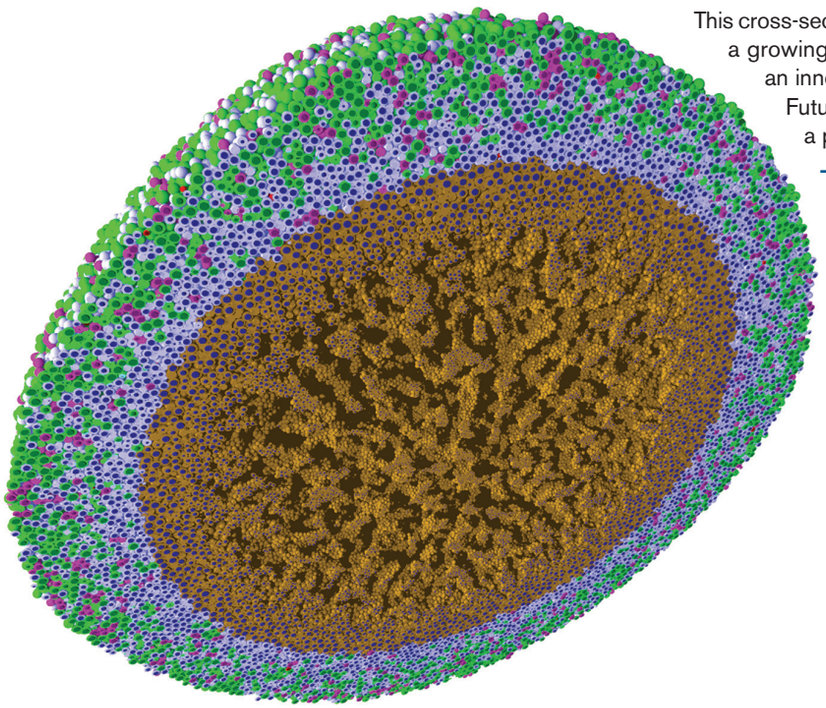
By **Bryn Nelson, PhD**
Edited By **Terence J. Colgan, MD**



This cross-section of a 3-dimensional tumor simulation depicts a growing tumor with an outer region of living cells and an inner region of dead cell debris (shown in brown). Future models may incorporate digitized versions of a patient's personal cancer cell line

Solving the Equation for Personalized Cancer Care

Mathematical models that predict tumor behavior aim for more individualized care decisions

Kristin Swanson, PhD, professor and vice chair of neurological surgery at the Mayo Clinic in Phoenix, Arizona, grew up playing mathematical games with her father, who served as an engineer and pilot in the US Air Force. His rapid decline and death due to lung cancer when Dr. Swanson was in college fueled her desire to combine math and oncology in a way that would give doctors more concrete handholds to help guide their clinical decision making.

"As you watch anybody go through cancer care, you really get that sense of lack of precision, not just in the precision medicine context of what drug for what patient but also in how care is delivered," Dr. Swanson says. Clinical decisions, for example, are often based on the average effect of a therapy on outcomes in an average group of patients. From her own experience, Dr. Swanson knew that every patient was different.

She believes mathematics has the potential to dramatically improve the personalization of care decisions by essentially giving patients their own mathematical equations. To maximize this potential, Dr. Swanson and other like-minded researchers are building up the infrastructure of a field whose tools for making sense of cancer's complexity are more often associated with hurricane and financial forecasts. Collaborative teams are developing computational models to more accurately assess how a tumor might grow, proliferate, and otherwise behave in response to therapeutics or other stimuli.

Among the efforts, scientists at Dana-Farber Cancer Institute in Boston recently developed a mathematical model to predict how a patient's breast tumor may evolve in response to preoperative chemotherapy. Separately, scientists from Roswell Park Cancer Institute in Buffalo, New York, and the French National Institute for Computer Science and Applied Mathematics (INRIA) in Bordeaux published a collaborative model that calculates the relationship between a tumor's size and the risk of disease recurrence after surgery.

Dr. Swanson's own research, which focuses on how to generate more patient-specific models of glioblastoma, has been aided by a database of greater than 1500 patients. Because glioblastoma rarely, if ever, metastasizes beyond the brain and central nervous system, it lends itself well to local and regional models of tumor growth and evolution. However, the cancer tends to be diffusely invasive, meaning that magnetic resonance imaging (MRI) often reveals only the "tip of the iceberg," Dr. Swanson says. By capturing 2 key parameters from the image data, proliferation and invasion, her team built an MRI-based proliferation-invasion model to more accurately predict the extent of the tumor's diffuse invasiveness.[1]

For patients with a less diffusely invasive tumor, Dr. Swanson found that surgery removing the "tip of the iceberg" nearly doubled the average length of survival. Those patients, her model suggested, had fewer cancer cells remaining after the surgery compared with patients with a more diffusely invasive tumor and a greater hidden volume. Without her computational model, the surgical benefits for the subset of patients with minimal residual cancer were being largely obscured by averaging all patients' outcomes together. "My point is that standard therapies are not being matched in optimal ways to individual patients," Dr. Swanson says.

