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COMMENT

Hand-made biology

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But tonight, we shall hurl the gauntlet of science into the frightful face of death itself.
Young Frankenstein (1974)

It's alive! It's ALIVE! ... Oh, in the name of God! Now I know what it feels like to BE God!
Frankenstein (1931)

Craig Venter would never be Central Casting's first choice to play Dr Frankenstein. And I can't see Hamilton Smith as Igor, either. But when these two genome biologists and their coworkers announced, in the May 20th issue of *Science*, that they had 'created' a bacterium, one would have been forgiven for thinking, based on the language they used and the turgid - even hysterical - reports in the press, that they were auditioning for the parts. Here is the opening paragraph of the account of their work in *The Economist*, a publication not customarily given to hyperbole:

In the end there was no castle, no thunderstorm and definitely no hunchbacked cackling lab assistant. Nevertheless, Craig Venter, Hamilton Smith and their colleagues have done for real what Mary Shelley merely imagined. On May 20th, in the pages of Science, *they announced that they had created a living creature.*

But did they? Is their achievement 'creation' in the literal, and Frankensteinian, sense of the word (the action or process of bringing something into existence), or is it something else entirely? And if it is something else, is it still as monumental as some people, and the authors themselves, claim?

In case you were in a coma and missed it, here's a brief summary of what they did. They took a 'host' strain, that of the small, free-living bacterium *Mycoplasma capricolum*, and deleted the genes for its own restriction enzymes (this would correspond to the cadaver in the Frankenstein tale). The restriction enzyme genes were deleted so that the host would not cleave the 'foreign' DNA they planned to insert. (The equivalent to this procedure would be immune suppressing a transplant recipient so that they would not reject the foreign organ.) Venter, Smith and colleagues then inserted into this strain a completely synthetic chromosome (the 'brain') for the related strain *Mycoplasma mycoides*. In synthesizing the 1.08 million base pairs of this genome, the team at the J Craig Venter Institute deliberately deleted 14 genes that might have conferred pathogenicity on the new strain, and also inserted into the DNA sequence a set of watermarks: specifically designed segments of DNA that spell out words and phrases. The watermarks prove that the genome is synthetic, and identify the laboratory of origin. Encoded in the watermarks is a new DNA code for writing words, sentences and numbers. In addition to the new code there is a web address to send emails to if you can decode it, plus the names of 46 authors and other key contributors to the work, and these three quotations: 'To live, to err, to fall, to triumph, to recreate life out of life' - James Joyce; 'See things not as they are, but as they might be' - from the book, *American Prometheus*; and 'What I cannot build, I cannot understand' - Richard Feynman. After about 30 generations, there was no trace of the original bacterial genome in the new organism (presumably, it had been destroyed by the restriction enzymes encoded by the synthetic chromosome), and the proteins and other macromolecules in the cell were entirely those from the inserted DNA. That's the achievement. What does it mean?

First, can we all agree that there is nothing surprising here? No one should have been amazed that this worked. Not only was it likely to work; it HAD to work if it was done properly. The surprise would have been if it HADN'T worked. In an interview given at the time of publication, Venter, a truly great scientist whose genius extends to a talent for self-promotion, said, 'Really, it has changed my view of the definition of life and how it works.' Which makes me want to ask him just what his view of the definition of life and how it works used to be, because it must have been remarkably naïve. This is no conceptual breakthrough, no matter what language is used to describe it.

Venter, who headed the private team that sequenced the human genome 10 years ago (along with the public effort headed by Francis Collins), calls the result a

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'synthetic cell', but it isn't one. It's no more a synthetic cell than Frankenstein's monster was a synthetic human. 'Synthetic' means a substance that is made by chemical synthesis, often in imitation of a natural product. The genome that Venter and Smith inserted into their cadaverous host was synthetic, but the host was not. It was an actual bacterial cell, produced naturally. To have made a synthetic cell, Venter and Smith would have had to synthesize abiotically not only the DNA, but also all of the proteins, carbohydrates, lipids and other molecules that make up the cytoplasm and shell of the organism. They are a long way from doing that.

