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Need a doctor? Send in your digital twin!

Max Rauner, Science editor at *ZEIT Wissen*, the popular science magazine of Germany's largest weekly newspaper *Die ZEIT*, won the *Cancer World* Journalism Award for best article on research, with this piece on the use of modelling 'virtual patients'. The award recognises the value of journalism that explains cancer research and its potential application in a way that is accurate, relevant and exciting.

For oncologist Sebastian Ochsenreither at Berlin University Hospital – the Charité – Patient 19 is a person of flesh and blood; he has shaken hands, taken his blood pressure and discussed the CT scan of his mucosal tumour with him. For bioinformatician Thomas Kessler, Patient 19 is a file containing 22,117 differential equations that are linked to 600 gigabytes of genome data. For human geneticist Hans Lehrach, Patient 19 represents the future of medicine.

Hans Lehrach, Thomas Kessler and Sebastian Ochsenreither are currently testing an idea that sounds like the stuff of science fiction. They are simulating people on a computer to identify the right drugs for them. Patient 19 is one of 35 patients with melanoma who are participating in the study. Kessler and his colleagues make a digital copy of each patient. They then use the computer to identify the substance that will best help the copy, or 'digital twin'. The decision on which drug the patient receives is taken by a human. For Patient 19, this person is Sebastian Ochsenreither of the Charité.

The project is inspired by the vision of personalised medicine, and the person to speak to first is Hans Lehrach, the

greatest visionary of them all. Lehrach has an enormous office at the Max Planck Institute for Molecular Genetics, with a giant desk and giant screens. The 70-year-old was Director of the Institute for many years; he set up biotech companies, conducted research in Boston and London, and helped decode the human genome. His achievements have already earned him immortality in the scientific community.

He could be enjoying retirement and spending his mornings walking in the Grunewald forest, but instead he continues to throw himself into his work. "Why should I rest on my laurels," he asks, "when we can improve treatment for millions of patients?"

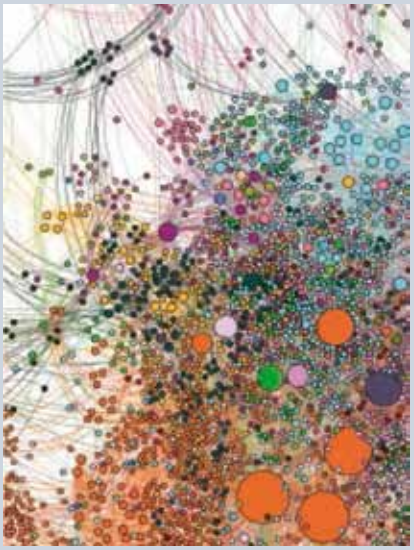
It is Lehrach's dream that one day every person will have a digital twin, and that before prescribing a drug for the real person, the doctor will try out various treatments on the digital twin. "From birth to old age, everyone should have a twin *in silico*", says Lehrach. The phrase *'in silico'* – a reference to the silicon in computer chips – has been coined to refer to work done on the computer. "The twin will also be used when you train for a marathon. The simulation will tell you how to handle your nutrition during training." And if at some point in the future there are digital copies of millions of people, clinical trials could be conducted on an army of virtual doubles, without anyone coming to harm.

It is a hot day in mid-June, and Hans Lehrach has come to the office in shorts and sandals; he talks with the charm and sense of humour that German-speakers call Viennese Schmäh, with frequent sarcastic comments about the health system. This man should not be underestimated. He has drummed up support for the digital twin from more than 70 research institutes and companies. The initiative is called 'Future Health', and these days Lehrach often flies to Brussels, because Future Health is in the final round of a process that could result in research funding worth €1 billion. Naturally, he uses the word 'revolution' and, as befits the leader of a revolution, he has written a manifesto. In it he cites the moon landing as a model.

Hans Lehrach comes up with comparisons that he uses to persuade others of the benefits of the digital twin – or the 'virtual patient' as it is often called. "When we build a skyscraper," he says, "we don't wait to see whether it collapses in the next autumn storm. Instead we conduct a simulation beforehand." Aeroplane pilots train in simulators, and cars are put through crash tests on the computer. "It is better to make mistakes on the computer than in reality. Medicine is the only field in which we don't do that."

