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Cancer modelling

Malignant maths

Mathematical models aid the understanding of cancer

PRACTITIONERS of so-called hard sciences—those backed up by the mathematical rigour of formulae and equations—have traditionally looked down on the squishy end of research. That disdain has evaporated a bit over recent years, as government money has migrated from physics to biology and medicine. But it is disappearing as biologists show that they can be just as quantitative as their hard-edged colleagues.

And one example is in the field of cancer research. According to Hans Othmer, a mathematician at the University of Minnesota, in Minneapolis, who has written a review of the subject forthcoming in the *Journal of Mathematical Biology*, a rapid growth in the understanding of the microscopic processes behind cancer is allowing useful mathe-matical models of the disease to be developed. Indeed, the field is booming, which is why the ponderously named *Discrete and Continuous Dynamical Systems—Series B*, another scientific journal, is devoting a special issue to the subject in February.

One paper in this special issue, by Zvia Agur and her colleagues at the Institute for Medical BioMathematics, in Bene Ataroth, Israel, presents a model that attempts to describe how angiogenesis—the process by which a tumour creates its own blood vessels—works.

When a tumour first develops from a cell whose genes have mutated in ways which cause that cell to reproduce frantically, its growth is limited to about a millimetre across. This is because no blood vessels penetrate the tumour, and therefore cells deep within it are not able to get nutrients or oxygen.

Bloody essential

Tumours of this size pose little threat to a person's health. Indeed, many tumours stay this small. But in some, further mutations cause the production of chemicals called growth factors, which stimulate the formation of blood vessels. This process is dangerous for the individual not only because it allows tumours to grow in size, but also because cancerous cells can now enter the bloodstream, travel around the body, lodge in other places, and then continue to grow. Such dispersion results in the formation of secondary tumours, known as metastases, which are what kill the patient in many cases.

Dr Agur examined magnetic-resonance images of tumours undergoing angiogenesis, and then set up a system of differential equations to simulate what she saw. Differential equations relate the rate of change of a variable (for example, the amount of growth factor being produced) to its current value and, in some cases, its past values. And they are the staple of virtually all mathematical models of cancer, which usually consist of a set of “simultaneous” differential equations, one per variable, whose results feed into one another. Solving such systems is difficult; indeed, precise solutions can only rarely be found. Instead, researchers rely on numerical simulations, or else analytically describe the rough form that solutions might take.

In Dr Agur's equations, the variables are the number of cells in a tumour, the concentration of the angiogenetic growth factors within it and the volume of the blood vessels supporting it. The result was the discovery that there are circum-stances in which a tumour oscillates in size, instead of growing steadily. In other words, it is contained. If such circumstances could be replicated in reality, it would be a powerful way of controlling tumour growth.

Stemming angiogenesis would stop a tumour in its tracks. But if it is too late for that, different methods are called for. In the past, there were only three ways of treating cancer. The first was to remove the cancerous cells by surgery. The second was to treat them with chemicals that would inhibit their growth, or kill them off. The third was to blast them with ionising radiation, or with heat.

Helping those who help themselves

In the past few years, however, a fourth method has come into being. This is to stimulate the immune system. Because cancer cells contain mutations, they produce proteins that appear “foreign” to the immune system. That system is designed to attack such cells—and, indeed, it often does so of its own accord. But sometimes it needs a helping hand, in the form of an external stimulus, such as a drug.

Because immunotherapy is still in its infancy, its potential, and the behaviour of cancerous cells when they interact with the immune system, are not that well understood. This makes the field particularly fertile ground for mathematical modelling. In another of the special-issue papers, Denise Kirschner of the University of Michigan, in Ann Arbor, describes her investigations into how a novel treatment, known as “small interfering RNA” (siRNA) therapy might suppress the action of a molecule called “transforming growth factor beta” (TGF-beta), which large tumours use to elude the immune system.

The equations of Dr Kirschner's model describe four quantities: the number of immune-system “effector cells” (those that combat tumours), the number of tumour cells, the amount of interleukin-2 (a protein that enhances the body's ability to fight cancer), and an additional variable to account for the effects of TGF-beta.

At the moment siRNA therapy has been tried only in a test tube, so Dr Kirschner's simulation may provide a quick way of deciding whether it is worth pursuing actual animal experiments. According to her paper, it looks promising. In the model, a daily dose of siRNA over the course of 11 successive days succeeded in counteracting the effects of TGF-beta, and so allowed the immune system to bring the tumour under control, although it did not succeed in eliminating the tumour entirely.

Back to basics

Both Dr Agur's and Dr Kirschner's work look promising. Not all of the mathematical models discussed in the special issue are as abstract, though. Pep Charusanti and his colleagues at the University of California, Los Angeles, looked into how a drug called Gleevec acts against chronic myeloid leukaemia.

Gleevec works by preventing the phosphorylation of a protein called Bcr-Abl, which is crucial to the development of the cancer. Phosphorylation is an energy transfer process, the energy in question being transferred from molecules known as ATP, which are the end-result of the process of respiration. Because the model focuses on a specific cancer, and a specific drug, it is more detailed than any of the others. It goes back to basic equations of “biochemical kinetics”, the study of how fast biological chemicals interact. And it focuses on the specific pathway by which Gleevec blocks the action of ATP.

Gleevec successfully induces remission in some patients, but it does not work during the final stage of chronic myeloid leukaemia, which is known as a blast crisis. Mr Charusanti's model, which closely matches the behaviour of the drug in laboratory mice, shows that cells in blast crisis expel the drug too quickly for it to be useful as an ATP-blocker. That suggests it might be useful to come up with a chemical which would slow down the pumping process by which malignant cells clear them-selves of the drug.

Physicists can still feel smug. None of these models is a truly faithful representation of what is going on in and around a tumour. The situation is far too complex. But they are creating useful insights. As Richard Feynman, a Nobel-prize winning physicist, once said, “mathematics is a deep way of describing nature, and any attempt to express nature in philosophical principles, or in seat-of-the-pants mechanical feelings, is not an efficient way.” If cancer is ever to be understood properly, mathematical models such as these will surely play a prominent role.