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A big step towards an artificial yeast genome

Success would usher in true genetic engineering.

BIOLOGY'S biggest division is not between plants and animals, nor even between multicellular and single-celled creatures. It is between prokaryotes and eukaryotes. Prokaryotes—bacteria are the most familiar sort—are simple. Their DNA is an unadorned circular molecule between 500,000 and 10m genetic "letters" long. As such, it is fairly easy to replicate from off-the-shelf chemicals.

The DNA of eukaryotes—animals, plants, fungi and so on—is both more abundant and more complex than that. It may have hundreds of millions, even billions, of letters and it is organised into several elongated chromosomes inside a cell's nucleus. Synthesising a eukaryote's genome is thus a far harder task than creating its prokaryote equivalent. But if biology is ever to be brought within the realm of technology in the ways that physics and chemistry have been, it is an essential task.

This week has seen a big step towards that achievement, with the publication in *Science* of recipes for five artificial chromosomes for yeast cells. Yeast, a fungus, is one of the workhorses of eukaryotic genetics. The chefs who have devised these recipes are members of a consortium called the Synthetic Yeast Genome Project (Sc2.0). In 2014, as an aperitif, Sc2.0 created a single artificial yeast chromosome. The latest set of papers are the meat of the matter, meaning that over a third of the yeast genome has now been synthesised. The remaining ten chromosomes are still cooking, but they will be served up soon.

Rather than building entire chromosomes in one go, Sc2.0's researchers proceed in stages. They start with pieces of DNA 750 letters long. These, known as oligonucleotides, can be synthesised, by special apparatus, with the genetic letters in any desired order. The consortium's teams then stitch appropriate oligonucleotides together to build chunks about 10,000 letters long. Finally, they splice these chunks into "megachunks", with 30,000-60,000 letters each. Those get inserted one at a time into natural yeast chromosomes by being swapped for corresponding sections of existing DNA. The result is tested each time by checking that the modified chromosome still allows the cell it is in to grow and reproduce. Once it has passed that

test, another megachunk can be swapped in, and the process repeated until the whole chromosome is made of synthetic DNA.

Shock and awe

There would be little point to all this, though, if the DNA going in was the same as that coming out. The value of being able to synthesise a genome lies in being able to manipulate it. And this, tentatively, is what the members of Sc2.0 are trying to do.

First, they are clearing out the rubbish. The final synthetic genome, as currently planned, will be 8% smaller than a natural one. The difference is bits of DNA that seem to serve no useful purpose. Such DNA is not always easy to identify, for many parts of chromosomes that were once believed useless are now known to have functions. But some useless DNA does exist and the Sc2.0 researchers are getting rid of it.

They are also cleaning up the genetic code's punctuation in their new chromosomes—reducing the number of types of three-letter "stop" signals that mark the ends of genes from three to two. Their hope is that the redundant signal's triplet code (one of only 64 available) can then be used to extend from 20 to 21 the range of amino acids, the building blocks of proteins, which the new chromosomes can encode. That would permit the production of completely new sorts of protein. And they are moving certain genes that sometimes get in the way of DNA replication to a special extra artificial chromosome that will exist in addition to the conventional 16, in effect quarantining them.

The aim of all this is twofold. One goal is to make a genomic "platform" that can be adapted to do useful things. Genetically modified yeasts already make vaccines, drugs and speciality chemicals. Sc2.0's technique means that it will be possible to design completely new yeasts, and the range of products will widen.

That will be to the good. But the other goal may disturb some people, for it is to test techniques that could then be used on other eukaryotes. It is here that a pause should be taken for thought. The trivial modifications that have already been made by genetic engineers to crops and animals are as nothing compared with what might be possible if whole genomes could be manipulated at will. Even CRISPR/Cas9, a technique much in the news at the moment, modifies only small bits of DNA at a time. The Sc2.0 approach writes entire genetic sequences from scratch. The results could be awesome. To make sure they are not also shocking, people should start thinking about them now.