The Economist

A special report on the human genome

Inhuman genomes

Every genome on the planet is now up for grabs, including those that do not yet exist

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IF THE history books do come to recognise the idea of biology 2.0, then the date it began may well be recorded as May 20th 2010. That was the day when Craig Venter announced JCVI-syn1.0, the world's first living organism with a completely synthetic genome.

The Frankencell project, as it was known jokingly at the beginning, had been going for 15 years—ever since Dr Venter started to wonder what was the minimal genome necessary to support a living organism. To find out, he took a bacterium called *Micoplasma genitalium*, which has a particularly short genome anyway, and knocked its genes out one at a time to see which the bug could live without (at least in the cushy circumstances of a laboratory Petri dish). The answer was around 100 of its original complement of 485.

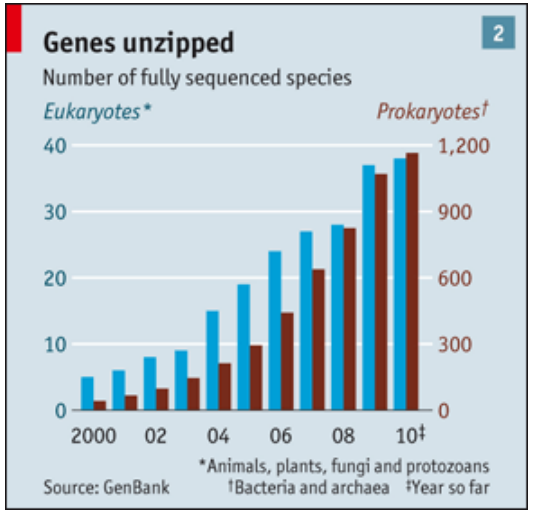
The genetic flexibility this hints at—of a core set of genes and a penumbra of others useful in particular circumstances—has, over the past decade, been confirmed for many other species of bacteria. Indeed, the way biologists think about the whole idea of "species" when they study these micro-organisms is beginning to shift rapidly. This is part of a general broadening of genomics. Though navel-gazing into *Homo sapiens*'s own genome remains of intense interest, the study and manipulation of non-human genomes may ultimately have greater impact.

Dr Venter certainly hopes so. His company, Synthetic Genomics, based in San Diego, plans to patent the new bug. It argues that although it is a living organism, which would normally be

outside the scope of patent law, it is also a true artefact, not just the product of selective breeding. The firm will then be able to use it, and the method used to construct it, in its programmes to make fuels and vaccines.

Technology and magic

On the other side of America, in Boston, George Church is taking a different approach. Unlike Dr Venter, who focuses his energy on one firm, Dr Church is a promiscuous entrepreneur. He has been involved in the foundation of several companies, including LS9 and Joule Biotechnologies (which hope to manufacture biofuels) and Microbia (which plans to make speciality chemicals). Like Dr Venter, Dr Church has something up his sleeve. This is MAGE, a somewhat contrived acronym for multiplex automated genome engineering.



Instead of making new genomes from scratch, Dr Church plans to make lots of parallel changes in existing ones. The idea is to induce simultaneous random mutations in all of the genes in a particular cellular pathway by introducing pieces of DNA which match parts of those genes, but which are attached to short sequences that do not. As a cell replicates, the foreign DNA is absorbed and the genes in question are modified by the non-matching short sequences. Thousands upon thousands of different versions of the pathway are thus created, and all are subsequently isolated and tested to see which are most effective. The process is then repeated on the winners until the desired outcome is achieved. This can replicate at a cost of thousands of dollars the sort of genetic modifications that have previously cost millions.

Even without the new platforms, non-human genomics is beginning to pay dividends. Several firms, including Synthetic Genomics, LS9 and Joule, are engineering micro-organisms (sometimes bacteria, sometimes single-celled algae) to turn out biofuels resembling the petrol, diesel and kerosene that people put in cars and aircraft. Existing biofuels, based on ethanol, are less good.

Ethanol is corrosive and has less energy per litre than petrol and diesel.

