Simulating your cancer treatment on a computer

Arnoldo Frigessi is the main person behind the new idea of making tens of thousands of virtual copies of the individual cancer patient and then testing all the treatments in a simulation model to find the most optimal treatment. Credit: Ola Sæther

In ten years, computers will be able to propose the most suitable cancer treatment for you. The idea is to simulate how all possible combinations of existing cancer treatments will work on your particular tumour.

Each year, 10,000 Norwegians die of cancer. Researchers at the University of Oslo are now developing a computer program that can help oncologists find the best personalised treatment for each patient. The hope is to be able to cure far more patients.

One of the most common cancer diseases with poor prognoses is lung cancer. Each year, 3,000 are diagnosed with this sinister disease. 2,200 die of it. In fact, lung cancer takes as many years of life as breast cancer, prostate cancer, and

intestinal cancer combined.

“Although treatment has improved, we are still lacking tools to be able to decide the best treatment for the individual,” says Åslaug Helland, who is both a professor at University of Oslo in Norway and clinician for lung cancer patients at Oslo University Hospital, Radium Hospital.

Some of her patients start treatment with chemotherapy, others with immunotherapy. Immunotherapy is a modern treatment that stimulates the body’s own immune system to fight the cancer. Although many people get good help from immunotherapy, it only works for half of the patients.

“The problem is that we don’t know who benefits from immunotherapy. If the drug does not work after two or three rounds, we will try something different, such as the classic chemotherapies, but by then we will have already squandered time that could have been spent on other treatment. We therefore need a system that says what is the best and most effective treatment for each patient – and with the fewest possible side effects,” Åslaug Helland points out to the research magazine Apollon.

This is precisely the great idea of Arnoldo Frigessi, professor of statistics at the University of Oslo, who leads both the Oslo Centre for Biostatistics and Epidemiology and BigInsight, a centre for research-based innovation.

His idea is to use mathematical and statistical methods to develop a computer program that will propose the best cancer treatment. Arnoldo Frigessi is an expert in describing biological processes with mathematical models. He works closely with everyone from oncologists and pathologists to molecular biologists, statisticians and mathematicians.

“Today’s treatment does not help three out of ten cancer patients. The cancer cells can also become resistant to the

drugs they receive. The drugs then need to be replaced. Might one of the solutions be to give the patient several cancer drugs at the same time?” asks Arnoldo Frigessi.

This is far more challenging than one would think. Imagine that your oncologist has the possibility to choose between 300 different drugs for a particular cancer disease. If the doctor is to choose the best combination of two different drugs from this selection, he has as many as 45,000 different treatment choices.

“This multiplies the possibilities to the point where it becomes impossible for the doctor to figure out which combination of drugs works best.”

It is not possible to test all the possible combinations of drugs with traditional clinical trials. In classic clinical trials, two groups of patients are compared. One is given drug A, the other drug B. However, the doctor now wants to provide personalised medicine to a patient group that consists of just one patient. This makes it impossible to carry out classic trials of different types of treatments.

Instead, Arnoldo Frigessi’s solution is to make hundreds of thousands of virtual copies of the patient and test all the treatments on a simulation model on the computer to find the best treatment.

Lung cancer expert Åslaug Helland believes that such a simulation model can change the future of cancer treatment. “We strongly believe that it can be possible to attack the cancer from different fronts at the same time. Then we need to know which combinations of drugs work best in each individual case,” says Åslaug Helland.

The combination of options increases even more by testing different doses and the order in which the drugs are taken.

“There are endless possibilities here, and there’s a lot we

don’t know. The simulation model can help us determine which combination is the best treatment for the individual patient, rather than spending time on treatments that do not help,” Åslaug Helland points out.

This simulation model is a so-called multi-scale model, with mathematical models of what is taking place from the molecular level up to the size of the cancer tumour.

“We collect all possible data from the patient and can calculate how the treatment affects the chemical and physical reactions in millions of different cells. We can then simulate how the cancer would have developed with all the different therapies. Machines work fast. Our goal is that we might be able to test a hundred thousand different treatments over the course of one night and then say which ten drugs work best,” points out Arnoldo Frigessi.

To accomplish this, scientists need to mathematically describe how the lump of cancer functions, how many cells it consists of, how dense the cancer cells are and where the blood vessels are. They have also described the energy balance and the chemical and physical reactions in the cells.

Their data includes genomic biomarkers, histopathology and magnetic resonance images.

“We can then use the mathematical model to describe the condition of the cancer cells for the next twelve weeks, while bombarding them with various medications. Some drugs can only kill the cell at the moment it splits into two. We describe how each cell lives, develops, splits, and dies. We also need to calculate the amount of medicine needed to kill the cells and the probability of this happening.”

