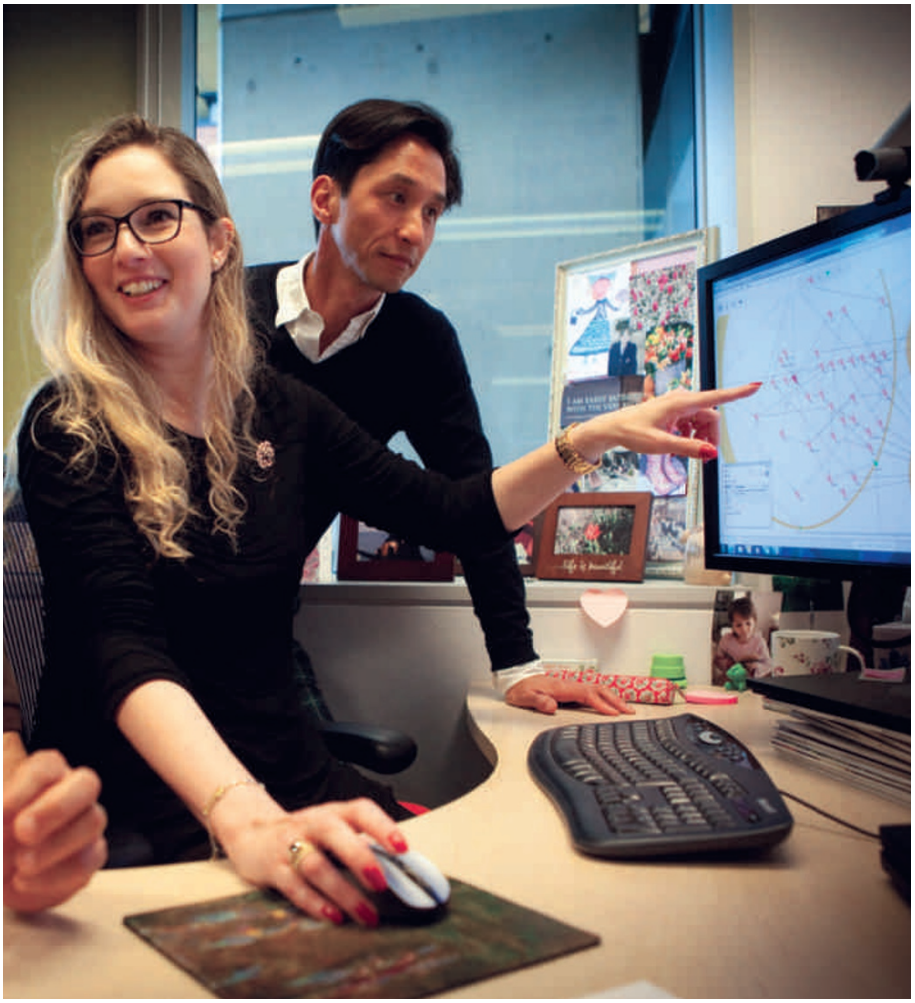

JASMIN FISHER

Jasmin Fisher's computer models help biologists understand the molecular pathways in cancer cells.

MODELLING

Computing cancer

Software models of complex tissues and disease are yielding a better understanding of cancer and suggesting potential treatments.

BY NEIL SAVAGE

When the drug Avastin was approved as a treatment for breast cancer in 2004, physicians and researchers saw it as a powerful weapon in their armoury. Growing tumours need increased amounts of oxygen, so they send out chemical signals that coax the growth and development of new blood vessels, a process known as angiogenesis. Avastin (bevacizumab) interferes with this process by cutting off the tumour's oxygen supply, causing it to shrink. But doctors found that Avastin often left more invasive tumours in its wake. A subsequent study found that, although Avastin did suffocate tumour cells, the lack of oxygen encouraged the growth of cancer stem cells, resulting in more aggressive tumours. The US Food and Drug Administration revoked its approval in 2011.

Cancer is not a simple disease. Tumours are made up of various types of cell in different stages of their life cycle, and these cells send out and respond to a wide range of chemical signals. They are laced with blood vessels and interact with the surrounding tissue, with the organs they invade, and with any drugs used to combat them. Gene sequencing and proteomics have yielded reams of data that scientists are only just beginning to parse. To understand this complexity, and to explain why a drug such as Avastin doesn't work as expected, researchers are turning to computer models that help them visualize how cancer grows, generate ideas about how to combat that growth, and simulate the potential results of possible interventions.

BEATING THE SYSTEM

"The amount of understanding, knowledge and information we have at hand is huge, but it's too complicated to make sense of, in terms of what's going on in the system," says Jasmin Fisher, a neuroimmunologist in the Programming Principles and Tools group at Microsoft Research in Cambridge, United Kingdom.

With all this information, it's possible to miss the cancer forest for the cellular trees, says biophysicist James Glazier, director of the Biocomplexity Institute at Indiana University in Bloomington. Researchers have tended to focus on genes and proteins, but to understand and fight the disease, it must be viewed as a system, rather than merely as a set of cellular activities. According to Glazier, the recent focus on genetics and pathways in individual cells has caused many researchers to neglect the systemic view. "No amount of information about what happens inside a single cell can ever tell you what a tissue is going to do," he says. "Much of the information and complexity of tissues and life is embedded in the way cells talk to each other and the extracellular environment."

It was this need to investigate cancer as a holistic system that prompted mathematician Philip Maini, head of the Center for Mathematical Biology at the University of Oxford, UK, to model the behaviour of antiangiogenic drugs. Because these drugs are most effective when used in combination with radiation or another chemotherapy, the theory that they work strictly by cutting off blood flow and starving the tumour just didn't make sense. Maini's model shows that its is the blood-vessel density inside the tumour that holds the key to the drug's effectiveness[1].