One firm, Amyris Biotechnologies, is already scaling up to industrial production of such biofuel, but in Brazil, where cheap cane sugar provides the raw material, rather than in the United States, where it is based. Joule plans to use an even cheaper raw material: the carbon-dioxide exhaust from power stations. It is one of the firms working on single-celled algae, tweaking their metabolic pathways to improve the rate at which CO2 is fixed by photosynthesis and then converted into hydrocarbons that can be used in cars.

Fuels are an attractive alternative to drugs for the new generation of synthetic biologists because they are not subject to regulatory whim to the extent that drugs are. If anything, regulation is likely to favour them because their raw material is, either directly or indirectly, carbon dioxide that has come from the atmosphere or would end up there. That makes them green in the eyes of governments, and therefore a good thing.

The smell of money

Fuel, however, is a low-value commodity. A more profitable way to avoid the regulators may be to make complicated high-price chemicals such as fragrances. This is what Allylix, of San Diego, California, is doing. The firm's founders realised that biological synthesis of certain sorts of molecule is much more efficient than chemical synthesis. Many organic molecules contain what are known as chiral centres. These are places where the atoms can be arranged either left-handed or right-handed. In biochemistry, handedness can matter. Left- and right-handed versions may, for example, smell different. Traditional chemical synthesis cannot distinguish between left- and right-handed versions, so they have to be separated afterwards, which is tedious. Moreover, if there are lots of chiral centres in a molecule, and each matters, the yield of the version with the right combination can be minuscule.

Allylix gets around this by engineering the genes for new biological pathways into yeast cells. The molecular family it concentrates on is the terpenes, which are used as fragrances and flavours. Some are very costly. Sandalwood essence, for example, is a terpene, and the demand for its potent smell means the tree it comes from is becoming rare. Allylix has duplicated the smell of sandalwood industrially, by extracting the genes for the relevant enzymes from sandalwood trees. Indeed, its researchers have improved on nature. They have identified the parts of the enzyme molecules that carry out the reactions, and tinkered directly with the DNA that describes these parts, in order to improve their efficiency. Microbia plans something similar, using Dr Church's MAGE technology, though its first products will be colourings rather than fragrances.

If genes are to be the raw material of a new technology, then it would be useful for researchers to know how many there are out there. The answer is, a staggering number. Most of them are bacterial. Though the average bacterium has fewer than 5,000 genes, compared with around 20,000 protein-coding genes in the average mammal (bacteria do not go in much for RNA-only genes), there are lots of species of bacteria. In his round-the-world cruise after he left Celera, Dr Venter reckoned he identified 5m new bacterial genes—and that was just a start.

Measuring bacterial diversity in genes rather than species makes sense because it is no longer obvious exactly what constitutes a bacterial species. In the view of Julian Parkhill, of the Sanger Institute, near Cambridge, England, bacteriologists need to shift the focus of their investigations from organisms to systems. The geneticists' workhorse, *E. coli*, for example, has about 4,500 genes. Only 1,500-2,000 of these are always present, however. The remainder of any given *E. coli* bacterium's genome is drawn from a pool of about 20,000 other genes that the organisms swap with gay abandon. In only a tenuous sense, then, is *E. coli* a species in the way that, say humans or mice are species.

The same thing is true of other well-studied bugs, such as those that cause typhus and plague, and is likely to be true of most bacteria. Thirty-four years ago Richard Dawkins, an evolutionary

biologist at Oxford University, proposed the idea that “selfish genes”, not individual organisms or entire species, are the units on which evolution acts. In the case of bacteria, which seem to exchange genes promiscuously, that seems an excellent way of looking at things.

In a sense, such profligacy extends to humanity, too. Add in the genes of the bacteria that live in peaceable collaboration with the average human (in his gut, on his skin and so on), and the “human” genome expands from 23,000 protein-coding genes to something more like 3m, according to Francis Collins. Nor is it pure sophistry to think of these genes as part of an extended human genome. Many of the bacteria in question are genuinely mutualistic with their hosts, helping the process of digestion or warding off pathogenic bugs.

