

Cancer crunch

Could a bunch of outsiders help tame a global killer, asks **Lizzie Buchen**

WHEN Danny Hillis spent a day watching a top surgeon perform keyhole cancer surgery, he was left both exhilarated and depressed. The clinical precision with which the surgeon opened up the patient, used state-of-the-art robotic tools to remove their tumour, and sewed them back up again was breathtaking. It was also deeply disheartening. “With all our science, the best we can do is try to cut the cancer out with a knife,” says Hillis. “That is the caveman approach to disease.”

A few years ago, what he thought would not have mattered. Hillis is a celebrated computer architect who pioneered the concept of massively parallel computing. His accomplishments include using a children’s construction set to build a computer, now exhibited at the Museum of Science in Boston, designing a mechanical clock that will keep time for 10,000 years and creating cutting-edge computer systems for Walt Disney theme park rides and animations. Impressive, but hardly a convincing resumé to pronounce on the shortcomings of modern cancer surgery.

But Hillis’s thoughts and expertise do matter. According to the World Health Organization, this year cancer is set to overtake heart disease as the leading cause of death in developed countries. While traditional biological approaches to understanding and combating cancer have had some great successes, mortality rates remain stubbornly high. That’s why last year the US National Cancer Institute (NCI) enlisted Hillis and other high-powered researchers from physics, engineering, mathematics and computer science to see what extra ammunition they might supply.

The newcomers will not be required to

design new death rays or high-powered imaging devices for tumours, the traditional metier of physical scientists. Instead, they will harness the mathematical tools and the broad-brush approaches of their disciplines for a new goal: to find simple laws that describe a cancer cell’s fate as surely as they do a falling apple.

That is a world away from the traditional, “bottom up” approach to looking at cancer. For the past few decades, research into the disease has focused on its molecular basis: identifying the genetic mutations and protein abnormalities that underlie it, and designing drugs to treat them. The US Food and Drug Administration has approved something like 150 cancer medicines stemming from this approach. Coupled with earlier diagnoses, the result has been a decline in death rates from almost all cancers in wealthy nations.

