Biology

All systems go

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A powerful way of studying biology looks set for take-off

SEVEN years ago, one of the attractions at the now-defunct Millennium Dome in London was what looked like a remarkably detailed video of a beating human heart. People could admire the heart's delicate tracery of blood vessels with the muscle stripped away and hear a display of its electrical activity that would not have disgraced a disco. The voiceover described it as “one of the most powerful tools we have in the fight against disease”, but few of the visitors understood why.

Actually, the beating heart was no simple video. It was, instead, the output of a stupendously complex computer model of a heart, developed over more than 40 years. This model is an example of “systems biology”, an approach that represents a significant shift both in the way biologists think about their field and in how they go about investigating it.

A central tenet of most scientific endeavour is the notion of reductionism — the idea that things can best be understood by reducing them to their smallest components. This turns out to be immensely useful in physics and chemistry, because the smallest components coming from a particle accelerator or a test tube behave individually in predictable ways.

In biology, though, the idea has its limits. The Human Genome Project, for example, was a triumph of reductionism. But merely listing genes does not explain how they collaborate to build and run an organism. Nor do isolated cells or biological molecules give full insight into the causes and development of diseases that ravage whole organs or organisms. A complete understanding of biological processes means putting the bits back together again—and that is what systems biologists are trying to do, by using the results of a zillion analytical experiments to build software models that behave like parts of living organisms.

You can't beat the system

The pharmaceutical industry stands to gain much from this approach. Around 40% of the compounds that drug companies test cause arrhythmia, a disturbance to the normal heart rate. Drugs such as the anti-inflammatory medicine Vioxx and the diabetes treatment Avandia have been linked with an increased risk of heart disease. The result is that billions have been wiped off their makers' share prices.

Not surprisingly, the pharmaceutical industry has sought out Denis Noble of Oxford University, the creator of the beating-heart model, to help. Dr Noble is now part of a consortium involving four drug firms—Roche, Novartis, GlaxoSmithKline and AstraZeneca—that is trying to unravel how new drugs may affect the heart. Virtual drugs are introduced into the model and researchers monitor the changes they cause just as if the medicines were being applied to a real heart. The production of some proteins increases while others are throttled back; these changes affect the flow of blood and electrical activity. The drugs can then be tweaked in order to boost the beneficial effects and reduce the harmful ones.

Systems biology thus speeds up the drug-testing process. Malcolm Young is the head of a firm called e-Therapeutics, which is based in Newcastle upon Tyne. Using databases of tens of thousands of interactions between the components of a cell, his company claims to have developed the world's fastest drug-profiling system. In contrast to the two years it takes to assess the effects of a new compound using conventional research methods, Dr Young's approach takes an average of just two weeks. Moreover, the company has been looking at drugs known to have damaging side effects and has found that its method would have predicted them.

Testing for reactions in this way could also offer a more rigorous route to assessing alternative therapies, such as herbs and clinical nutrition (which seeks to control disease through the use of particular foodstuffs). These remedies are often dismissed as unscientific because they have a multitude of effects on the body that are hard to quantify. Studying multiple effects, however, is precisely what models like the virtual heart are able to do.

Nor need such models be confined to people. In biological terms, mice are better understood than men, and a team in the Netherlands is using a computer model of mouse physiology to investigate the effects of a high-fat diet, by monitoring the concentration of various components of the blood. The team, from a firm called SU BioMedicine, which is based in Zeist, found that the active ingredients of a particular concoction of Chinese herbal medicines have the same effect on blood composition as the anti-obesity drug Rimonabant. The hope is that systems-biology studies like these will eventually trace out the pathways the herbs are affecting.

Such models may also help to pin down the causes of diseases that arise from the interplay of genetic and environmental factors. Andrew Ahn of Harvard Medical School cites the example of diabetes, for which the standard clinical test is a measure of the level of glucose in the blood. But that is a single snapshot in time. Dr Ahn suggests that the way toward a fuller understanding of diabetes is to track glucose levels against other factors such as diet, sleeping habits and psychological health. He proposes to employ a systems-biology model to do so.

