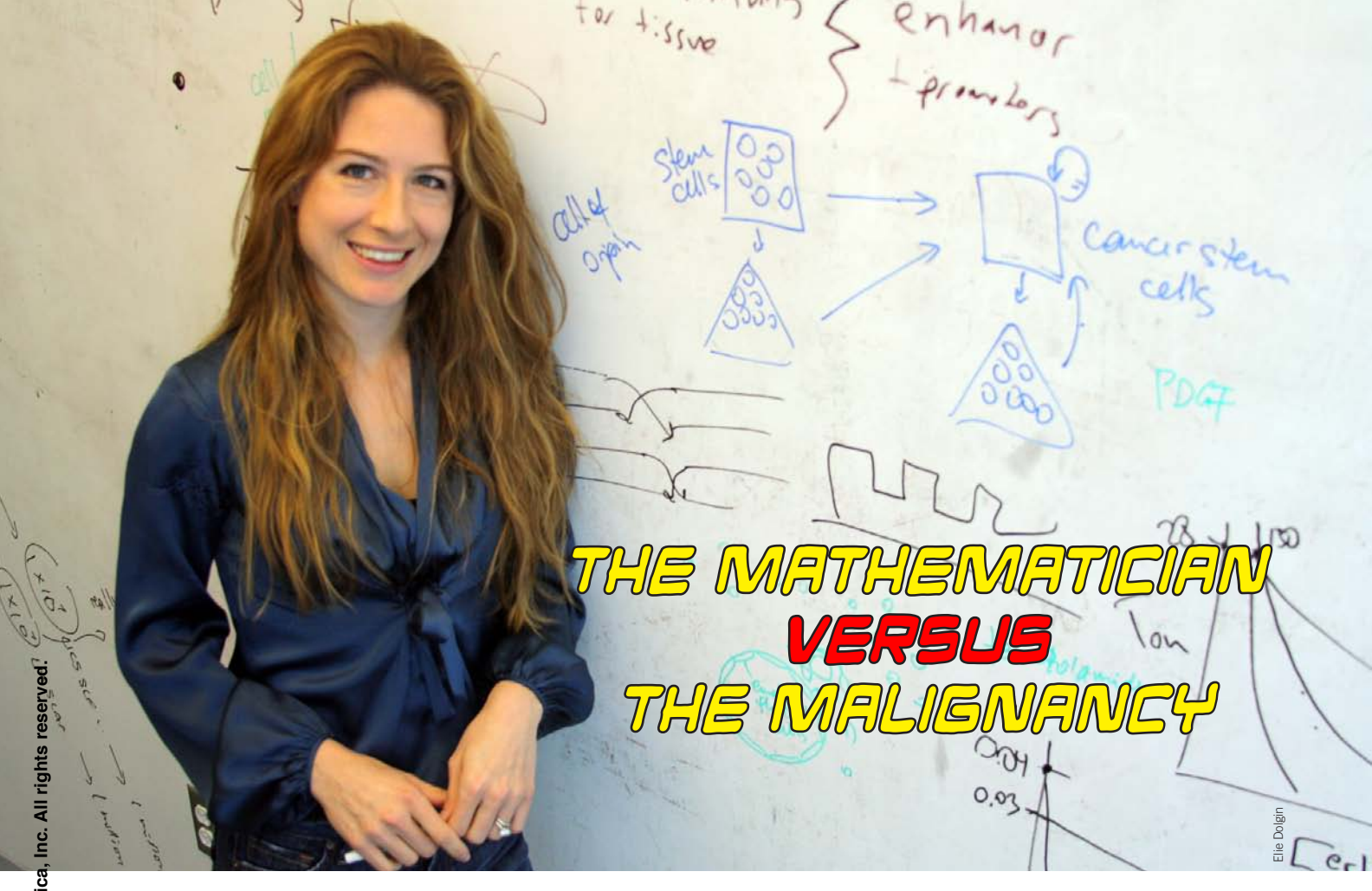


THE MATHEMATICIAN VERSUS THE MALIGNANCY

Elie Dolgin

Patients have long received cancer treatments at the maximum tolerated dose on a regular schedule. Could a more sophisticated approach save lives? **Elie Dolgin** meets one mathematical biologist whose theories are now being tested in the clinic to see if they can improve the efficacy of today's anticancer arsenal.

The way in which people receive cancer therapy is pretty much the same as it's been for decades: researchers determine the highest dose of a drug or treatment that does not cause unacceptable side effects; oncologists then administer that dose to patients on a standard timetable—usually daily tablets for oral chemotherapeutics and other pill-based regimens, infusions on a weekly schedule for injectable drugs and Monday-through-Friday treatments for radiation therapy.