Forecasting Tumor Growth

Heiko Enderling, PhD, assistant member at Moffitt Cancer Center in Tampa, Flori-

CONTINUED *from previous page*

da, cautions that personalized medicine, by its very definition, poses a huge challenge. "Each patient is a sample size of *n* equals 1," he says. However, he agrees that mathematical models from data routinely collected in the clinic (such as computed tomography and MRI scans, blood work, and biopsies) can improve patient-specific treatment recommendations.

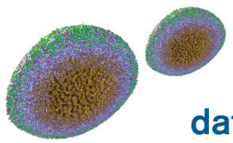
For his tumor modeling work aimed at decisions regarding radiotherapy, Dr. Enderling is exploiting the typical 40-day to 60-day gap between diagnostic and subsequent treatment planning scans in US patients with cancer. "So we have the luxury of time-dependent information," he says. "We can actually see: how did the tumor evolve between diagnosis and treatment planning?"

Based on the changes in tumor volume over time, his model predicts how a patient's tumor might continue to progress and simulates how a specific radiation protocol might alter that progression.[2] "Which approach has, mathematically, the highest likelihood of succeeding?" he says. The next step is to validate and refine the proof of concept with prospectively collected patient data.

Dr. Swanson's laboratory is similarly using computational modeling to help oncologists know when they are on the right treatment path. The majority of MRI-based results yield ambiguous answers regarding whether a tumor is responding to therapy. However, similar to a hurricane prediction map, the models constructed by her laboratory predict how big or fast a tumor would grow if left alone. The clinical tool could help physicians to determine how much they have knocked the tumor off its original growth curve.

Small but exciting pilot studies, Dr. Swanson says, suggest that spatial and temporal differences in tumor growth appear to be highly correlated with length of survival. If further studies confirm those results, the patient-specific model could provide a much more accurate baseline by which to assess whether an individual's tumor is responding to therapy and to what degree. Clarifying the true responsiveness, in turn, could provide better guidance for how promising therapies really are performing in clinical trials.

However, multiple models might fit the limited data equally well. Similar to how forecasters often use the average from more than a dozen models to predict a hurricane's behavior, Dr. Enderling says, his experimental forecasting work indicates at which point the majority of models converge to chart a tumor's likeliest track. Refining such forecasts may require considerably more longitudinal data, which is no small task. Even more importantly, he and other experts say, the field requires more analytical expertise and mechanisms to store and identify the bits and pieces of information needed for relevant mathematical models. "There's a lot of groundwork that needs to be laid to make clinical data useful for mathematical modeling and then, of course, the mathematical model useful for personalizing medicine," Dr. Enderling says.



There's a lot of groundwork that needs to be laid to make clinical data useful for mathematical modeling and then, of course, the mathematical model useful for personalizing medicine.
—Heiko Enderling, PhD

Building a Digital Infrastructure

Paul Macklin, PhD, associate professor of intelligent systems engineering at the School of Informatics and Computing at Indiana University in Bloomington, is helping to assemble some of the critical infrastructure by spearheading a collaboration called the MultiCellular Data Standard Project (or MultiCellDS), which seeks to standardize data describing the behavior of cancer cell lines. "If we want to learn from each other, we need to have a way to pass that information around together and share it and improve each other's work," he says.

The growing database, which includes "digital cell lines" annotated with standardized descriptions, could help researchers to construct ever more accurate models and systematically share their knowledge via a group-curated repository. "You can't do big data if you can't even write it down," he says.

For his own research, Dr. Macklin is focusing primarily on patient-specific modeling for ductal carcinoma in situ (DCIS), using pathology slides as a starting point. His group has extracted measurements such as the percentage of cells that score positive for proliferation and death markers, plugged the numbers into a simulator, and examined whether they could predict how quickly DCIS grows along a breast duct, on average. The resulting model suggested a growth rate of 1 centimeter per year, a "very reasonable rate" based on clinical reports but one that requires further validation, he says.

Collaborators are creating synthetic breast ducts to provide a controlled environment for Dr. Macklin's follow-up measurements. Other studies are examining archived mammography data from patients subsequently diagnosed with DCIS to determine whether there is any prior evidence of DCIS that might have been missed. If so, the technique could help to capture 2 snapshots of the tumor and measure its actual growth rate as a basis of comparison. Ultimately, Dr. Macklin says, the modeling studies could help to answer more real-world questions: "Is DCIS even a real cancer? Is it important to treat or can you just observe it? If you can observe it, do you need to do that in everybody or do you need to figure out who's at risk?"

Despite the challenges, experts say the recent successes bode well for incorporating math into daily clinical decision making. As for her ultimate vision of the future, Dr. Swanson foresees an iPad application that a tumor board could use to model how available therapeutic options might play out in an individual patient to provide the best possible chances for success. "That's the point that we'd like to get to," she says. ■

References

1. Jackson PR, Juliano J, Hawkins-Daarud A, Rockne RC, Swanson KR. Patient-specific mathematical neuro-oncology: using a simple proliferation and invasion tumor model to inform clinical practice. *Bull Math Biol.* 2015;77:846-856.
2. Prokopiou S, Moros EG, Poleszczuk J, et al. A proliferation saturation index to predict radiation response and personalize radiotherapy fractionation. *Radiat Oncol.* 2015;10:159.

DOI: 10.1002/cncy.21815