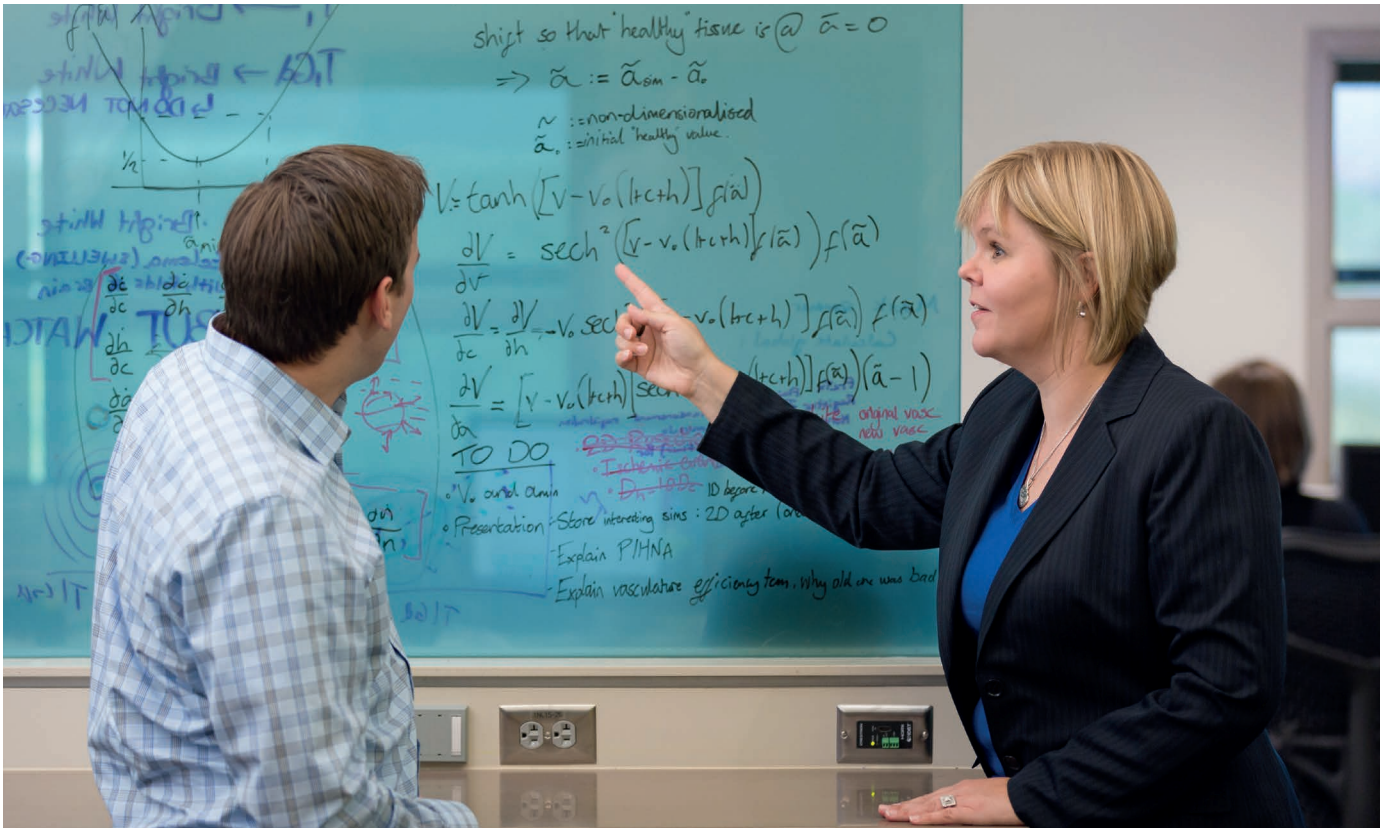

MAYO CLINIC

Kristin Swanson is using her mathematical background to improve modelling of brain-tumour growth.

MODELLING

The human equation

Mathematical modelling of brain tumours could deliver more-personalized treatments and improved survival.

BY KAT ARNEY

As a mathematician, Kristin Swanson has an unorthodox background for a professor of neurosurgery. But while she was finishing her undergraduate degree, her father was diagnosed with lung cancer.