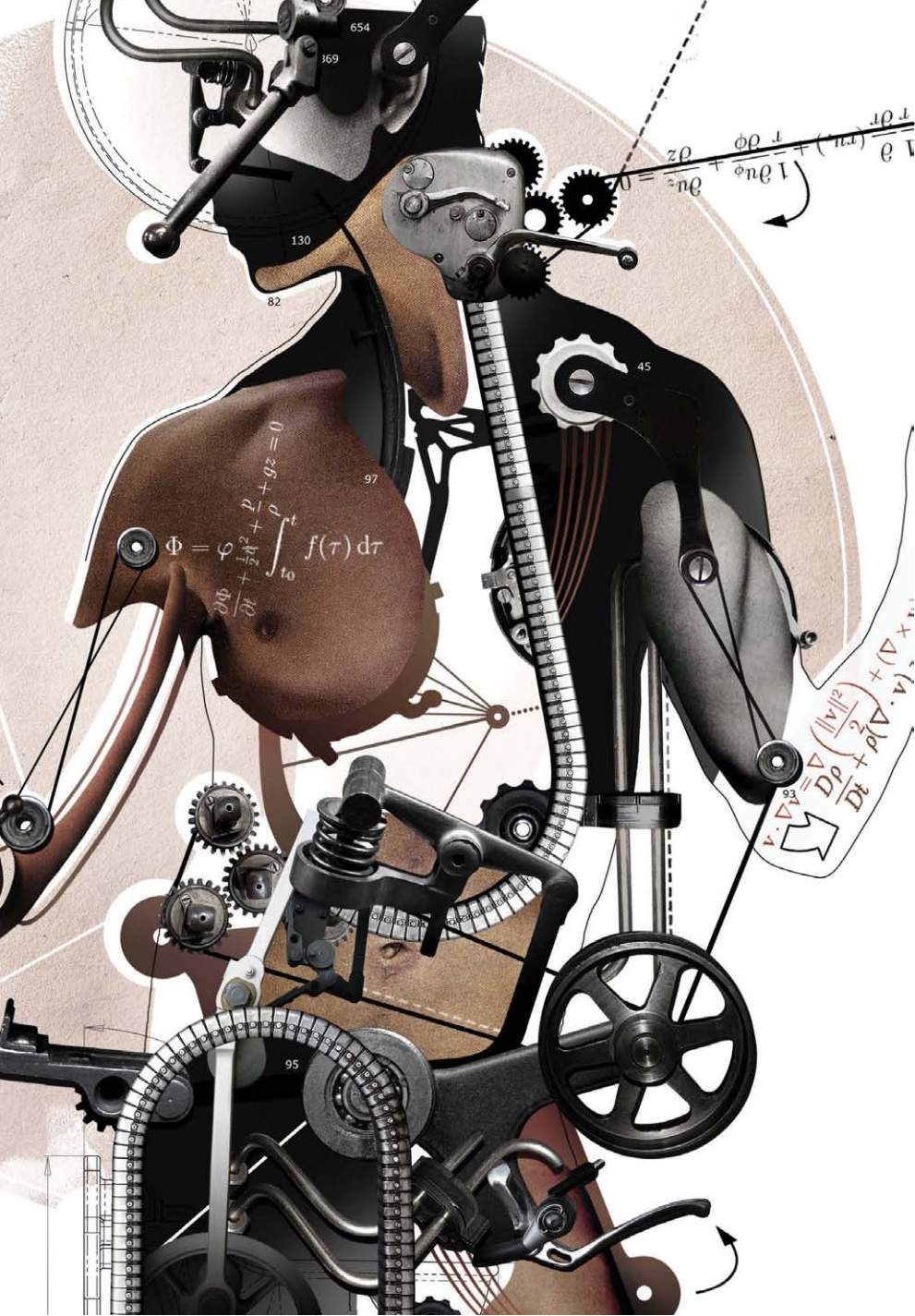
Yet all too often those advances have been incremental. In the US, for example, the five-year survival rate for pancreatic cancer increased from 3 per cent in 1975 to just 5 per cent in 2004. “We have a lot of drugs, but they’re not doing that much,” says David Agus, an oncologist at the University of Southern California (USC) in Los Angeles. “They haven’t really changed the playing field.”

The trouble is that if its normal pathway to growth is blocked by a drug, a tumour will often simply evolve and find new molecular channels through which to grow and prosper. “We keep hammering at each individual signalling molecule, but we forget that there’s this whole complex system that it is interacting with,” says Agus.

It was Agus who invited Hillis to see cancer surgery at first hand. Bizarrely, the impetus for their collaboration came from former US vice-president Al Gore. In 2003 Gore visited



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immune system, grows and spreads in mice. The project showcases the sophisticated technologies physicists and engineers already contribute to cancer research: nanoscale sensors for analysing protein interactions, microfluidic tools for looking at genetic changes in single cells and even microscopic techniques that allow a direct peek at tumours growing inside living organisms.

The real innovation, though, is what Agus, Hillis and around 20 other scientists from disparate disciplines are doing with all the data streaming in from that research. They are testing a set of interlocking computational models they have developed from basic principles to describe and predict different aspects of the disease: from protein interactions and modifications within cells, through a tumour's growth and genetic evolution, to the host's response to the disease and various therapies.

Personalised therapy

Within five years, the team hopes to have a single, all-embracing model of mouse lymphoma that fits the data as convincingly, and has as much predictive power, as a theory of gravity or electric fields. If they can pull that off, transferring the insights to humans will be the next challenge. The dream is to produce a model that, by plugging in key parameters – sex, blood pressure, genetic sequences and the like – could predict an individual's response to various combinations of cancer therapies. "We could run a simulation for each patient, and design a complex treatment specific to that patient," says Hillis. "Maybe we would use some radiation for while, then heat them up, then change the glucose level in their blood."