Such modelling can be used to determine whether a drug is likely to work, or even to suggest targets for future drugs. "You can test the ideas in a simulation without even killing a rat," Glazier says.

Creating these complex simulations requires computational modelling, says Adriano Henney of the University of Heidelberg, director of the German Virtual Liver Network, a collaboration to develop computational models of the entire organ. "This approach is going to be important if we are to understand how medicines operate in complex diseases."

OPEN-SOURCE MODELLING

In one step towards such simulations, Fisher is developing computational models at Microsoft that describe molecular pathways within cells, how those pathways operate, and the way cross-talk between them affects the process of determining a cell's fate. "We look on a

biological process as if it were a computer program, so we ask 'what is the algorithm inside the cell that is affecting behaviour?'," she says.

Fisher calls this modelling approach "executable biology", as it takes a biological understanding of cellular processes and turns them into a set of formal instructions that a computer could execute[2]. For instance, a stem cell follows a different series of steps depending on whether it differentiates into a blood cell or a heart muscle cell. Several of those changes occur simultaneously and can be altered by feedback the cell receives as it matures. Because living processes are complex and nonlinear, Fisher's program makes it easier for researchers to perform manipulations, such as changing the sequence of events or decreasing the strength of a signal, to see whether the steps they have modelled lead to an outcome that matches up with experimental results.

The challenge in developing models for different levels of organization, Maini says, lies in finding the right mathematical approach for each scale. It might be best to describe intracellular activity, such as forming a protein, by using differential equations, for example, whereas cell-to-cell signalling might require a different approach, such as rule-based programming, to define how cells interact.

To deal with these different scales, Glazier has developed an open-source modelling methodology called CompuCell3D that treats cells, components within cells, or cell clusters as discrete objects. The user can input biochemical information into a model of a cell — such as how it responds to chemical stimuli, or how strongly it sticks to other cells — and watch how the system responds[3].

Glazier started developing the model in 2000, basing it on a previous model he built that simulates the growth of grains in crystalline structures. This turned out to be similar to the way bubbles grow in liquid foam, which in turn could be extended to describe the interaction of cells in developing embryos.

IN SILICO INSIGHTS

The models developed by Glazier, Fisher and others are designed to allow cancer biologists with little or no programming knowledge to create their own simulations to run *in silico* experiments. "We wanted to build a platform that would allow you to create simulations that other people could run, adapt, modify and so on, so the models would be shareable and reproducible," Glazier says. This involves replacing detailed computer coding that describes biological processes with simplified representations of those processes that biologists can easily understand. In Fisher's program, a biologist can select particular cells, proteins and genes, and then drag-and-drop them on a computer screen to create the conditions for the simulation.

By using CompuCell3D as a tool to build a model of a tumour, Utah State University researchers Nicholas Flann and Gregory Podgorski have been exploring angiogenesis, hoping to find ways to inhibit it and prevent tumour growth[4]. A microtumour emits a protein called vascular endothelial growth factor (VEGF), which signals blood vessels in nearby tissue to grow towards it. In the body, that process can take from 24 to 72 hours; on the computer, it takes about five minutes.

Flann, a computer scientist, and Podgorski, a biologist, gave the model 40 biochemical parameters, such as a cell's ability to detect a particular growth factor, or how strongly the tip of a growing blood vessel would stick to a stromal cell in the surrounding tissue. The software then chose three parameters, changed one at random, and looked to see whether the change improved or reduced blood-vessel growth in the model. In all, there were about 100,000 possible parameter combinations that might deprive the tumour of nutrients. To give the results statistical strength, each combination was tested 128 times, running in parallel on two large computer networks belonging to the US National Science Foundation and the US Air Force. Parallel processing allowed the researchers to perform in a few months simulations that would have taken a single processor about five years.

The first clue that the algorithm was effective was that it suggested known interventions, blocking pathways that existing drugs already act on. But it also produced other, previously unknown results. For instance, according to the model, manipulating the adhesion between the endothelial tip cells on the leading edge of blood vessels and the surrounding tissue causes the resulting vessels to become trapped, unable to provide adequate blood flow to the tumour. This, says Flann, suggests a possible avenue of attack for drug developers. In a system comprising hundreds of cells interacting, moving, secreting and reacting to chemicals, simply knowing the genetic mutation behind the tumour or the pathways within the cell would never have led to that kind of insight, says Flann. "The system is a complex spatial and dynamic system that just can't be predicted."

Computational models can run experiments *in silico* that would be too expensive and time-consuming to carry out in the lab. They can generate and test new hypotheses, and provide a way of tracing the steps that led to a particular outcome. But the models must also be validated, as they are no use unless they accurately represent disease in the real world. Maini worries that computational models that combine data from disparate sources — mixing mouse models and rat models with human cells, for example — might lead researchers astray. For instance, the anti-angiogenic drugs he examined starve the tumour more directly in mice than in humans, so an accurate model of human tumours is required. And the computer modellers say that scientists will need to tie the results of the computer simulations to data they can replicate in their labs.

Even so, the models are already giving scientists new ways to explore cancer's complexity

"It's a toolbox that is a way of handling the mass of complex data we've accumulated in a way that our brains can't," says Henney. "It's an approach that applies engineering principles, physics, chemistry and mechanical engineering to biology. I can't see how we can handle the complexity of the post-genome world in any other way than using mathematics and physics principles." ■

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MODELLING TUMOUR GROWTH

This computer model of tumour vascularization, a process known as angiogenesis, allows for a close examination of how cellular growth is affected by blood-vessel development.