Ultimately, the aim is to build an entire virtual human for researchers to play with. But reductionism is still needed to get there. Human bodies are made of cells, and the best way to build a model body might be to construct a general-purpose virtual cell that can be reprogrammed into being any one of the 220 or so specialised sorts of cell of which the human body is composed. That, after all, is how real bodies develop. And a collaboration organised by the European Science Foundation is hoping to do just this, through what it calls the Blue Cell project.

Keeping track of the data needed to carry out systems biology on this scale will be a Herculean task, and may turn out to be the driver of future developments at the heavy-number-crunching end of the computer industry. Dr Noble is in negotiations with Fujitsu, a Japanese computer firm that is developing a machine capable of performing some ten thousand trillion calculations a second. That would make it the world's fastest computer, but it comes with a price tag to match—about a billion dollars. This is a little more than the $6m paid for that fictional bionic man, Steve Austin, even allowing for inflation. But it is only about a quarter of what the Human Genome Project cost. And this time, it might produce some answers that prove immediately useful.

Cosmology

The lesser spotted universe

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A cosmic defect that appeared at the beginning of time has come to light

GOD does not play dice, or so said Einstein. But might he knit? If so, physicists seeking to explain the fundamental nature of the universe think they may have spotted a point at which a stitch became tangled, creating a flaw in the fabric of reality.

The universe was born in the Big Bang some 14 billion years ago. The first snapshots of the infant universe, showing it aged a mere 300,000 years, before the first stars coalesced, are taken in the light (or, rather, the microwaves) from that explosion. The cosmic microwave background, as it is known, reveals the early universe to have been a remarkably uniform fireball. Today's universe looks very different. It is lumpy, with clusters of galaxies scattered through it. Physicists have therefore spent years examining the baby pictures in the hope of discerning telltales of how the change happened.

What they have found are subtle variations in the cosmic microwave background, including a large spot that is distinctly colder than the rest. Over the past year, several ideas as to what caused this spot have been proposed and then quashed. The latest suggestion, made by Neil Turok of the University of Cambridge, in England, and his colleagues, and published this week in Science, is that the spot is a blemish which formed as reality crystallised, rather as ice cubes contain irregularities and air bubbles.

At the precise moment the universe began, its constituents—which today appear as fundamental forces such as gravity and electromagnetism, and subatomic particles such as electrons and quarks—were unified into a single substance in the extreme heat of the explosion. As the universe expanded, though, it cooled. And as it did so, it went through phase changes, just as steam condenses to liquid water that then forms ice as the temperature falls.

At each point at which the phase of the universe changed, one of the forces of nature became distinct, or a type of matter emerged as being different from the others. Only when this process was complete did the familiar pattern that makes up the laws of physics properly emerge.

One theory, devised several years ago, has it that each of these phase transitions is marked by the formation of defects. Such imperfections are analogous to the misalignments between ice crystals that often form when water freezes. These can be seen both in ice cubes and on frost-covered windowpanes in the places where growing crystals have met. Cosmic-defect theory, as it is known, holds that a similar process would have happened as the newborn universe cooled.

One type of defect proposed by Dr Turok is called a “texture”—a knot of energy that could be anything between a few millimetres and many light years across. Like other cosmic defects, once formed, textures would unravel at the speed of light. They would, however, leave behind a trace of their existence. That is because the process of unwinding concentrates mass into a rapidly shrinking region, creating a gravitational field that attracts nearby matter. This, in turn, would lower the frequency of microwaves (or any other form of electromagnetic radiation) in the region by a process called gravitational red-shifting. A lower frequency corresponds to a lower temperature, so these spots would appear cold.

Of course, the explanation for the cold spot could be something else entirely. The team are being careful not to claim they are certain they have seen a cosmic defect. Indeed, they propose further tests that might show them to be wrong. If the cold spot is merely a random fluctuation in the cosmic microwave background, for example, that could be revealed by examining the polarisation of the microwaves coming from it. But, having conducted a statistical analysis of the microwave background, the team reckon that it is most likely that the cold spot is, indeed, caused by a defect.

If they are correct, it would be a boon not only for cosmologists but also for particle physicists. Spots such as this (if more can be found) would give them a way to study how fundamental forces and particles formed that is far beyond the capabilities of the puny (but very expensive) machines they use on Earth. And, based on Dr Turok's results, the pattern they eventually discover might look surprisingly like “knit one, purl one”.

