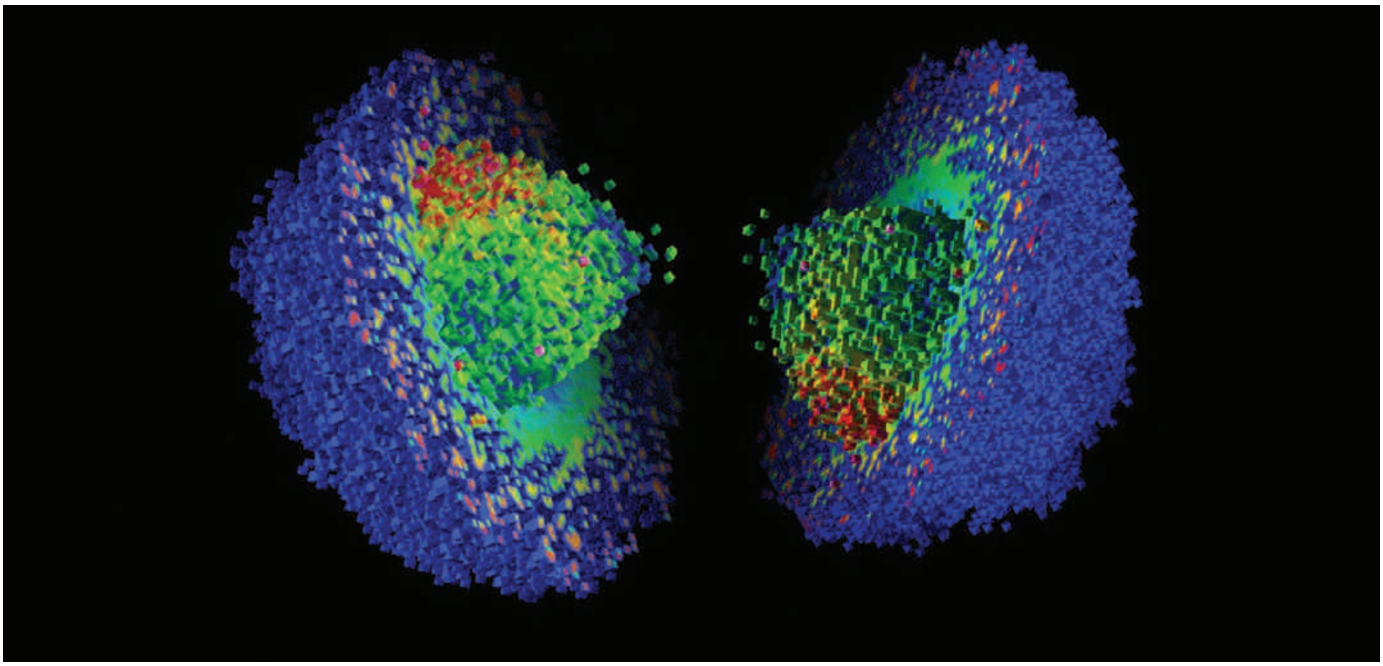


ALEXANDER R. A. ANDERSON, WWW.MOFFITT.ORG/IMO

The inside of a tumour can be visualized on a computer by using mathematical models.

MATHEMATICAL MODELLING

Forecasting cancer

Complex mathematical models are helping researchers understand cancer's evolution and providing clues on how to thwart drug resistance.

BY KATHARINE GAMMON

Einstein once called pure mathematics "the poetry of logical ideas". It is a poetry that has allowed astronomers to understand the movement of planets, and it has shaped our understanding of the physical world around us. Now it is set to reshape our view of cancer. From speeding up clinical trials to predicting cellular mutation and evolution, mathematical models are helping to transform fundamental ideas underlying the disease.

Mathematicians are making inroads in oncology with approaches that used to be the realm of biologists: building intricate models of cancer ecology and evolution. It's a logical transition. The forces of environmental selection and adaptation that act on organisms also govern the way cancer cells develop, and a better understanding of how the disease evolves and adapts to environmental changes can help researchers find a way to stop it. "Evolutionary theory is the theory for cancer," says Carlo Maley, a computational and evolutionary biologist at the University of California, San Francisco. "If we can engage with this evolutionary process, we can slow it down or shunt it in a direction that's more manageable."