That would be an extraordinary turnaround for cancer therapy. "The science behind what we do every day as oncologists is almost 50 years old," says Mitchell Gross of the Westside Prostate Cancer Center in Beverly Hills, California, who is also involved in the USC centre. The experiments that form the scientific basis for giving chemotherapy and radiation were done in the mid-1950s, he says, and since then optimisation has been largely about coming up with less toxic and more effective chemicals, or using a different schedule of treatment. "Patients ask me, 'Why are you giving me six doses of this chemotherapy instead of four or eight?'" says Gross. "The reason is, the other thousand patients got six doses of this chemotherapy, so we have to give you the same thing."

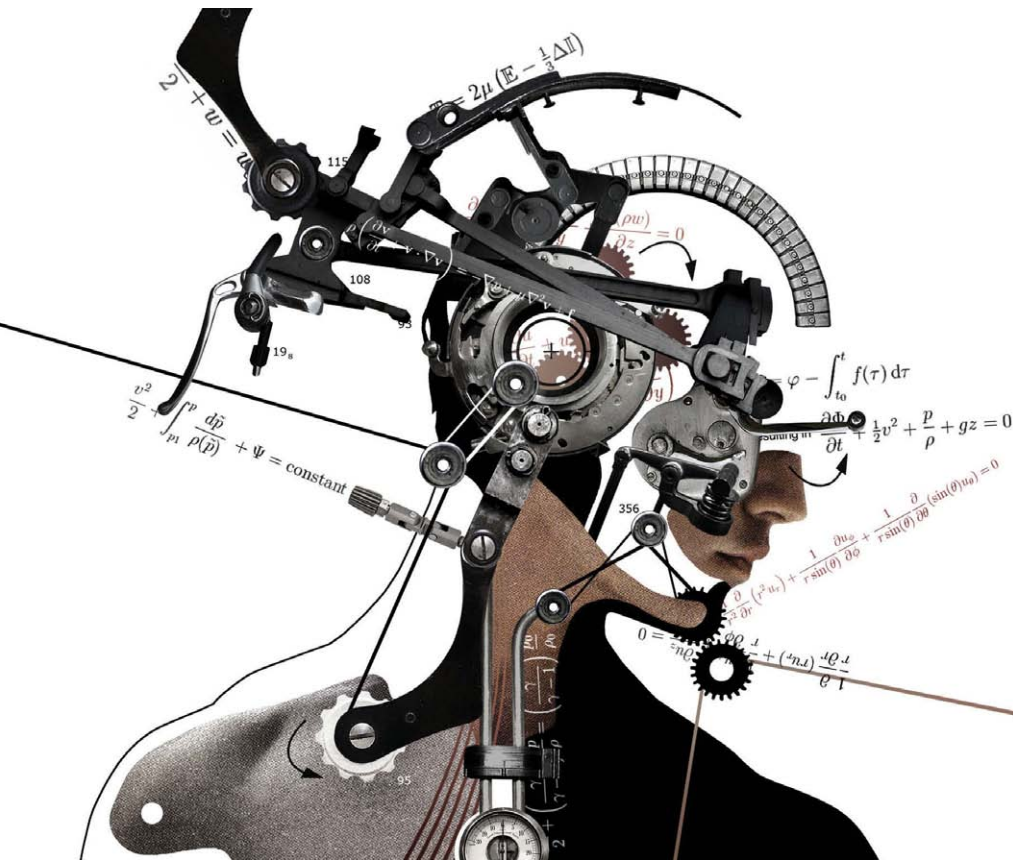
Not everybody is convinced by the new ➤

the centre in Los Angeles where Agus was pioneering techniques to understand how communication between proteins affects the onset and progression of cancer. The project was producing huge amounts of data, and Gore suggested it might benefit from specialist number-crunching expertise. "He said I could really benefit from getting an engineer or a mathematician involved, and suggested Hillis," says Agus. "I thought, do I really want to meet a guy from Disney who builds computers?"