Genome sequencing of patients – analysing their entire genetic make-up – should become routine, says Hans Lehrach, and it should be subsidised in the same way as electric cars and solar cells. "After all, it's only human lives we're dealing with here," he says sarcastically. On his left wrist he wears an Apple watch with a heart rate monitor; on his right is a Fitbit movement sensor. One day the data from such devices will also feed into the twin simulation.

Can artificial intelligence help heal people?



Personalised medicine envisages that drugs will be adapted to the metabolism and DNA of the individual being treated. There are two ways in which computers could help doctors achieve this. The first involves Big Data: software is used to analyse as many disease records and trials as possible, and when someone becomes ill with, say, cancer, the artificial intelligence searches the mass of data for parallels. This is what IBM is doing with its supercomputer Watson. The second method involves simulating the biochemical processes in the body, as described in this article. The figure on the left shows the molecular network of a tumour cell in the model used by Alacris. A circle represents a gene, a protein or a biochemical reaction. The larger the circle, the greater its importance for the network. The colours show which parts of the cell are well networked. "If personalised medicine is to benefit everyone, there must be open access to the data," says Jonathan Chen of the Center for Biomedical Informatics Research at Stanford University. "That is easier said than done, because many companies and institutions hoard their data, either for security reasons or because they can make money from it."

What about data protection? "Data protection is for healthy people," says Lehrach.

According to Lehrach, the personalising of drug therapy is the great unsolved problem in medicine. A drug affects dozens of biochemical processes. But every human body is different. The doctor does not know what effect a drug will have on a particular individual. There are clinical trials of course, but they depict an average over hundreds of people. "It's like saying: 'Your left arm is broken, but we'll put the right one in plaster, because more right arms have been put in plaster in clinical trials'." Listening to Hans Lehrach for a while leaves you wanting to delay falling ill until the future has come a bit closer.

Personalised medicine does not mean that the doctor asks more questions about your family (that would be more personal medicine, which is a different issue). Instead it means that each patient receives treatment that is tailored to their body, their genome, their metabolism.

This vision is based on an assumption with which students have been disrupting philosophy seminars ever since the time of Aristotle – the assumption that humans work like a machine. Scientists spent a long time searching for a vital force (*vis vitalis*) that would distinguish a living organism from a pile of dead matter. They searched in vain. In the 19th century people came to realise "that the living cell was no more than a bag of interconnected chemical reactions", writes the doctor Siddhartha Mukherjee in his bestseller *The Gene*. The new science of biochemistry was born. In the 20th century biochemists decoded DNA, the building block of life. Since then humans have been regarded as beings that, while complex, are in some respects entirely calculable. "Cancer is a very mechanistic problem," says Hans Lehrach. "You can happily leave discussion of the soul out of it."

Then he climbs into his Mercedes and drives a short distance through the Dahlem district of Berlin to an unpretentious concrete building. It houses some offices that have been rented by Alacris Theranostics, a biotech company founded in 2008 by Lehrach, his colleague Marie-Laure Yaspo, and George Church of Harvard Medical School. On the second floor he uses a security code to open the door. Welcome to the realm of digital twins.

At a rough estimate, a human body consists of around 40 billion cells. They form the skin, the liver, the heart, the lungs and other organs, the muscles, blood, nerves, nails and hair – in fact absolutely everything. Through its outer membrane each cell absorbs nutrients and molecules from which it obtains energy; in the interior it produces proteins and processes fat and sugar molecules. It multiplies by cell division, and when it is no longer needed it launches a self-destruct programme and disappears. This is life from a biochemical perspective. And it can be simulated like a chemical plant? Not quite.

