Hacking the Hardest Science

Andrew Hessel

October 2012, Volume1 Issue 4

Forget math and physics. Biology is the hardest science.

Engineers in other fields have built quantum computers whose operations come uncomfortably close to magic. They've made the Large Hadron Collider (LHC), a gigantic instrument for studying physics at its limits. And they've landed a 2,000 pound rover on Mars using a complicated, never-before-tested sky crane system. These projects were difficult but clearly doable.

Now consider biology. Even after hundreds of years of collective effort, life scientists still don't know exactly how the cell, the most basic unit of life, actually works.

Biology is hard. Seriously hard.

But some progress is being made – and it consists in the creation of virtual cells. This last July, Karr et al published the first comprehensive computer simulator for a cell. It's a metabolic model for the bacterium *Mycoplasma genitalium*, a parasite that can cause urinary tract and genital infections. It's a simple bug, about as simple as a free-living life form gets. It has a tiny genome of a mere 521 genes. It was also one of the first genomes ever to sequenced in the mid-1990s.

Karr's simulator links together 28 sub-models of metabolic processes to produce a comprehensive dashboard for the bacterium, one where the various activities of the cell can be watched in real time. It's like mission control for metabolism. The dashboard also allows researchers to design and run virtual experiments. It's pretty cool.

However, even with this model, science is still a long way from completely understanding how life works, because underneath the model's hood is little more than a series of formulas, and formulas are just too rigid to reveal the true biodynamics of a living cell.

What researchers really need is an agent-based simulator. In an agent-based model system, every molecular structure that makes up a cell (and there are millions or even billions of these molecules) would have a digital avatar that is biophysically accurate. Each avatar would be autonomous. Combined, they would interact to produce a virtual cell that behaves much as a real cell would in the real world, opening the door to a multitude of virtual experiments. That's the idea, anyway. Only such a model has yet to be made.

Again, biology is hard. But picking up where a visionary Canadian project left off almost a decade ago might just lead to the creation of the agent-based virtual cell.

Spearheaded by the University of Alberta's Dr. Michael Ellison – who might know more about virtual cells than anybody else in Canada – *Project Cybercell* was a $15.6 million dollar effort to computationally model the gut bacterium *E. coli*.

Cybercell was a visionary project. Unfortunately, like most visionary projects, it was also just slightly ahead of its time. Even with its relatively large budget, Cybercell was too ambitious for the technology of the day. There was simply too much data in life science for one group to collect and not enough computational horsepower to crunch the data it was able to get. Although it led to a few useful databases, simulations, and research, the project ran aground.

But a lot of things have changed since 2002 and perhaps it's time to revisit the idea of a virtual cell. It would make a great community project for scientists, a place where thousands of researchers could add and curate data about the molecules or mechanisms they know intimately – like a wiki for metabolism. And if it were made, it would allow anyone to hack life with little more than a laptop by running virtual experiments. The cell died? No problem. Just reboot it.

This isn't to say that making a virtual cell is easy work. It would take an unprecedented level of coordination and cooperation among life scientists. But if physicists and rocket scientists were able to do it, biologists should be able to as well.

The LHC had a budget of $9 billion, and Curiosity came in at about $2.5 billion, numbers that go a long way to explaining why the first stab at making a virtual cell failed. Taking another stab at a virtual cell would be free, but there would be no reason to spend billions, either – not with cheap networks, cheap computers, and crowdsourcing. (Science games have proven quite popular in recent years.) If the project could get rolling, there's a reasonably good chance it could snowball.

A biologically accurate cell simulator would go a long way to helping researchers understand everything from basic cellular mechanisms, to drug interactions, to how molecular systems change in disease states or cancer. It would be a fantastic educational tool. Plus it would allow metabolic or genetic designers to safely and cheaply test out new ideas in virtual cells, or virtual organ systems, or even virtual organisms. This could give biological engineering a big boost

The timing couldn't be better. Over the last few years, synthetic biology, a type of computer-aided genetic engineering technology, has opened the door to serious scientists and beginners alike to start reprogramming cells to make everything from biofuels to new medicines. If the virtual cell is made, the hardest science of all could end up becoming a lot simpler for everyone.