Initially, Hillis was no less sceptical. But the two agreed to meet and soon found they had a lot to talk about. As a systems engineer, Hillis

was puzzled by the way oncologists reduce cancer to the action of genes, when it is a disease that affects a whole organism. Agus too found himself looking at cancer in a different way. "The natural inclination of physical scientists is to step back and say, 'Listen, I know I'm not going to understand every component of that system. But it doesn't mean I can't control that system,'" he says.

Since last year, their collaboration has been formalised within the new Physical Sciences Oncology Center at USC, one of 12 that the NCI has set up across the US. Agus and Hillis are now working together to create a model of how lymphoma, a cancer of the



"We can model how a star works. Why should the same not be true for living organisms?"

approach. Many biologists doubt the human body will give up its mysteries under crude mathematical scrutiny. Such an approach implies a degree of simplification and loss of detail that could never do justice to the complexities of a dynamic and variable system, they argue. "You can come up with computational models, and they may be very interesting, but the question is whether they reflect reality," says Leonard Augenlicht, an oncologist at the Albert Einstein College of Medicine of Yeshiva University in New York.

Paul Davies of Arizona State University in Tempe, a distinguished theoretical physicist and cosmologist recently recruited by the NCI to its new programme, takes a different view. "Every system around us is in practice very complicated," he says. Armed with basic rules of nuclear physics, magnetic fields and heat radiation, for example, we can produce pretty good models of how the sun works, without knowing the details of what every particle inside it is doing. Why should the same not be true for living organisms? Augenlicht counters that whereas stars such as the sun develop according to a well-defined pattern, biological entities evolve in response to their

environments in ways that might not seem inherently logical or efficient. "Trying to derive a model of how cells behave, how tumours behave, is very different to working out how the universe behaves," he says.

Paul Newton is one researcher taking up the challenge. He cut his teeth in USC's aerospace and mechanical engineering department developing numerical models of hurricanes. As a project leader at the new physical sciences oncology centre at the Scripps Research Institute in La Jolla, California, he is now also applying his modelling expertise to metastasis – the poorly understood and lethal process by which tumour cells break away from their original site and spread via the lymphatic and blood circulatory systems.

Break it down

Newton aims to tackle metastasis as a physicist or engineer would: by breaking it down into simple steps that can each be modelled using equations. "We write down the fundamental equations of fluid mechanics for the blood flow and for a deformable cell, model what a deformable cell is, model the

vessel walls the blood is going through, model the pumping of the heart and the pulsatory fluid motion that's driving the whole system, and then numerically simulate it," he says. "In principle, the equations are all there."

What he needs, and is getting, are the specifics: basic stuff such as how stiff cancer cells are and how far they can stretch and squish without breaking. In his centre in Tempe, similar questions are on Davies's mind. "It's quite clear that cancer cells are physically distinct from healthy, and as they become more and more malignant those changes become more and more pronounced," he says. His team is looking closer at those changes, using the technique of atomic force microscopy to measure the shape and stiffness of cancer cells and how the nanoscale structure of chromosomes changes as the disease progresses.

No one knows how informative this concentration on the mechanical properties of cells rather than its genetics will turn out to be – perhaps not very, says Larry Nagahara, director of the NCI's physical sciences initiative. "But if it is, it will open up a new field."

"Some people definitely feel that the approach is a little abstract, or that we're oversimplifying things to the point where they're irrelevant," says Parag Mallick, a proteomics researcher at the USC centre. Beverly Mitchell, an oncologist at the Stanford Cancer Center in California, welcomes any fresh approach, but questions the likelihood of quick insights. "It's exciting and new, something we haven't tried before," she says. "But the speed at which this develops into something useful in diagnosing and treating cancers, that's still up in the air."

Those involved stress that it is about learning from each other, not about physicists taking over and showing biologists everything they are doing wrong. "We don't have the knowledge of the biological system," says Hillis, the computer scientist. "There's no way we could do this ourselves."

To Agus the oncologist, meanwhile, that knowledge gap might turn out to be an advantage: great insights often come from those unencumbered by intellectual baggage. "Galileo would go out every night and map stars," he says. "After four months he had a beautiful map where he could predict where every star would be. But he didn't even know what a star was." ■

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