

Can Mathematics Treat Cancer?

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(Translated by Mindy Szeto)

*The combination of mathematical models and biological data will change cancer research into a quantitative and predictable science.*

Kristin Swanson is a 33-year-old female mathematician, and is an Associate Professor of Pathology at the University of Washington in the United States. Her work sounds very cool – using mathematics to study cancer.

“For mathematicians, all of the world’s problems are mathematical. All phenomena in daily life can be explained by math,” she told our reporter. “Cancer is no exception.”

When her father died of lung cancer eleven years ago, she was a graduate student in the Department of Applied Mathematics. It was a very difficult time. She acquired all her knowledge and interest in math from her engineer father, who played math games with her when she was young, and trained her in the habit of quantitatively analyzing everything. After his death, she chose to research mathematical biology at the medical school, where she studied under Ellsworth Alvord, a well-known Professor of Neuropathology and brain cancer specialist. She did not choose to study lung cancer in the first place; it was too difficult for her to face, since her two older brothers had died of lung cancer as well. Though mathematics may not be able to explain fate, at least it could explain cancer, she believed.

"A naive graduate student, with the crazy idea of saving the world, hoping to use math to solve the world’s biggest problem,” she said with a laugh to our reporter, over the phone. "At that time, a lot of cold water was poured. Even today, if you say that cancer is manageable and predictable, you will still encounter suspicion and even ridicule. This doubt is reasonable. Cancer’s occurrence and mutations are so complex, with many elements to the data, how could it be simplified into a few mathematical formulae?"

Not long ago, U.S. *Newsweek* published an article exploring problems in the human war against cancer. They concluded that a cancer cell could outsmart 100 top cancer specialists. With greater understanding, cancer was found to be even more complex than expected. As it invades the immune system, passes through the blood vessels, and colonizes other organs, it recruits normal cells to support its rebellion. ... .. Molecular biology research has discovered more than 25,000 types of cancer-related gene variations; this number continues to increase. A recent study from Johns Hopkins University in the United States showed that pancreatic cancer alone involves 1007 different gene mutations. Additionally, the growth of cancer cells is affected by the status of the blood supply, nutrients, and the immune system.

From the "war" point of view, the addition of mathematicians provides powerful external aid. In fact, as early as 50 years ago, mathematicians have tried to use mathematics to explain cancer, but it was not until the last 10 years that these studies have gone from rarities in academic journals to mainstream medicine. Especially when the biological data on cancer accumulates at such an alarming rate, the medical profession as a whole urgently needs a tool to quantify and analyze the data.

"Now, all cancer research has focused on the level of molecular biology: genes, cell signaling, and recently microRNA. The financial resources of the country and even the whole world are concentrated on a small gene variation. The question is, how can we link micro-level data and information to a specific patient's tumor?" Kristin said.

Years ago, she chose to study medicine in a clinical environment, in order to work with real patient data. "I am not a clinician, but because of my research I come into contact with patients every day and witness their misfortune. I want to apply my research findings to patients as soon as possible," she told our reporter.

Going past the molecular level, she starts with the perspective of clinical imaging, which is after all the most common means of visual monitoring, and has a direct impact on the process of patient diagnosis and treatment. The present problem with clinical imaging is that it cannot detect all of the tumor; many cancer cells are hidden under the surface, which means that a lot of information is lost when doctors attempt to understand the patient's tumor. Surgery cannot remove the whole tumor, and other forms of treatment have limitations. Therefore, she would like to design a model that allows a doctor to see "below the water's surface."

Kristin focuses on the study of brain glioma. This is the most common and most dangerous malignant brain tumor because of its high proliferation. Imagine the glioma as a hand opening slowly, until the time of diagnosis, where it is often accompanied by hundreds of genetic variations. Clinical imaging detection equipment such as MRI (magnetic resonance imaging) reveals only the tip of the iceberg; 99.9% of cancer cells cannot be displayed.

Her model is a set of partial differential equations based on the patient's MRI history, and calculates the division and proliferation speed of cancer cells in the brain tissue to simulate the path of its spread. Not only does it show the current real distribution of cancer cells in the brain (including those non-visible on MRI), it can also calculate the next most likely position and velocity of invasion. It can accurately predict how long a patient can survive, rather than a rough "median survival time." More importantly, it can predict a patient's response to radiotherapy and its effectiveness. According to the present standard procedure, a brain cancer patient must receive radiotherapy every 6 weeks (often accompanied by serious side effects), but her model showed that some patients' tumors progressed slowly, and a reduced amount of radiotherapy could achieve the same effects. Some patients with rapidly progressing tumors are suitable for low-dose radiotherapy two to three times a day to improve survival. Another likely benefit of this model is that patients can try to avoid dangerous surgery that may be hopeless. Brain surgery is very risky and could lead to paralysis and affected vision or speech. Sometimes no treatment is the best treatment, and could prevent much unnecessary suffering.

