THIS WEEK

Biology from the bottom up

Scientists have overturned the conventional approach to studying cells to instead build life's systems from scratch.

Evolution has famously never produced a wheel. Humans famously did — and have spent much of the time since urging each other not to reinvent it. This example illustrates a clear difference between two approaches to problem solving. Nature works with what it has from the bottom up, and eventually finds a solution through an inefficient process of trial and error. Nature has never explicitly asked itself: how can I move this bulk from here to there as quickly and easily as possible? Hence, no wheeled animals, although plenty of legs, wings and other ways of getting about. Humans tend to take the opposite approach: reduce, simplify and break down a complex problem to find the most efficient solution.

This human framing of a problem is often described as top-down analysis, and that's usually how research into cell biology proceeds. Even where the overall intention of the science is simply to expand knowledge (compared with the specific task-focused goal of engineering), the cell is too complex and sophisticated an object to analyse without being broken down conceptually.

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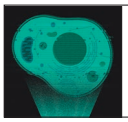
Top down involves a decomposition process. So although a researcher can make a career out of unpicking the workings of a cellular machine such as a ribosome or mitochondrion, the starting point for such projects has always been the role of these structures in existing cells. The work is directed by the context in which it originated and into which it will fold back once complete.

Decomposition and working out from the top down how systems function is a valuable approach, but it might not be the best way to make a cellular process work better — or to produce a different one that does the same thing but more effectively. To do that, researchers must be able to put aside the context, the system that evolution generated, and instead design and construct a system afresh from component parts, the so-called bottom-up approach.

Take the very real challenge of finding a way to copy the natural process of photosynthesis — which could revolutionize energy production. As we discuss in a News Feature on page 172, one approach cell biologists are taking is to mix unusual combinations of enzymes — including some taken from bacteria and the human liver — to make different versions of metabolic pathways involved in photosynthesis and incorporate them into an artificial chloroplast.

That research, and other work in a similar vein, is at the forefront of bottom-up biology. Biologists, physicists and chemists are attempting to reconstruct cellular processes by looking afresh at the constituent parts. In doing so, they argue, bottom-up science can extend the reach of researchers and perhaps offer some novel insight and solutions to long-standing problems.



BOTTOM-UP BIOLOGY
A *Nature* special issue
go.nature.com/bottomupbiology

In a special issue this week, *Nature* brings together a series of articles that discuss and explore some of the challenges, opportunities and complexity of this emerging field. At its most far-reaching, bottom-up biology could construct a reproducing artificial 'cell' completely from scratch. But it is important for researchers to focus on the benefits of such ambitious projects, not just the intellectual or practical challenges. A Comment piece on page 177 urges bottom-up biologists to set their sights on definite applications, such as artificial blood.

Bottom-up biology is typically seen as different from 'synthetic biology', which usually refers to an emerging branch of biotechnology that aims to assemble some highly derived (synthetic) products by bringing many separate parts together in complex sequences of elementary steps. In pursuing this goal, synthetic biology uses both top-down and bottom-up approaches.

The creation of living systems according to human design throws up some powerful questions — not least who gets given the responsibility to do it and how the work and what results from it can be controlled and regulated. So it's important that scientists, policymakers and the public are kept informed and consulted about where this research could lead. ■

Launch sequence

Life on Earth is to have its DNA analysed in a welcome conservation effort.

An ambitious project launched last week aims to slow the decline in biodiversity by sampling and decoding the DNA of every species of plant and animal on Earth. Called the Earth BioGenome Project, the effort is seeking funding to help it get off the ground. It is asking for US$4.7 billion to sequence all 1.35 million known eukaryotic species — those with a cell nucleus enclosed by a membrane — over the next 10 years.

Given the colossal scale of the crisis that faces life on the planet, genomics might seem an unlikely saviour. Biology has certainly advanced to a different realm since physicist Ernest Rutherford's famous quip that science was either physics or stamp collecting. But how much — really — can reading the DNA sequences of species save the organisms from the threat of climate change, the destruction of their habitats or human over-exploitation of natural resources through fishing and farming? To someone with a hammer, every problem looks like a nail. Are scientists with DNA-sequencing machines falling for the same logical fallacy? Is this a project that is being done because technology means that it now can, rather

than because the need for conservation says that it must?

The organizers have yet to make their case fully — after all, the project is still on the drawing board — but the early signs suggest that it is worthwhile. Yes, it is likely to be relatively expensive to accomplish fully, but so is much of modern science on a grand scale. In today's money, the Human Genome Project cost $5 billion, and few people would argue that this was not money well spent. The construction of the Large Hadron Collider, which discovered the Higgs boson, cost about the same amount. (And as Harris Lewin, the organizer of the London launch of the Earth BioGenome Project, provocatively asked: "What has the Higgs boson done for you lately?")

What can genomics do for conservation? Quite a lot, actually, and the vast scope of the project can easily obscure the intensely local insights that might emerge. To point to one small example reported this year, an analysis of 3,095 DNA variations called single nucleotide polymorphisms in the genome of the endangered eastern tiger salamander (*Ambystoma tigrinum*) in Long Island, New York, found that, because roads were restricting the animals' movement between breeding ponds, genetic fragmentation of populations was occurring (E. McCartney-Melsad *et al.* Preprint at bioRxiv http://doi.org/gdcd5x; 2018). The finding highlighted the need for conservation efforts to focus on mitigating this development.