You can't talk to digital twins like you can to Apple's Siri, but they do have a representative: Thomas Kessler and three other bioinformaticians are sitting in a room with the blinds closed, their heads concealed behind screens. Many of the 20 employees at Alacris previously worked at the Max Planck Institute. Kessler opens the folder labelled Model_2016Q2

and calls up Patient 19. The image doesn't remotely resemble a person; it looks more like a map of the railway network. There are blue squares – those are the genes. Red circles are proteins and coloured lines represent biochemical signalling pathways. What you don't see are the 22,117 equations with which a computer cluster spent three days calculating how the molecules travel.

This isn't a complete copy of a person, but just a building block. The hope is that one day the digital twin will be like a biochemical construction kit, with components representing the cardiovascular system, the organs, and perhaps even the functions of the brain. To start with, the researchers at Alacris have programmed this building block for cancers.

What you don't see are the 22,117 equations with which a computer cluster calculated how the molecules travel

Even the world's fastest computer cannot possibly imitate the interaction of 40 billion cells. But the nucleus of each cell contains the same genetic information – the DNA, also called the genome or hereditary material. This simplifies the task. The DNA contains more than 20,000 genes. They are the building instructions for proteins. The proteins in turn protect cells from attackers; as hormones and enzymes they regulate the metabolism; and they ensure that tissues remain stable. When something goes wrong with this process so that cells divide uncontrollably, a tumour may result.

Alacris is limiting its computer model to 800 genes and 45 biochemical signalling pathways – those that regulate cell division and death. They hope that this will enable them to understand why a tumour cell runs amok. And what drugs could halt the dangerous proliferation of cells.

When the White House announced in the year 2000 that biochemists had decoded the human genome, the British Prime Minister Tony Blair joined in from London. His wife had given birth to a healthy son, Leo, a month earlier. Leo's life expectancy had just risen by 25 years, said the then US President Bill Clinton. It was a little joke, behind which lies a great hope: as the cost of genome scanning continues to fall – it is now less than €1,000 per patient – many sick people regard it as the first step towards a cure.

Knowing which genes are involved in a tumour cell is rarely enough, however; the disrupted signalling pathways – the incorrect signals in the biochemical programme – must also be identified. The activity of individual genes is switched on and off by proteins. For this reason, Alacris not only looks for mutations but also studies the transcriptome. The transcriptome (from the Latin *transcriptio*) is in effect the transcript of the genome that provides the basis for the formation of proteins. Thomas Kessler has never met Patient 19 in person, but a section of his tumour is kept in the refrigerator in the corridor for use in these analyses.

The researchers liken cancer simulation to weather forecasting: both involve reducing nature to sets of rules, in the form of mathematical equations. In this case they reduce the cancer to a model of the tumour cell. Weather forecasting also needs data on atmospheric pressure, winds and temperatures worldwide. The cancer simulation needs transcriptome and genome data.

On a Tuesday at the end of June, Thomas Kessler and a dozen other people are sitting in conference room 03001 at the Charité for the molecular tumour conference. The digital twins have come along in Kessler's laptop. From the window one can see the hustle and bustle of Berlin Central Station, with people going about their business, oblivious to the fact that life-and-death decisions are being taken just a stone's throw away. At the tumour conference the doctors discuss particularly difficult cases. Most of the patients have already tried a number of treatments.

The doctors have removed their white coats – there are no patients present. The head of the oncology department is there with a colleague: they know the patients. The pathologists, who are experts in tumour tissue, are there. Two young doctors have been researching the clinical trials that are being conducted around the world. The geneticist Marie-Laure Yaspo of the Max Planck Institute has the genome data at her fingertips. Thomas Kessler talks about the twins.

"We have a new patient," says the oncologist [to preserve anonymity, details have been changed]. This patient was diagnosed with a tumour of the eye in 1998. Her eyeball was removed, she received radiotherapy, then had further surgery in 2002. There then followed lung metastases, chemotherapy and liver metastases; part of her liver was removed. In 2013 she had immunotherapy; in 2015 the cancer spread to the skin and she underwent chemotherapy. She has now been enrolled in the Treat20plus study – the digital twin research project – as Patient 22.