Almost all current cancer therapies are given this way. And although the approach has undoubtedly extended countless patients' lives, given that more than $80 billion is spent on cancer care in the US alone, it's worth asking: are these schedules really yielding the best results for patients? And could alternative timetables produce better outcomes?

Franziska Michor hopes to answer these questions. The 31-year-old mathematical biologist from the Dana-Farber Cancer Institute in Boston sits beneath a whiteboard of multicolor equations and schematic diagrams. To one side are computer printouts of her young toddler; on the other side are empty champagne bottles from bygone celebrations of her most important academic accomplishments. She plugs away at a desktop keyboard, modeling how tumors grow and evolve.

Michor has turned to math and evolutionary theory to determine whether clinicians can make existing therapies work better simply by altering the time course by which they are administered. Her models are now being put to the test in prospective human clinical trials. This is something that few mathematical biologists see in their entire careers. Michor's career is barely a decade old.

Last autumn, oncologists at the Memorial Sloan Kettering Cancer Center (MSKCC) in New York launched a phase 1 trial that aims to test the safety of an unconventional dosing schedule proposed by Michor and her colleagues for the treatment of non–small-cell lung cancer, a disease with several targeted therapy options, all of which are prone to acquired resistance. The trial involves Tarceva (erlotinib), an oral drug that blocks the epidermal growth factor receptor, a cell surface protein that promotes tumor growth.

For patients with lung cancer, the recommended dose of Tarceva is 150 milligrams taken daily on an empty stomach. Clinicians and pharmaceutical companies arrived at this dosing schedule largely on the basis of its safety profile and how quickly the drug is metabolized. But as lung cancer specialist William Pao points out, the current schedule does not consider "what you need to do to maximally delay [drug] resistance from actually happening."

This month, Pao joined the Swiss drug company Roche to lead its oncology unit. But back in 2008, when he and Michor were both at MSKCC, the two researchers teamed up to determine the best way to delay the onset of drug resistance and, thus, prolong the impact of Tarceva. They first quantified differences in the growth kinetics of lung cancer cells that respond to treatment and those that have mutated to become drug resistant. They repeated these *in vitro*

measurements at varying concentrations of Tarceva.

Using a type of mathematical formula known as a continuous-time Markov chain to model cell birth and death dynamics, Michor and her then-postdoc Jasmine Foo next considered various time-dependent dosing strategies to arrive at a predicted optimum. The math suggested that occasional high-dose pulses of Tarceva, on top of low-dose administrations of the drug the rest of the time, impeded the outgrowth of drug-resistant cells to the maximum extent[1,2]. Laboratory studies led by Pao (who had moved to the Vanderbilt-Ingram Cancer Center in Nashville, Tennessee) bore out this prediction.

According to Michor, the approach proved optimal because the continuous low-dose drug levels inhibit drug-sensitive cells, while the high doses slow down the overall growth of the resistant cell population. What's more, the absence of treatment breaks prevents selection for further drug resistance. "It makes sense, and it's certainly worth exploring," says MSKCC oncologist Gregory Riely, who is co-leading the phase 1 trial, the first prospective study of this dosing strategy in humans. "We could do better in terms of making patients' responses to treatment last longer and potentially lead to better responses with the same drugs."

Instead of receiving 150 milligrams of Tarceva daily, the 58 participants in the trial are taking high-dose Tarceva two days a week and 50 milligrams the other five days. In March, the trial completed enrollment for the last of four planned high-dose levels (all of which doctors have previously tested in weekly 'pulsatile' treatment regimens but not in combination with continuous low-dose administration). Since the trial participants tolerated the highest pulse dose—1,050 milligrams—and the responses looked favorable, Riely and his colleagues are now considering whether to modify the study protocol to add an even higher dose level. Meanwhile, Michor is already in discussions with other physicians at MSKCC about clinically validating some of her other hypotheses. Brain cancer is next.

Anything but routine

It may seem obvious that clinicians should test models like Michor's if simply altering the dose and schedule of currently approved therapies could potentially enhance their efficacy for the estimated 14 million people worldwide who are newly diagnosed with cancer each year. But when it comes to improving upon the manner by which patients receive the mainstays of cancer treatment, examples are scant. "There's really a dearth of strategic ideas for how can we improve treatment with existing drugs," says Richard Simon, chief of the Biometric Research Branch at the US National Cancer Institute (NCI) in Bethesda, Maryland.

> "We could do better in terms of making patients' responses to treatment last longer with the same drugs."