Oxygen to the cancer cells

The researchers also model how the cells talk to each other, how the blood vessels grow and die and how the oxygen is

distributed in the tissue. The blood carries oxygen to the cancer cells. If the supply of oxygen stops, the tumour may die.

“The cells need oxygen to breathe. If the cells don’t get enough oxygen, they’re in trouble. The mathematical model explains how the cells are doing depending on the amount of oxygen,” says Arnoldo Frigessi.

The simulation model is very complicated. They have to build it up piece by piece. An essential part is precisely to simulate what is needed to reduce the supply of blood to the tumour.

Some of the simulations show that the cancer flares up again. “It may be because the drug was given too seldom or at the wrong time.”

Cancer needs a lot of blood to grow. To get the blood they need, cancer cells produce a special protein that gives notice where the blood vessels should grow. Their model must therefore also take into account how the amount of this particular protein changes. A delicate balance is at work here.

“If the blood vessels are destroyed, the chemotherapy will not reach the cancer cells.” The drugs follow the blood vessels and must leave the vessels where the cancer cells are located. The program describes how much medication is leaching from the blood vessels and when it occurs.

“This varies from patient to patient and must therefore be determined before the simulation can be run.” The procedure is simple. The patient takes a contrast agent. Then it is possible to study how quickly the contrast agent leaches out of the blood vessels on an MRI scan.

Unfortunately, the information is well hidden in the enormous amounts of data from the MRI scan. Arnoldo Frigessi must

therefore develop statistical methods in order to determine how fast the blood vessels of the individual leach drugs.

Numerical paradise

The simulation model is bursting with stochastic models, which describe random events, multi-scale models, which provide a mathematical description of how the cancer develops in different dimensions, and last but not least: partial differential equations describing developments in time and space.

The simulations must be run hundreds of thousands of times. It is then important to optimise the program so that they run as fast as possible. This is where the numericians enter the scene. Numerical analysts are experts in solving mathematical problems with the computer. Here, Arnoldo Frigessi has roped in Marie Rognes, chief researcher at the Simula Research Laboratory.

With her expertise, the equations can be solved many hundred times faster. It will then be possible to simulate much larger parts of the tumour without losing time.

Vessela Kristensen notes that the simulation model can improve current cancer treatment so that more survive the disease. Credit: Yngve Vogt

“We simulate how the tumour develops every half hour. Numerically speaking, it is imposible to do it less often. The calculations will then be inaccurate. A number of calculations must be made for each unit of time. And the simulations must

be conducted for all the different proposals for each cancer treatment," says Marie Rognes.

She has taken two big steps to optimise the program. One is to create a code that guesses the right solution far faster. The second thing that she will eventually work on is to program the code so that the simulations can be run in parallel on a high-performance computer simultaneously by thousands of data processors.

Tested on breast cancer

The simulation model has been initially tested on patients with breast cancer. There are a number of different types of breast cancer. About 3,500 contract breast cancer each year. Nine out of ten survive.

Researchers have received detailed data from Ullevål Hospital/Radium Hospital on how four patients who had already been treated for breast cancer fared.

"The simulation program reached the same results about how the cancer developed." This means that their simulations matched the reality.

In their simulations, they have currently only modelled the effect on two types of chemotherapy. "We must include all the drugs that are used. They all work differently," says Frigessi.

Breast cancer can be divided into two main categories: Cancer cells with and without oestrogen receptors. Cells with oestrogen receptors are the easiest to stop by blocking the receptor. The other group is more difficult. Chemotherapy works well on those cells that divide quickly, but unfortunately some patients suffer a relapse.

Clinicians have guidelines on how they can treat breast cancer, depending on how the cancer cells look and what kind

of receptors they have.

“These guidelines build on many years of experience and knowledge from clinical trials. There is a plethora of treatment options and possibilities. Before we go and throw ourselves at all the medical combinations outside the guidelines, there are still niches within these that we can study further,” says Professor Vessela Kristensen at the University of Oslo. She is one of the country’s foremost researchers in breast cancer.

She says it’s important to knock out all the cancer cells. It’s not enough to knock out the lion’s share. “The few remaining cancer cells are the dangerous ones. The point is therefore to have a mathematical model for those patients whose treatment is not working. Although most people survive breast cancer, which is the most frequent form of cancer in women, the small percentage that suffer a relapse still totals many women,” Vessela Kristensen points out.

Chief physician Olav Engebråten, who is an expert in the project, is sceptical about whether the simulations can improve treatment in the short term. He is a clinician and one of the foremost experts in treating breast cancer at Oslo University Hospital.