"That's a complex case," says Yaspo, the coordinator of the Treat20plus study. There are 31 mutations in the tumour cell's genetic makeup. The most striking is the mutation of the GNA11 gene; the MET gene is also upregulated. One of the young doctors comments that there is

a phase I study of this in which a MET inhibitor is being tested. The drug could be purchased. What does the computer simulation say?

Molecular targeted drugs have come on the market in recent years. They aim to switch off a tumour by intervening very precisely in the cells' biochemistry. Several dozen of these substances have now been approved and many more are being tested. Thomas Kessler has 300 of them in his database. On the computer he performs a simulation to identify those that might help each of the 35 melanoma patients. The simulation ranks the most effective drugs. For Patient 22, the substance at the top of the list is one that is usually used to treat leukaemia. After discussion, the oncologists at the tumour conference opt for the drug that is ranked second – one that is approved for the treatment of kidney cancer. Its advantages are that it has been tested on skin cancer in some individuals, and also it has fewer side effects than the substance that came out on top.

In the late afternoon, Sebastian Ochsenreither is updating electronic patient records in his consulting room at the Charité. In the morning he sent Patient 19 for a CT scan, and he then attended three tumour conferences – lungs from noon until two o'clock, the molecular tumour conference with the digital twins from 2.00 till 2.30, and then ear, nose and throat from four o'clock until 4.45.

"We are adding months to people's lives, but not years – to put it otherwise would be misleading"

"We are on a learning curve," he says, referring to the Treat20plus study, "but we are still right at the bottom of the curve." According to him, the simulation comes up with a useful recommendation for roughly every second patient. "We are adding months to people's lives, but not years – to put it otherwise would be misleading." For ethical reasons, the computer simulation cannot be used until the standard treatments have failed. One cannot exclude the possibility that the computer will make mistakes. Furthermore, the treatment is "a shot in the dark", says Ochsenreither – there is simply not enough experience of individualised therapies of this sort. This is in fact the dilemma of personalised medicine – each case is a one-off.

Patient 19 was considered to have exhausted his treatment options when he was referred to the Charité in September 2016. Chemotherapy, immunotherapy, radiotherapy, surgery – the mucosal tumour in his frontal sinus seemed indestructible. In the computer simulation, everolimus appeared to be effective. This is a substance actually approved only for the treatment of breast and kidney cancer. Sebastian Ochsenreither prescribed the drug for his patient, opting to use it off-label.

After a couple of months a biopsy showed that tumour growth had slowed. Seventy per cent of the cells had previously been dividing – now it was only 15%. The disease was static. "Sometimes it works," says Ochsenreither. "That is the luck of the individual." However, a problem for doctors is that tumour cells are constantly evolving. When a suitable drug has been found, cells may become resistant to it. "That is microevolution at its finest level," says Ochsenreither, "as in Darwin." Then he looks at the clock and jumps up. He needs to get to his tango session with his wife. For the 40-year-old oncologist, there is life after death. "I'll be back here at 7 a.m. tomorrow," he says.

In science, every answer throws up new questions. That is good for scientists – they always have something to do. For terminally ill patients, it is only the answers that matter. The doctors stand somewhere in the middle. The most important question for everyone is whether the digital twin is ultimately of more help to the patient than other methods. To come up with a reliable answer to that question one would have to enrol far more than 35 patients in a trial, and treat some of them with the help of the digital twin, others by conventional means. Things haven't yet got that far.

Hans Lehrach is deliberating again – this time about how to save the health system. Costs are rising faster than GDP; that is not a good thing. If genetic analysis and computer simulation become routine, he speculates, treatment costs might eventually fall in the same way as the cost of solar cells has fallen. He recently raised the subject with two members of the German Bundestag – one a Social Democrat, the other a Christian Democrat – but clearly found the experience unsatisfactory. "It was like looking for someone on the Titanic who is interested in icebergs."

He is no longer a youngster, but he is not going to let age be an obstacle. A couple of weeks ago, Lehrach had his own genome sequenced. He is not ill, but curious. He would like to compare his genetic makeup with that of super-centenarians – people who live to 110 and beyond.

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