"I sat with my dad as he was dying, and realized that there was nothing quantitative or analytical about the way he was being treated," she says. "The doctors would just react to what was happening and try something else — there was no real prediction of what the outcome might be."

The experience persuaded Swanson to apply her mathematical mind to the challenge of treating cancer. Because working on lung cancer would hit too close to home, she chose to focus instead on a condition with even more dismal prospects for survival: glioblastoma multiforme (GBM). This aggressive form of brain tumour is fast growing and highly invasive. Survival is measured in months rather than years (see page S40).

Surgery to remove the tumour is usually the first-line treatment for GBM, followed by regimens of chemotherapy and radiotherapy that are essentially the same for each patient. Yet there is a wide variation in outcomes.

"All GBM patients receive the same standard of care," says Swanson, who is based at Mayo Clinic in Phoenix, Arizona, "but some of them just blow through the therapy", without responding. In others, "the tumour melts away — we have no idea which of them will be which". It therefore makes no sense, she suggests, to manage all such people in the same way. "We need to know we're on the right track for an individual."

Personalized therapy has enabled researchers to make great strides in the treatment of blood cancers and other solid tumours; decisions about which therapy to use are guided increasingly by the mutations that are present in tissue samples gathered during a biopsy. For GBM, however, the high level of genetic diversity that exists both between and within tumours makes this a difficult proposition — assuming that surgery is even possible. So the search is on to find alternative ways of selecting the most appropriate treatment and predicting outcomes on the basis of non-invasive imaging approaches.

GETTING PERSONAL

Swanson and her colleagues are addressing this challenge by building personalized mathematical models of tumour progression for patients, using data collated from magnetic resonance imaging (MRI) scans rather than from biopsy samples. The team's models rely on observations that revealed that tumour cells in GBMs exist in one of two states: migration or proliferation — a situation also known as 'go or grow'.

This means that the rate of growth of a tumour can be calculated by a simple equation that combines just two terms. The first describes how quickly cancer cells migrate through the brain, and is calculated using the increase in size of the area covered by a person's tumour over time, as observed on MRI scans. The second reflects tumour-cell proliferation, through the overall rate of production of such cells. Both terms can

be estimated by closely analysing a person's pretreatment MRI scans. Plugging the resulting values into the equation then generates a virtual tumour that should behave in the same way as the patient's real one. This provides the basis for more-personalized decisions about treatment.

One of the most immediately useful applications of these models is facilitating the decision about whether to operate on a tumour. Researchers have found GBM cells lurking more than four centimetres away from the main tumour, but these pockets of migratory cells are too small to be detected by MRI. Although neurosurgeons typically aim to remove 99% of GBM cells from the brain, the combination of their invisibility and invasiveness makes it difficult to know where the margins of such tumours lie.

By building models from MRI scans of almost 250 people, Swanson and her team found that GBMs tend to fall into two categories: diffuse tumours made of cells that are highly invasive but that proliferate slowly, or nodular cancers that are packed with rapidly proliferating cells that stay put. These two types of tumour might look similar on an MRI scan. But the diffuse cancer will be dispersed over a much wider area than can be determined by MRI, meaning that much of it will remain after surgery.

By reviewing the outcomes of the people whose tumours her team had modelled, Swanson found that those with nodular cancers survived for an average of eight months longer following surgery that aimed to completely remove the tumour, whereas those with diffuse tumours saw no such benefit at all. Given the risks associated with brain surgery, including the potential for neurological damage, it makes sense to operate only on people who are likely to gain the most from such radical treatment.

The story is similar for radiotherapy, which works by killing actively dividing cells. By adapting their equation to account for cell death as a result of that treatment, Swanson and her team can pick out the highly proliferative tumours that are most likely to respond to radiotherapy, as well as the less proliferative, diffuse cancers that will not.

EMERGING PROPERTIES

Whereas Swanson's team is using data from real tumours to derive their models, Haralampos Hatzikirou at the Helmholtz Centre for Infection Research in Braunschweig, Germany, and Andreas Deutsch at the Technical University of Dresden, Germany, are taking a different approach: inputting parameters that are based on the properties of the local environment that surrounds the tumour cells, as well as the tumour cells themselves, to see what kinds of virtual tumour they can grow.