Cancer's heterogeneity is the main reason it is so difficult to treat — if it retains a diverse enough population, a few impervious tumour cells can survive chemotherapy or radiation and re-establish their hold on the body. So mathematicians are creating models to predict in which direction a mutating cancer cell will change, in the hope of stopping evolution in its tracks.

ELIMINATING GUESSWORK

Through modelling, researchers can now predict the behaviour of some of the toughest cancers. Historically, oncologists have evaluated the prognosis of glioma, an aggressive form of brain cancer, on the basis of imaging and histological data. But that grading system didn't match up with reality, leading researchers at the University of Washington in Seattle and the Moffitt Cancer Center in Tampa, Florida, to develop a mathematical model based on cell proliferation, invasion rates and changes in appearance. The model marries data from imaging studies with other models that incorporate blood-vessel growth patterns and tumour microenvironment, and was able to reproduce the growth patterns of each patient's specific tumour, and also reliably predict how it would progress — validating the method and improving on the existing grading.

Such models are starting to have an impact in the clinic. Alexander Anderson, a mathematical and computer modeller at the Moffitt centre and one of the team who worked on the glioma study, is using the model to investigate how cancer moves and spreads[1]. His lab has built computer models that focus on the changes to individual cancer cells. The models integrate information from different *in vitro* experiments with factors from *in vivo* environments to gain a better understanding of how cancer progresses one cell at a time. Anderson recently used clinical data from 650 prostate-cancer patients. Each patient's tumour was sliced multiple times and stained for 250 markers. He then integrated that biopsy information into a model, creating a digital version of the biopsy. When he and his colleagues move the model forward in time and space, they can create a predictive measure of whether a tumour will be aggressive.

This detailed ability to predict invasiveness is particularly important in diseases such as prostate cancer, in which some tumours are removed unnecessarily and treated aggressively. To assess the model's predictive accuracy, Anderson's team, working with a biologist, is testing it in mice. If the model works, it would be the first to predict a tumour's aggression before the start of treatment, providing oncologists with a guide for treatment options.

Beyond evolutionary dynamics, mathematical

models are helping to reshape the way some researchers approach cancer treatments. The improved understanding of cancer evolution provided by the models provide has led some researchers to a counter-intuitive conclusion: for most cancers, targeted therapy just doesn't work. When you use drugs that target specific mutations, Anderson says, "our models tell us that you're destined to see drug resistance because there's another route to the same phenotype". Cells that survive the first wave of therapy can evolve to have the same malignant characteristics but without the same vulnerability to the drug. What's more, the evolutionary dynamics of tumours suggest that trying to eliminate cancers speeds up the development of drug resistance, reducing a patient's chances of survival. Models show that there might be a better way.

CHANGING THE GAME

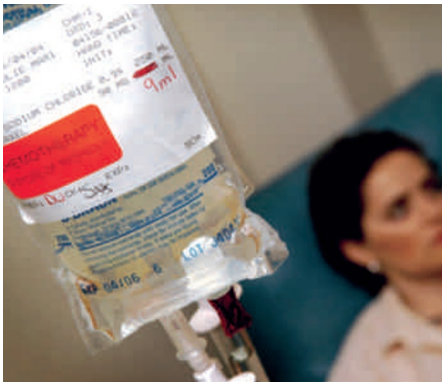
Some researchers are looking for ways to hack cancer's programming and turn it against itself. Robert Gatenby, an oncologist at the Moffitt Cancer Center, has been seeking fundamental laws he can exploit. One way to attack tumours is to make them similar to each other; the more homogenous they are, the lower the odds that they will become resistant to treatment, and the greater the chances that therapy will be effective. In essence, he is looking for tricks to prevent the evolution of drug resistance.

Mathematical models allow Gatenby and others to determine the right combinations of drugs, and the optimal sequence in which to give them, to best combat resistance. In one mouse study of triple-negative breast cancer — a hard-to-treat subtype characterized by a lack of receptors for oestrogen and other hormones — researchers used models to determine when they should use different drugs, and in what sequence. The results suggested that dosing the animals with extra oestrogen to would encourage the disease to adapt to a high-oestrogen environment. By guiding evolution's natural resistance mechanism, the cancers that emerged were oestrogen dependent — and were thus treatable with oestrogen-dependent cancer drugs, such as tamoxifen.