This is scarcely explored territory. Dr Collins estimates that 90% of these human symbionts cannot be cultured by normal laboratory methods. America’s National Institutes of Health, which he heads, is backing yet another of genomics’ big collaborative efforts, the Human Microbiome Project, to help put that right.

Nor is the human microbiome merely of academic interest. For example, some think that the mix of bacteria in a person’s gut can affect his chances of becoming obese. If those studying the genetics of obesity concentrate all their efforts on the genes in human cells, they might thus be looking in the wrong place.

The other area where genomics is likely to have a big practical impact is agriculture. At the moment, despite the brouhaha they have created in some countries, genetically modified plants are primitive things. Most of them have had but a single gene tweaked, either to make them poisonous to pestilential insects or resistant to a particular herbicide so that it can be used freely. Even so, GM crops are big business. A recent report by the International Service for the Acquisition of Agri-biotech Applications, a not-for-profit outfit that monitors the use of GM crops, suggested that more than three-quarters of the world’s soyabean plants are genetically modified, along with half the cotton and more than a quarter of the maize.

Fire burn and cauldron bubble

The next generation will be bigger business still. Ceres, a small biotech firm based in Thousand Oaks, California, is collaborating with Monsanto, a giant agribusiness company, to make crops better in all sorts of ways. Their genes are being tweaked to increase the plants' drought-resistance and improve their absorption of nitrogen.

Ceres's collaboration with Monsanto involves traditional crops such as maize, but Ceres is also interested in the energy business. Before fossil fuels became ubiquitous, plants—in the form of firewood—were one of humanity's main sources of power. Ceres hopes those days will soon return. One way to release useful energy from plant matter is to ferment it into biofuels, as Synthetic Genomics, LS9 and Amyris are trying to do. Ceres is involved in this business, too, but Richard Hamilton, the firm's boss, is hedging his bets.

Whether biofuels have a big future is a moot point. At the moment the car industry seems to view electricity as the motive power of the future. But that does not worry Dr Hamilton because even if the cars of the future are electric, the electricity will have to come from somewhere—and if that somewhere is not fossil fuels, then it might be from burning plant matter.

Viewed in this light, plant matter is just an alternative form of solar energy. In hot, dry parts of the world, turning sunlight into electricity directly with solar cells or indirectly with solar-powered steam turbines makes sense. In places where it is cooler and wetter, the equation changes. Growing plants and burning them may be a better way. Moreover, plant matter, once grown, is available 24 hours a day. It can thus provide an electrical baseload in a way that traditional solar power (which goes off at night) cannot.

To this end, Ceres is tinkering with three species of grass: *Miscanthus*, switchgrass and sorghum. Its researchers have fiddled with the genes of these so-called energy crops to increase the amount of lignin in them, at the expense of carbohydrates like cellulose. That makes them more "woody", increasing their energy content. Ceres is also applying to its energy crops the sorts of genetic modification that it has been developing in collaboration with Monsanto for use in food crops—in particular, improved drought tolerance and the more efficient use of nitrogen. Ceres energy crops are already on sale and several pilot projects that use them are under way.

Genomics, and the new biology it is bringing, thus promise a bright, practical future. But some

scientists wish to understand things merely for the joy of it. David Haussler, of the University of California, Santa Cruz, is one of them. Dr Haussler wants to sequence 10,000 vertebrates, a sixth of the total number of species of fish, amphibians, reptiles, birds and mammals. Last month the BGI, in China, announced it would take on the first 100 of these, for delivery within two years.

Dr Haussler's aim is to work out the core vertebrate genome and see how it has been modified to produce the incredible diversity of animals with backbones. The Genome 10K project will, he reckons, cost $50m. That is not small change, but it amounts to only $5,000 a species, showing, once again, how the price of sequencing has tumbled.

Dr Haussler has focused on vertebrates because he is one. Uncovering the genomic essentials of this ancient group would be a coup. But genomics can also help to answer more recent evolutionary questions, in particular about how humans emerged and why they are unique.

Special reports