“The idea is exciting. It may be interesting in the long term, but the problem is the wide variation that cancer diseases pose per se. The trademark of cancer is variation and instability. The systems must be good enough to pick out the medications that work or do not work based on the characteristics of the tumour,” Olav Engebråten points out.

Some patient groups receive targeted treatment. Others do not. Among those who do not receive targeted treatment, there are seven to eight different standard treatments. “Some standard combinations are well-proven,” says Olav Engebråten.

He is particularly sceptical about having to deal with a

computer program that will suggest an optimum combination of drugs that have not been tested before. “Combining and adjusting drugs is very challenging. Many of them work on the bone marrow and other tissues. In the clinic, we usually do not combine drugs until the effect is well tested. When we calculate a patient’s drug dosage, we need to know if the patient can withstand the treatment. The normal tissue must survive,” he says, adding:

“We will always experience that patients die from the disease. We can’t cure everyone, but it’s extra important that we do what we can to prevent patients from dying from the treatment itself. We can’t throw precaution overboard.”

He is also sceptical about the current simulation model of the blood vessels in the tumour. “This model is a simplification of the reality. All of the assumptions are not enough. We also need more data,” notes Engebråten. However, he adds that in the long term the simulations may be interesting for those patients who are not benefiting from current treatment.

The survival rate for patients with breast cancer is up to 90 per cent. However, the prognoses are poorer for those with extensive illness, such as when it spreads to the lymph nodes. “The poorer the prognosis for survival, the greater the potential of the simulation model. We might then be able to save more lives in the long term. It would therefore have been fantastic to have such a simulation tool that could help us to choose the right treatment for such patients,” notes Engebråten.

Arnoldo Frigessi appreciates the scepticism of the clinicians. “I’m glad that the clinicians are sceptical. It helps us to improve the models so that they can become more realistic. I think one day that simulations will be part of clinical practice, but we are not there yet,” says Frigessi.

Åslaug Helland is not as critical as Olav Engebråten. She

thinks it might be interesting to simulate blood vessels. “Although it is natural to think that we kill a tumour by taking away its blood supply, the results of this strategy have varied. We can still use the simulations to show who can benefit from this treatment,” Åslaug Helland hopes.

Vessela Kristensen notes that certain treatments destroy the formation of blood vessels. “Simulation of blood vessels is still only one of the many things that are part of the simulation model. The number of blood vessels is easy to measure. We are therefore trying to simulate the cancer-fighting effects of destroying blood vessels.”

She believes the model can show a correlation with the blood vessels not previously known about, adding: “Currently, we only simulate a small part of the reality. The simulation model can still change future cancer treatment. Medical treatment is based on experience. This experience takes a long time to build up. Sometimes it doesn’t work. The simulation model can accelerate this process,” Vessela Kristensen believes.

Her entire point is briefly summarised:

“Now we don’t have to wait for generations to die to accumulate enough experience. The mathematical models can find the essence of all the experiences and come to faster conclusions. We therefore save both time and lives with these models. They can improve current practice,” Vessela Kristensen believes.

Mouse model

When the simulation program has made its proposals, the oncologists can double check the treatment in the laboratory before the patient is medicated. “One possibility is to take pieces of the tumour in different vessels and test whether the cancer cells die with the various combinations of drugs,” says lung cancer specialist Åslaug Helland.

Another possibility is to test the proposed treatment on mice or in zebra fish. A few cells are then taken from the tumour and inserted into the test animals, which receive individual treatment. In the United States, clinics are already testing the tumour in mice and trying to treat mice with different types of treatments. The method nevertheless has its weaknesses:

“Not all tumours grow in mice, the experiments use a lot of mice, and the method is very expensive,” says Vessela Kristensen.

Probability

Arnoldo Frigessi emphasises that the simulation model will not be able to provide a 100 per cent certain result.

“However, the doctor will receive an answer from the program whether the result is 80 or 40 per cent certain. It makes a difference. The program must be able to say that the result is uncertain because some parameters, such as the amount of medication leaching from the blood vessels, are uncertain. I therefore believe that it is important to quantify the uncertainty. The program must also be able to say whether the treatment of a patient will be easy or difficult,” Frigessi points out.

Norwegian Medicines Agency

Ultimately, the clinicians must have confidence in the simulation program. “No doctors dare use the recommended combination treatments when no one has done it before. The doctors must have confidence in the algorithm. My question is how to enable doctors to put their trust in these algorithms.”

His idea is that the algorithms in the simulation program need to be approved by the authorities before they are used. “Because the recommended combination of drugs is tailored to the individual patient, the Medicines Agency must approve the

algorithms for the therapy and not the therapy itself. Perhaps our simulation program can be approved for every single disease, such as breast cancer and lung cancer," Frigessi hopes.

Cancer growth in the body could originate from a single cell – targeting it could revolutionise treatment

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