For a cancer patient, a standardized treatment plan is a cruel and desperate choice. They often meander before finding the correct treatment program, and then it is likely that not much time is left. This is the current medical reality – it has never been personalized. However, Kristin’s mathematical model proves that personalized treatment may not have to wait until all of the genetic code is deciphered by scientists. Current technology may not cure cancer, but it can at least maximize treatment effects and reduce harm.

“Considering all patients, you will find there is no pattern at all; for the same cancer in different patients, the growth and proliferation may be entirely different. But from the point of view of the individual, growth and proliferation patterns can be tracked and predicted. The prediction is not difficult.” In fact, her model is very simple; there are only two key parameters, but the predicted results are amazingly accurate and have been verified in more than 350 patients.

“Mathematics has an impressive ability to predict,” Kristin said. “Imagine a weather forecast. If in the future there is such a model only needing the input of patient data, whether the results of genetic tests or MRI, it will automatically analyze the tumor’s behavior and simulate the growth, proliferation, and transfer of the tumor, predicting the patient’s prognosis and calculating the best combination of drugs and treatment programs. Then, 1000 different patients will have 1000 different treatment options.

This is not just a good idea. In fact, mathematical models have already provided some possible answers and even solutions to problems that have been troubling doctors for many years. For example, what degree of chemotherapy is actually beneficial to patients? U.S. University of Virginia researchers use the genetic analysis of cancer to design a mathematical model that predicts the effectiveness of a chemotherapy drug on different patients with up to 85% accuracy. This model has been verified for bladder cancer and breast cancer, and potentially applies to all cancers; it will soon enter clinical trials.

When a doctor faces an early-stage cancer patients, the first question usually is: how aggressive are the cancer cells? How likely is it to metastasize? Does the patient need aggressive treatment, or a more modest program? Although MRI and CT can reveal the size and shape of the tumor, it could not accurately estimate its potential aggressiveness.

U.S. Vanderbilt University professor Vito Quaranta’s mathematical model found that the aggressiveness of cancer cells not only depends on the gene mutation itself; the surrounding microenvironment also determines its formation and aggressiveness. As long as there is change in one of the variables, such as oxygen content, the aggressiveness of the tumor can be adjusted.

Twenty-five years ago Ukrainian mathematician Roman Polyak proposed a “non-linear scaling algorithm” (a kind of “optimization algorithm,” using tens of thousands of variables and constraints to find maximum efficiency). Recently, German researcher Rembert Reemtsen used it to calculate radiation beam angle, intensity, and duration to destroy tumors with the greatest efficiency without harming surrounding healthy tissue. Some hospitals in Germany have applied this system in their radiology departments.

University of Maryland Applied Mathematics professor Doron Levy's chronic myeloid leukemia (CML) model is even more exciting. CML is the "simplest" cancer, because it involves a single gene mutation. In 2001, after the invention of the targeted drug "Gleevec" the 5-year survival rate for patients with chronic leukemia increased from 50% to 95%. But the problem is that patient must rely long-term on Gleevec; upon cessation of drug use, the number of cancer cells in the blood will return to pre-treatment levels or even higher. If the patient has resistance to Gleevec, the situation will become very terrible.

Professor Doron Levy's model basically allows the patient's immune system to replace Gleevec to fight cancer cells, thereby removing dependence on Gleevec. He spent four years tracking, collecting, and analyzing the immune response of CML patients taking Gleevec. He discovered that at diagnosis, the patient's immune system is weak, but when they start taking Gleevec, the anti-leukemia immune response is enhanced until it peaks and then falls slowly. Meanwhile, cancer cells still exist, but the relatively small amount remaining leads to weakened immune system sensitivity. At that time, a simple cancer vaccine (early on, cancer cells in the patient's blood at diagnosis are killed and the blood is transfused back into the patient) can re-activate the immune system. The model provides the key for calculating the best time to vaccinate patients, where it is likely to ultimately cure leukemia under the guidance of treatment.