A rare exception is an idea put forward nearly 40 years ago by Simon himself. In the 1970s, he and Larry Norton, then a medical oncology fellow at NCI, found that small tumors tend to grow faster than larger ones. They also showed that faster-growing tumors are generally more sensitive to many drugs. Off the back of those findings, the researchers developed a mathematical model: it indicated that tumors given less time to grow between treatment cycles would be more likely to be killed[3]. This 'dose-dense' strategy encompassed by the Norton-Simon hypothesis, as the idea came to be known, ran counter to the prevailing view that chemotherapy killed a constant fraction of cancer cells, regardless of a tumor's size.

Getting a trial off the ground proved difficult, though. "Nobody believed it would work, despite the fact that we had really exciting preliminary data," recalls Norton, who moved on to MSKCC in 1988, where he now serves as deputy physician-in-chief for breast cancer programs. "They said, 'It doesn't matter how you give the drugs, as long as you give the drugs,' and that's where they were totally wrong."

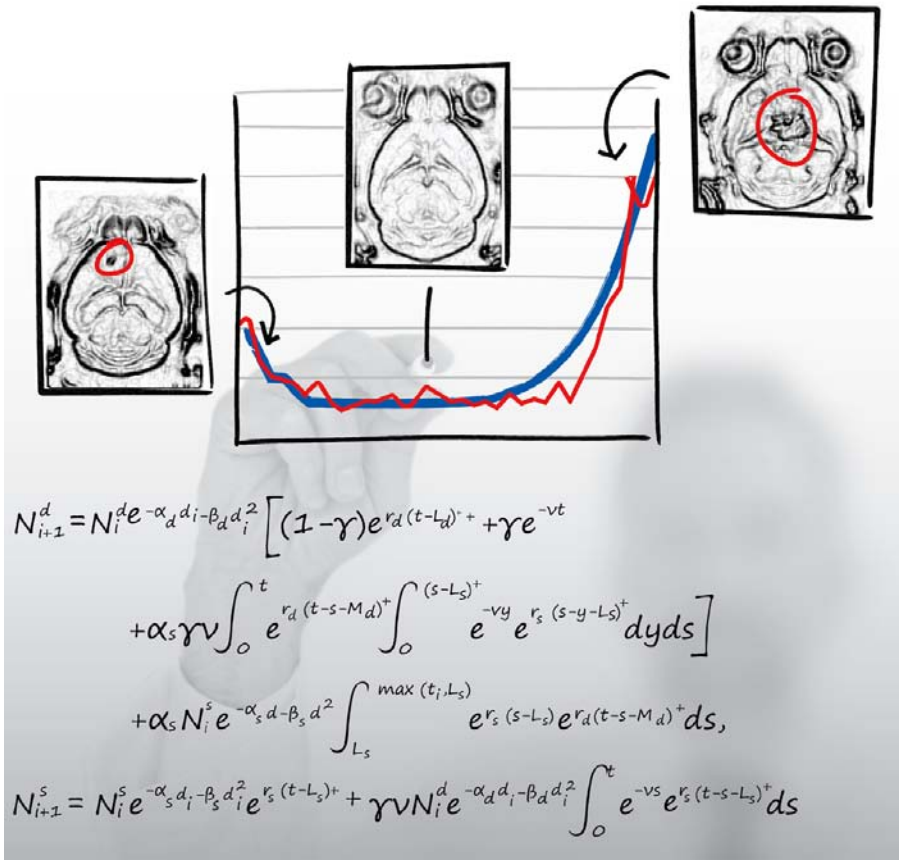
It wasn't until the late 1990s that Norton got the support he needed to test the hypothesis. In a 2,000-person clinical trial, he and his NCI-funded team showed that shortening the interval between chemotherapy treatments from three weeks to two—a more dose-dense treatment schedule—improved survival rates among women with metastatic breast cancer: 82% of participants on a two-week regimen remained disease free four years after starting treatment, compared to 75% on a three-week regimen[4]. Two-week protocols are now increasingly becoming the norm in the management of breast and ovarian cancers.

Astonishingly, that's the sole example of a clinically validated model of schedule optimization in oncology. "Dose and schedule are the forgotten parts of the puzzle," Norton says. "It's all about the anticancer drugs themselves; it's not about concepts anymore—and that's a tremendous shame."

One model that didn't stand up in the

Memorial Sloan Kettering Cancer Center

Collaboration is key: Franziska Michor (left) partners with doctors like Eric Holland (right) to test her models.



