

'Virtual cell' could bring benefits of simulation to biology

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Markus Covert is close to completing a computer model of the microbe *Mycoplasma genitalia*, a sexually-transmitted parasite. The bug is ideal for virtual re-creation because of its simplicity: only 521 coding regions.

(PhysOrg.com) -- In a matter of months, bioengineer Markus Covert, PhD, expects to unveil the first "whole-cell" computer model of an organism.

In a purely logistical sense, biology can really get in the way of biological research. Cells must be cultured, nurtured and then perturbed according to an experiment's protocol. It can be slow, demanding and expensive work.

While most kinds of scientists and engineers can use [computer simulations](#) to speed up their research, there has been no such thing as a

virtual cell. Now one is taking shape in the research group of Markus Covert, PhD, assistant professor of [bioengineering](#). In a matter of months, he expects to unveil the first “whole-cell” [computer model](#) of an organism.

“To me, this is a dream,” said Covert. “I still remember that 10 years ago I read a New York Times article that said the ultimate challenge would be to make a computer model of a cell because that implies biological understanding at a fundamental level.”

The microbe that Covert’s team is simulating is the *Mycoplasma genitalium*, a sexually transmitted parasite. The nasty little bug is a perfect candidate to simulate because of its simplicity. It has only 521 “coding regions,” the segments of DNA with complete instructions for doing things such as making proteins. Of those, about 420 are understood by biologists. As 2010 began, Covert’s model accounted for more than 300 coding regions with more joining the model every week.

In other words, about 75 percent of what biologists know about *Mycoplasma genitalium* is now being simulated on Covert’s computer. That’s already enough to give him two things: confidence about integrating the rest of the coding regions; and a simulation that already works well enough for his group to ask biologically interesting questions about the organism, such as why it grows so much more slowly than even its close relatives.

Success with this model will lay the basic groundwork for then tackling more complicated and biologically important organisms, such as yeast and *E. coli*. Covert won a National Institutes of Health Director’s Pioneer Award last October, which will fund his efforts to develop the models and use them for research with \$2.5 million over the next five years.

The speed of simulations

Ultimately, Covert's goal is to give biologists the same computational simulation tools that allow peers such as aircraft designers and nuclear physicists to perform accurate experiments that are cheaper and quicker (and often safer) than tests with real materials and environments.

“You discover things a lot faster with a computer model than you do without,” he said.

That's something Covert has done since he was the first computational researcher in the lab of Nobel laureate and Caltech biology professor David Baltimore, PhD. Covert still remembers how the esteemed professor brought him on as a postdoc in the mid-2000s.

Covert recalled, “I definitely had to prove myself there but the methods prove themselves.”

Within six months after Covert created a computer model of a cell's signaling system, he and his colleagues were able to discover some of the key causes and effects in the multi-step process the body employs to respond to bacterial infection.

Conquering the complexity

That simulation was about a cell's signaling network, which governs how cells interact with their environment and each other. A few labs around the world have produced other, more narrowly defined computer models, for example of cell membranes. But Covert's model incorporates many different systems that are at play in a cell, and will therefore give researchers a general platform for investigating a much greater set of questions. In fact, part of Covert's NIH award is meant to help him find out how cells age and why low-calorie intake corresponds to greater health and longevity.

To answer a broad question like that, Covert and his group have had to incorporate the genetics, math and algorithms to handle cell and molecular processes such as transcription of genetic information, translation of that information into proteins, RNA decay, RNA modifications and even the existence of special cell parts, or organelles.

At another level of cellular function, Covert is implementing an integration method he and his group discovered in 2007 to mesh simulations of three key cellular networks: signaling, metabolism and regulation of gene expression. He co-authored a paper on the method in 2008 in *Bioinformatics*.

Other groups have tried to take what they know about how to simulate one kind of network and try to apply it to other networks, but ever since he was a graduate student Covert has believed that each one works in a fundamentally different way and therefore has to be treated individually in terms of mathematics. That's why he saw the model-building task as one of mathematical integration. The result in the *Bioinformatics* paper is a blending of Boolean algebra, linear optimization and ordinary differential equations.

“Bringing all of that together allowed us to successfully integrate it all and show that no network was dominant, that each had a strong effect on the other,” he said. “The result was something more predictive and more inclusive than we ever had before.”

As the *Mycoplasma genitalium* model comes together, Covert's group is also working on creating a graphical interface that provides users with a dashboard view of what's going on in the cell. The collection of graphs and dials and other visual indicators will also allow researchers an easy way to tweak parameters, such as removing a coding region to perform experiments. Covert already has a prototype interface that depicts cell growth and division in yeast based on real data.

“I absolutely love this project,” Covert said. “We’ve developed a huge database and are including all the information we could possibly include and it’s given us an unprecedented view into the workings of a cell.” Soon he hopes to have a simulation to share with other biologists. If all continues to go well, they may come to love it as much as he does.

Provided by Stanford University Medical Center

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