"Our models come from the fundamental biological driving forces behind these cancers," says Deutsch. "We can give our virtual cells different attributes and see what kind of tumour emerges as they interact."

By making models that describe tumours as complex systems, Hatzikirou and Deutsch have found that there is a point at which the balance between growth and spreading is tipped, which causes a tumour to switch from being relatively contained, and therefore simpler to treat, to being wildly invasive.

"It's like any population of organisms," says Hatzikirou. "If you keep on growing, at some point you will run out of nutrients, so you migrate in search of more."

These findings suggest that providing extra supplies to GBMs might encourage them to stay in the more-controllable proliferative state, rather than switch to the more invasive one.

Hatzikirou and Deutsch's models might also help to explain why treatments that affect blood vessels inside or around tumours work well for some people but not for others. By incorporating parameters that are based on oxygen availability and consumption, they suggest that if a tumour is proliferating rapidly but not spreading — growing but not going — then cutting off its blood supply will reduce oxygen levels and trigger a switch to the more invasive form, with potentially lethal results. Conversely, boosting the blood supply to a tumour that is spreading aggressively will tip the balance in favour of proliferation, and might also make it more susceptible to the effects of radiotherapy.

"Our models come from the fundamental biological driving forces behind these cancers."

VIRTUAL TRIALS

Although such models are giving rise to ideas for potential treatments, they do little to help current patients. At best, chemotherapy and radiotherapy yield a partial response in which tumours initially shrink but then continue to grow — making it difficult to tell whether a treatment is working in the long run.

To tackle that problem, Swanson and her team have developed a model that they describe as a virtual untreated control. Effectively, this is a computer-generated worst-case scenario of how a patient's tumour would progress if it were left untreated. Comparing the trajectory of the virtual cancer with scans from the individual following treatment quickly reveals whether the treatment is having an impact on tumour growth.

Although the virtual untreated control cannot predict progression exactly — there will always be biological subtleties that an equation is unable to capture — it should give doctors an indication of whether the person being treated is on the right track. And even when a tumour continues to grow, the model can reveal if it would be better to stick to a particular treatment or to try another approach.

In the context of a clinical trial, comparing the responses of large numbers of people on various regimens to their virtual untreated controls could reveal which approach is most effective, as well as identify specific populations that are responding. Swanson is also hopeful that this approach could rehabilitate drugs that have failed in development, by helping researchers to fish out the handful of people whose tumours would respond from the sea of those whose would not.

NOT YET READY

Although Swanson is encouraging neuro-oncologists to start using her team's predictive models to inform treatment decisions, some researchers are unconvinced that the models are ready for the clinic.

"It's good that Swanson is trying to address clinically relevant and useful questions," says Emmanuel Mandonnet, a neurosurgeon at the Lariboisière Hospital in Paris. "But I think she is going a little bit fast in claiming that it is already applicable to clinical decision-making."

Mandonnet and his team have used a similar approach to build models from MRI scans and then compare them with outcomes for more than 230 people with GBM following surgery. Unlike Swanson, who found that only those with more compact, nodular tumours derived survival benefit from surgical intervention, Mandonnet found that all patients benefitted — including those who had more diffuse cancers according to the MRI data — which suggests that imaging data alone is not enough to accurately predict the outcomes of surgery.

He thinks that Swanson's models are being limited by the present capabilities of MRI. The equations that Swanson uses "are written to include a variable describing the tumour-cell density, but we have no way of working that out from our current imaging", he says.

As evidence, he points to work from his colleague Mathilde Badouad at Paris Diderot University, which shows that the estimates of cell density that Swanson's team derives from MRI scans are more likely to represent levels of fluid accumulation. "I'm still waiting for an imaging modality that can determine cell density," Mandonnet says. "If we had such a technique, then it would be possible to make a model that would help to guide treatment."

Swanson remains optimistic that her team's mathematical predictions will eventually make their way into clinical practice. "I'm definitely hopeful — we are on the cusp of having the right tools to be able to deploy our models into the clinic," she says. "We do need to get the broader community on our side [but] I think with time and perseverance we'll get through." ■

Kat Arney *is a science writer and broadcaster near London.*