But so far, scientists have just scratched the surface in terms of the diversity of organisms sequenced. And sequencing technologies are only now mature enough to generate high-quality (complete) genomes for in-depth studies. Of the 33,000 genomes in the archives of the US National Center for Biotechnology Information (which represent 0.2% of eukaryotic species diversity), only 50% are of high quality.

Arguably, the highest-quality (and the most expensive) genomes are not strictly necessary for conservation efforts to benefit, but they might reveal the route to new biofuels, drug leads and useful agricultural traits. Finding such applications, and so presenting the conservation of biodiversity as a boon to national economies, local cultures and the environment, should further help governments to take biodiversity issues even more seriously.

Certainly, the need is urgent and the statistics alarming: 50% of current biodiversity could be lost by the end of the century. Earth's sixth great extinction event is firmly under way, and ending this crisis will take much more than DNA sequences. But the Earth BioGenome Project can play a part, and early signs are that it might work.

It is right to seek commitment from participants, by asking them to chip in with money from their own grants. And a good sign is that it's not a top-down monolith. Unlike a typical genome-sequencing project, it has come together as a grass-roots initiative, driven by individuals who study diverse groups of organisms and who are already working to sequence the organisms' DNA. The new project includes ongoing efforts such as i5K (insects), B10K (birds) and the Darwin Tree of Life project, which aims to sequence all of the estimated 66,000 eukaryotic species in the United Kingdom. That suggests the pay-off could come more quickly because many of the genomes are already targeted by research communities keen to process and annotate them.

"Earth's sixth great extinction event is firmly under way."

One looming issue is how easy it will be to transfer samples and genetic data across national borders. A meeting of the United Nations Convention on Biological Diversity (CBD) in Egypt later this month will consider new controls on the sharing of digital genetic data. The proposals would extend the reach of the 2014 Nagoya Protocol, which provides for equitable sharing of the benefits obtained from using genetic resources. If properly implemented, such rules will create greater legal certainty and transparency for the countries that provide such resources and the scientists and companies that use them. They will also help to boost local scientific capacity in the many poorest countries that hold some of the world's richest biodiversity.

Extending the protocol to cover genetic data makes sense, but, if done clumsily, it could create a mess. The CBD has to its credit held extensive consultations with scientists and research institutions likely to be affected. The Earth BioGenome Project could help, by speaking as one voice for researchers. It's better to have one international effort to negotiate solutions for data sharing, instead of a hotchpotch of complex individual and bilateral agreements. And that will help to ensure that the Earth BioGenome Project really does benefit the entire Earth. ■

Note worthy

The Bank of England should put a female scientist on its next £50 note.

What does Marie Curie have in common with the bacteriologist Hideyo Noguchi and the theoretical astrophysicist Victor Ambartsumian? They are among the scientists who have featured on banknotes around the world (respectively, the old 20,000 Polish zloty, the ¥1,000 in Japan and the 100 Armenian dram). Now, the British public has the chance to choose who should join them. Last week, the Bank of England announced that it is looking for an inspirational scientist to appear on the next £50 note. It has invited suggestions and will pass them to a dedicated committee, which will make the final decision and announce it next year.

Scientists and engineers have featured heavily on UK banknotes since the bank started to print historical figures on their reverse sides in 1970. Generations of Britons have been paid with notes depicting Isaac Newton, George Stephenson, Michael Faraday and Florence Nightingale. The designs have not always pleased everyone. The £10 note released in 2000 featured Charles Darwin and his trip on HMS *Beagle*, but also threw in some hummingbirds — which many biologists felt were irrelevant.

Whoever is chosen (the only binding criteria are that they must be British and dead) will replace the steam-engine pioneers Matthew Boulton and James Watt on the £50 note, the highest denomination in circulation. It has yet to feature a woman, and this has led to suggestions that the Bank of England should choose a female scientist. *Nature* agrees. It's true that this would rule out deserving figures such as Alan Turing and Stephen Hawking (who died this year and who bank officials have said would be allowed, even though the bank usually expects banknote candidates to have been dead for at least 20 years). But here is an opportunity to celebrate the hugely important achievements of a woman in science, and to offer an important and inspiring role model at the same time.

A straw poll of some *Nature* staff highlighted some clear possibilities, none of whom will come as a particular surprise to readers. Mary Anning (1799–1847) was a prolific fossil hunter who changed the way we think about the history of life. Ada Lovelace (1815–1852) is credited with producing the first account of a prototype computer and its possible applications. Rosalind Franklin (1920–1958) was an X-ray crystallographer who played a key part in work to establish the structure of DNA. And Dorothy Hodgkin (1910–1994) remains the only British woman to win a science Nobel prize, for her research to unravel the structures of proteins including insulin.

We intend to determine and submit our choice before the 14 December deadline. We welcome the recommendations of readers everywhere as to who they would choose (e-mail: briefing@nature.com). And we encourage you to submit your own nominations at go.nature.com/2jrkt4y. The launch date of the note itself has not yet been confirmed, but it will not appear in circulation before 2020. ■