Treating cancer would be so much easier if oncologists could predict how it would react to treatment. At the moment, cancer treatment is an endless battle against an evolving foe, Gatenby says. "Cancer comes up, and we whack it and do another treatment." But he sees a better way. "We need to plan strategically how we treat patients, so that as we give one therapy, we're producing an adaptive response to be anticipated with our second therapy. Instead of whac-a-mole, we need to be playing chess."

Gatenby's team uses a game-theory model to show that cancers are good at adapting to their current situation but cannot anticipate the future. This insight gives oncologists a fundamental advantage: they can manipulate the tumour environment in ways that leave the cancer more vulnerable. The model lets researchers discard options that would increase resistance, narrowing the range of options for treatments, doses and dosing frequency.

The evolutionary game-theory model — in which each treatment was a move in the game, made in anticipation of cancer's response — suggested the development of that vulnerability and helped clarify results from a recent clinical trial[2].



ZUMA WIRE SERVICE/ALAMY

Prompting lung cancer to evolve one way might make traditional treatments more effective.

Patients with recurring, aggressive lung cancer who were treated with both traditional chemotherapy and a vaccine targeting the tumour-suppressing p53 protein fared better than patients who didn't receive the vaccine. The combination of treatments increased survival time by about 4 months and doubled the number of people surviving more than a year. "The tumour successfully adapted to an initial therapy, but that adaptation rendered it more susceptible to another therapy," Gatenby said. This is known as an evolutionary double bind. "We don't pretend that this could last forever, but if we could get an extra five to ten years out of evolutionary tricks, it would be a huge improvement."

DEVISING DOSING STRATEGIES

Mathematical modelling is also helping to speed up the clinical trials that test those drugs. Testing all the possible permutations of drugs and doses to determine the best course of therapy might take millions of clinical trials — and there are nowhere near enough patients or resources for that. So instead researchers are using mathematical models that make it possible to derive the same information from only a handful of experiments. Such models can describe the rate of mutation, calculate the likelihood of resistance, and even predict the chance that a certain tumour will respond to treatment.

Franziska Michor, a biostatistician at Harvard School of Public Health in Boston, Massachusetts, has built a model to predict the optimal dosing scheme for lung-cancer therapy. By accounting for the growth and death rates of different types of cell, their mutation rates, and how quickly the body metabolizes a drug, Michor's mathematical framework calculates the probability of the tumour developing resistance for different dosing strategies. "Eventually we have to validate with mouse and human trials, but the pre-validation studies can be on a computer," Michor says. The computer model can test just about every possible combination in a few seconds — much faster than doing clinical trials. "That's the advantage of maths," she says. "If you run an infinite number of clinical trials, you will grow a really long beard. But on the computer, it works quickly."

In 2013, the Memorial Sloan-Kettering Cancer Center in New York will run the first trial based on Michor's model. Researchers will test the dosing patterns the model deemed best to prevent or delay resistance in non-small-cell lung cancer. With this disease, resistance typically appears a year after treatment ends, but Michor's model predicts that the best dosing strategy will delay resistance by another year[3].

And there's more. Mathematical models can also help researchers understand, and even prevent, tumour development. Larry Norton, an oncologist at the Memorial Sloan-Kettering centre, has devised a model of tumour growth based on nineteenth-century mathematics. The S-curve model showed that while tiny tumours barely grow at all, medium-sized tumours grow at a rapid pace, and large ones grow slowly. Norton and his colleagues hypothesized that the rate at which a tumour shrinks would also be proportional to its size, with large tumours shrinking slowly and small ones rapidly.

The conventional view of chemotherapy dosing held that, because tumour growth was exponential, each treatment killed the same amount of tumour. Norton, however, used his theory to argue that giving the same total amount of chemotherapy over a shorter period of time should improve the cure rate. Because his model showed that young tumours have the fastest growth rate, he said, the less time they had to regrow between treatments, the better the cure rate would be. Norton's idea was vindicated in 2002, when a large breast-cancer trial showed that giving chemotherapy every two weeks instead of every three lowered the risk of disease recurrence by 26% over three years, even though the cumulative dose was the same.

Norton makes the point that none of this would be possible without integrating biological growth models into treatment research. "The biological sciences have become anti-maths, and it's just not working. Researchers see lots and lots of facts, but they're not connecting them together," he says. "It's like looking up at a starry sky and wondering how it worked. Only when Kepler and Newton came along did things fall into place." ■

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