Cancer and allergies

Win some, lose some

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Hyperactive immune systems may protect against cancer. Or vice versa

ALLERGIES cause heaps of trouble. Some people suffer the nuisance of seasonal hay fever, snuffling and sneezing as pollen flows through the air. Others react to materials such as metals, developing unpleasant rashes at their very touch. And some sorry souls go into shock at the mere presence of certain foods, particularly peanuts and shellfish.

The cause in each case is an oversensitive immune system that is reacting to harmless materials as well as to the pathogens it is supposed to be fighting. This creates annoying and sometimes life-threatening symptoms. Chronically over-reactive immune systems may not, though, be an entirely bad thing. Another role played by the immune system is to destroy malignant tumours before they take hold—and work carried out recently by Annette Wigertz of the Karolinska Institute, in Stockholm, and her colleagues suggests that the immune systems of those with allergies may be particularly good at this. However, in a nice example of the way that one set of data is sometimes capable of divergent—indeed, opposite—interpretations, she may instead have discovered a clue about how cancers shut down immune systems in order that they themselves may prosper.

This Manichean finding came after Dr Wigertz and her team interviewed 1,527 people with gliomas (a type of brain tumour) in Denmark, Finland, Norway, Sweden and the south-east of England. The researchers asked the patients in question whether they had a history of allergies, and then compared the results with those for 3,309 otherwise similar individuals who did not have brain tumours. As Dr Wigertz reports in the American Journal of Epidemiology, the tumour-free were, indeed, more likely to suffer from allergies. The presence of an allergy was associated with a 30% reduction in the likelihood of having a glioma.

This was not all that surprising. Previous research had detected similar inverse correlations between allergies and brain tumours, suggesting that a welcome side effect of allergy was resistance to cancer. But this new study went further. It looked carefully at the time in the patients' lives when their allergies were active, and it found that this timing was crucial. Dr Wigertz noted that the absence of allergy was correlated with the time when a glioma first formed. That was true even in people who had previously had allergies which had then cleared up.

Awkwardly, this result is open to two rather different interpretations. The optimistic explanation is that the hyperactive immune system associated with allergy does, indeed, protect against tumours. In that case, the coincidence was caused by tumours taking advantage, as it were, of the reduced immune surveillance that accompanied the disappearance of the allergy. The sinister interpretation is that tumours are doing something as they grow that suppresses the immune system and thus allergic reactions. Either way, tumour and lack of allergy coincide. And either way, something interesting is going on. But Dr Wigertz's result illustrates the perils of leaping to conclusions on the basis of incomplete data.

An auction of meteorites

Nature imitating art

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Tired of boring Picassos, Rothkos and Hirsts?

How about a stone from space?

PEOPLE who think that the explanation for the origin of species is the designing hand of an intelligent creator might pause to consider this. The most beautiful objects designed by the hands of that undoubtedly intelligent creator, man, are those usually designated as art. Yet a series of works of art up for auction on October 28th owe nothing to the hand of man and plenty to chance. They are the products of geological events 4.5 billion years ago, combined with the accident of having collided with the Earth at several thousand kilometres an hour. They are, in other words, meteorites. And they are on sale at Bonham's New York gallery.

You look like a million dollars

The stones in question come from what is known as the Macovich collection. This is owned by a small group of enthusiasts, one of whom, Darryl Pitt, acts as its curator. Mr Pitt, whose day job is managing the careers of musicians, built up the collection (which now includes stones from more than 500 falls) by buying specimens, and also by swapping them with museums. Since his interest lies as much in the aesthetics of the objects as in their scientific value, museums are often willing to trade beauty for science, to the advantage of both sides.

The beauty itself is sometimes the result of the way a specimen melted when it sped through the atmosphere and sometimes the consequence of its origin. Many meteorites are pieces of rock that formed inside small planets which were shattered by subsequent collisions. They therefore contain large, exotic crystals that can grow only at depth.

Specimens going under the hammer include several pieces of the object that formed Meteor Crater in Arizona; a bit of the Ensisheim meteorite, which landed in Alsace in 1492 and was pronounced an omen from God by Maximilian Habsburg (who later became Holy Roman Emperor); and a big chunk of the Willamette meteorite (see above), the largest known from North America, which is expected to fetch more than $1m.