Tolpa Studios, Inc., 2014

An optimal dose of math: Evolutionary modeling suggests an alternative treatment schedule for brain cancer.

face of clinical testing—but is noteworthy for the fact that doctors tested it at all—was the Goldie-Coldman hypothesis. In 1979, James Goldie and Andrew Coldman at the University of British Columbia in Vancouver, Canada, created a mathematical model based on the assumption that tumor cells acquire drug resistance at a rate dependent on their intrinsic genetic instability. One prediction of this model was that multiple chemotherapy agents should be administered in alternating courses—one, then the other, back to the first and so on. The model suggested that an alternating schedule would decrease the chances of tumors developing resistance to all of the given drugs[5].

Decades later, when researchers at Italy's National Cancer Institute in Milan compared this alternating dose protocol with a sequential one in women with breast cancer, the sequential schedule—a full course of one drug followed by a full course of another—proved superior[6]. The Goldie-Coldman hypothesis was wrong. This was presumably because the sequential schedule involved a dose-dense regimen with each drug involved, which offered an advantage, as predicted by the Norton-Simon hypothesis.

Adaptive approaches

Lately, there's been a resurgence of interest in tailoring cancer treatments, thanks in large part to the NCI in 2009 establishing 12 Physical Sciences-Oncology Centers (including one headed by Michor) to promote nontraditional approaches to cancer research. Now, more mathematically inclined researchers stand on the cusp of seeing their hypotheses tested in the clinic.

> "Dose and schedule are the forgotten parts of the puzzle—and that's a tremendous shame."

For example, at one of the NCI-backed interdisciplinary hubs, the Moffitt Cancer Center in Tampa, Florida, Robert Gatenby expects to soon launch two trials—one in patients with multiple myeloma, the other in men with prostate cancer—that will test what he calls "adaptive therapy," a treatment strategy that aims to extend patient survival by keeping tumor sizes static rather than eradicating them altogether.

Gatenby, a radiologist and mathematical biologist, laid out the theoretical framework for this approach in a 2009 paper in *Cancer Research*[7]. His team has since published laboratory data from tumor models showing how drug resistance can be avoided by implementing this adaptive scheme[8]. "The idea," Gatenby explains, "is to take an evolutionary approach and accept the fact that you can't cure these cancers"—but you can control them. "Instead of Whac-A-Mole," he says, "it should be chess."

Then there's Michor, a staunch advocate of using mathematical models to transform clinical practice. "It's a powerful concept because it allows us to think through all these quantitative cost-benefit things, which I just can't do in my head," she says. "Using such a mathematical model is a way to think clearly about it and, in a systematic way, to test our hypotheses and pick the one that's best."

Her conviction and collaborative nature have helped convince others of the promise of this approach. "She teams up with some of the best experimentalists so that her models aren't just pure theory but are actually fit to data," says cancer biologist Carlo Maley, director of the Center for Evolution and Cancer at the University of California–San Francisco Helen Diller Family Comprehensive Cancer Center. "She's not just interested in the mathematics," adds Tessa Holyoake, a hematologist at the University of Glasgow, UK, who has worked with Michor to model and retrospectively test theories of treatment for chronic myeloid leukemia[9]. "She's interested in it making a difference for cancer patients."

Shades of gray

A paper published earlier this year in *Cell* could prompt the next human study of Michor's theories. In that paper[10], Michor and her collaborators started with a simple question: is there a better way to give radiation therapy to people with glioblastoma, the most common and most aggressive form of brain cancer?

The standard schedule for glioblastoma treatment involves 2 gray (a measure of absorbed energy) given once a day, Monday to Friday, for six weeks, for a total of 60 gray. Alternative schedules have been tried,