The closest analogy to what they did is not Mary Shelley's fictional mad scientist and his unfortunate creation; it is a technique called somatic cell nuclear transfer (SCNT), and it has been used for years. In SCNT (sometimes referred to as therapeutic cloning), the nucleus of a somatic cell is removed and the rest of the cell discarded. At the same time, the nucleus of a host egg cell is removed. The nucleus of the somatic cell is then inserted into the denucleated egg, and after many cell divisions, a blastocyst (early stage embryo) forms, which is a clone of the original somatic donor organism. This is the process used to clone Dolly the sheep, and nearly all other animals that have been cloned. The success of this procedure guaranteed that the Venter team's procedure of reprogramming one bacterial cell with the DNA from another would work if done properly. The major difference is that they used a synthetic genome and carried out their experiments in a bacterial host rather than a eukaryotic one. For me, what they did is not creating life. It's making chromosomes and letting the machinery of an already evolved life form read the sequence and produce the desired output.

So now that I have, I hope, convinced you that this is no big deal, let me convince you that it is actually a very big deal. No, Venter and Company did not create life - at least not in the sense that the phrase is normally used. But what they did do is pretty monumental nonetheless.

For starters, they have shown that it is possible to synthesize functional chromosomes. That's a formidable technical achievement. *M. mycoides* has a very small genome, but the method they developed, of making the sequence in fragments and using the high rate of homologous recombination in budding yeast to assemble them, is clearly applicable to much larger genomes.

Second, they have single-handedly made Systems Biology into a viable intellectual discipline. It is now possible to design organisms to test the predictions and models from that ambitious field - organisms simple enough that the assumptions that go into the models may actually not be too bad. If I were the Systems Biology community, I'd be buying Venter and Smith a drink. Maybe lots of drinks.

But it's the third thing they've done that impresses me the most, because I think it is going to be a game-changer for all of us. In taking the first step towards the construction of a truly synthetic cell, Venter and colleagues have also taken the first step towards making biology into an engineering science.

Engineers design things and then build them out of pre-made, usually standardized, parts. Smith and Venter didn't quite do that, but they came closer than anyone has before, and they and others will come closer still, very soon. It won't be long until simple organisms can be designed and constructed, if not fully synthetically, then semi-synthetically as was done here - organisms with novel and useful properties. The Systems Biology folks will learn how to do the designing, and the Venters of the world will then make organisms to order. To facilitate such engineering, it would be nice to have reliable software to design the collection of genes and pathways needed for a particular set of desired properties, plus a set of premade, standardized parts (genes and prepared host cells), and there are people already starting to make both. In the end, designed organisms could churn out drugs like artemisinin (an antimalarial compound currently isolated from willow extract), or gobble up oil spills. Their uses will be limited only by our imaginations and our ability to predict what output a given set of parts will produce.

Engineers are problem-solvers and when engineering comes to biology (or is it the other way around?), we should be able to solve a number of very important ones. Unfortunately, some problems are military, and the solutions to these often involve making weapons. That's just the way it is. The fear that this new science of hand-made biology will be used to make bioweapons is overblown for now - the technology is too complex and expensive, and terrorists can, unfortunately, manage quite well with much simpler instruments of death - but doubtless at some point in the future some group, or rogue nation-state, will try. Prohibiting synthetic biology, or strangling it with regulations, is not the way to deal with this threat. Experience teaches that information cannot be confined, and in the end it is better to know what the forces of evil might do, so that we can plan our countermeasures from the beginning.

Something very much like this happened to chemistry in the past century. Using the science to make molecules became as important as fundamental discoveries in the structure and reactivity of matter. That change didn't diminish the centrality of chemistry as a discipline; it enhanced it. Of course, along with the plastics and the new drugs came nerve gas and high explosives. This loss of innocence can happen to biology, too. It probably will. But in the end, we will accept the risks in order to reap the benefits, like we did with atomic energy, and synthetic chemistry.

No, Venter and Smith aren't playing Frankenstein, and they aren't playing God either. What they're really playing is Thomas Edison. There is no divinity in this work; quite the opposite. It's being done for practical, commercial reasons, and partly because of that there will be a lot of safeties built in, especially in the early days. The religious right and the ethicists and the neo-Luddites and the average concerned citizen shouldn't worry too much about synthetic biology, at least not yet.

The ones who should worry are the synthetic chemists, because living organisms can make many polymers and drugs and novel materials faster, cheaper, and with more complexity and variety than chemists can. And what does the future hold for process chemistry when we can design our organisms to fit our manufacturing technology, instead of the other way around?

Yes, if I were a synthetic chemist or a chemical engineer, I'd be worried. Actually, if I were a synthetic chemist or a chemical engineer, I'd be learning how to do synthetic biology.

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