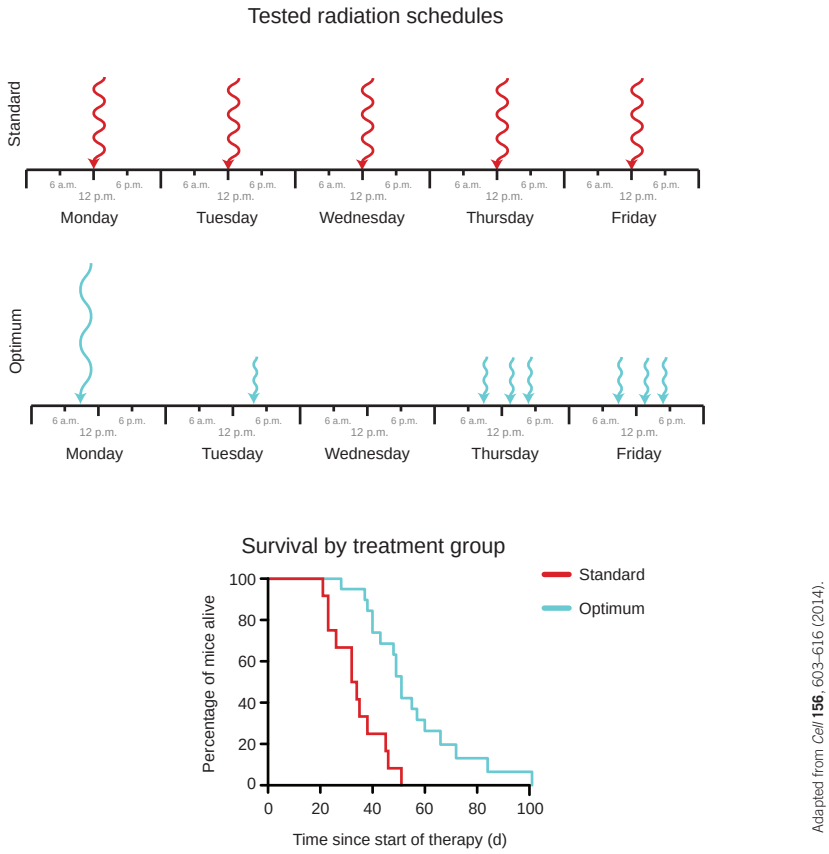
including higher doses per session, lower doses given more often and accelerated doses to shorten overall treatment times. None have led to improved results. Most haven't led to much worse results either.

Michor decided to revisit the scheduling question after scientists recently discovered subtypes of glioblastoma distinguished by unique molecular patterns[11]. Perhaps, Michor thought, different subtypes could benefit from different radiation schedules. She and her then-postdoc Kevin Leder chose to focus on the 'proneural' form of glioblastoma, a subtype that contains a small population of tumor cells with stem cell–like properties. These radiation-resistant stem-like cells can arise either through self-renewal or from radiation-sensitive cells through a process known as 'dedifferentiation'. This cellular transformation is accelerated by radiation, but it takes a few hours to complete, during which time another dose of radiation could help kill the cells. "All this then becomes a mathematical framework that takes into account the response to radiation, differentiation, dedifferentiation, death and growth," Michor explains.

Since the parameters involved in these cellular dynamics would be impossible to obtain in humans, Michor joined forces with her former MSKCC colleague Eric Holland, a brain tumor researcher and neurosurgeon now at the Fred Hutchinson Cancer Research Center in Seattle. Together, they obtained the molecular metrics from a mouse model of proneural glioblastoma. Mice can't handle as much total radiation as people can, so Michor and Holland just modeled how best to administer one week's worth of human treatment: 10 gray. To keep the model realistic, the researchers limited themselves to a Monday to Friday, 8 a.m. to 5 p.m. schedule—after all, radiation oncologists are known to maintain fairly regular office hours.

> "Using a mathematical model is a way to systematically test our hypotheses and pick the one that's best."

The math ultimately spit out a survival-maximizing schedule that looked nothing like the clinical standard of 2 gray per day. It involved 3 gray up front on Monday morning, 1 gray on Tuesday afternoon, nothing on Wednesday and then three doses of 1 gray each spaced evenly over would-be business hours on Thursday and Friday (see 'Radiation refined'). "It almost looks random," Michor says, "but it's certainly not."



Adapted from *Cell* **156**, 603–616 (2014).

Radiation refined: An optimized schedule improves survival in a mouse model of proneural glioblastoma.

When the researchers experimentally tested the optimized schedule in their mouse model they found a significant improvement in survival outcomes. Whereas six of the 12 mice given the standard schedule were dead one month after the start of the therapy, only one of the 18 mice on the optimized schedule had perished by this point. In fact, half the mice treated with the optimized schedule lived beyond 50 days, the longest life span displayed by any mouse on the standard schedule. Michor is now in active discussions with physicians at MSKCC about clinically testing a version of this model adapted for use in humans.

Susan Fitzpatrick, vice president and chief operating officer of the James S. McDonnell Foundation, a St. Louis–based nonprofit that funds research on brain cancer (but not Michor's work), applauds these math-inspired efforts to improve glioblastoma treatment. Existing therapies "are delivered on these schedules that are really kind of *ad hoc* in a way," she says. "We need to be taking these kinds of more thoughtful, evolutionarily and ecologically sensitive approaches."

Michor couldn't agree more: "I hope others will join in and help us address cancer in this way." If she gets her way, mathematical approaches could soon become a routine part of the treatment equation.

Elie Dolgin is senior news editor at* Nature Medicine *in Cambridge, Massachusetts.

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