Creating Accurate Models of Life

By Leslie Mertz

The ultimate test of understanding a simple cell, more than being able to build one, would be to build a computer model of the cell, because that really requires understanding at a deeper level.

—Clyde A. Hutchinson III, professor emeritus of microbiology and immunology at The University of North Carolina at Chapel Hill and distinguished investigator at the J. Craig Venter Institute, Rockville, Maryland [1]

"Hardly a day goes by that I don't think about that quote. It's an obsession," said Markus Covert, Ph.D., assistant professor of the Department of Bioengineering at Stanford University, California. Covert led the effort that, in July 2012, reported its construction of the first complete computer model of an organism (Figures 1 and 2). That effort, along with other recently announced computer models, is providing a never-before-seen view of life in all of its intricacy and complexity. Through these models, researchers are beginning to learn exactly what is going on within and between cells to divulge the mysteries of cancer and other insidious diseases and to understand how to stay on top of antibiotic-resistant bacteria (see "Computer Models Poised to Revolutionize Medical Care").

Merging Biology and Computer Science

In addition, these models are being used not only to identify new drugs and drug combinations but also to greatly expedite

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their development. "In my opinion, computational systems biology, including multiscale modeling, will be at the forefront of the transformation of medicine, a process that has just begun," commented Aleksander S. Popel, Ph.D., professor of biomedical engineering with a joint appointment as professor of oncology at The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Why We Need a Computer Model

One of the primary reasons computer modeling is important to systems biology is the sheer volume of information that is already out there. Even a cursory glance at the scientific literature reveals that researchers already know the minutiae of thousands of molecular pathways and proteins that together comprise living organisms. Additional details are coming at breakneck speed thanks to new automated methods, such as high-throughput gene phenotyping, which determines the role of each gene by inactivating (knocking out) one after another to see what happens to the organism.

At the same time, the glut of information poses a problem. Those many pathways and proteins play into and off of one another as an organism goes about its daily business and figuring out that elaborate and convoluted molecular dance is complicated to say the least. This is where computer modeling becomes necessary, said Popel. "The human mind cannot absorb beyond certain limits and cannot integrate this complex information beyond some simple relationships. Computer modeling is absolutely key and absolutely necessary to interpret all of this information."

Research teams have certainly taken a stab at the problem by generating mathematical equations and computational source codes that correspond to separate pathways and then combining the multiple source codes, explained VA Shiva Ayyadurai, Ph.D., when discussing his motivation for creating the computer-modeling start-up company CytoSolve, located in Cambridge, Massachusetts. VA Shiva is the founder, president, and CEO of CytoSolve, as well as a systems scientist who teaches systems visualization at the Massachusetts Institute of Technology (MIT), Cambridge. The approach he described worked only to a point. "People were maybe getting to 20 or 30 equations to describe a biological process, and then it would just become too hard to manage, so they would leave it," he said.

Still, the need was there. In 2006, the National Science Foundation put forth a grand challenge in systems biology to generate a computer model of a whole cell that included its myriad genes and proteins, all of the metabolic and signaling pathways, and each of the stages from replication to aging and death, plus disease and disease recovery. Such a model would coalesce what scientists have already discovered and show how it all fits together. From an applications standpoint, it could give researchers a potent tool for comprehending disease on a deeper and more complete level and for developing new drug therapies.

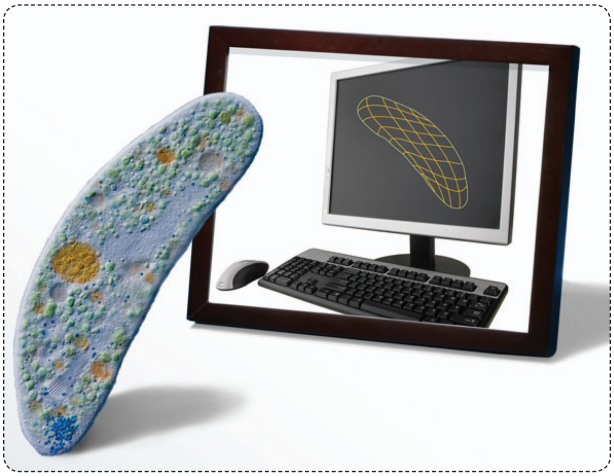

FIGURE 1 The first complete computer model of an organism, the bacterium *M. genitalium*, generated by the Stanford University team led by Markus Covert. The model accounts for every molecular interaction that takes place in the cell's life cycle. (Image courtesy of Erik Jacobsen, Threestory Studio, Inc., Palo Alto, California.)

From "Can't Be Done" to "Done"

Most researchers said it couldn't be done; there was simply no way to generate an accurate computer model of the enormous range of complex interactions occurring within a cell. Some even bandied about the tongue-in-cheek-name "ridiculome" to describe the ridiculously huge mountain of data that must not only contribute to but also be correctly simulated by such a computer model.

"The ridiculome is basically a way of compensating for the fact that we aren't truly understanding anymore what the results of our experiments are—they're too complicated," said Covert. "And that's exactly why computer models are so powerful; these models can help you interpret your data sets."

Then, in July 2012, Covert's research group at Stanford University announced that it had created the first complete computer model of an organism, the bacterium *Mycoplasma genitalium (M. genitalium)*. The Stanford model accounts for every molecular

FIGURE 2 Markus Covert. (Photo courtesy of Steve Fisch.)

Computer Models Poised to Revolutionize Medical Care

Not too long from now, that drug your doctor prescribes may have its roots in a computer model. This is because numerous research groups around the world are developing computer models of different biological processes, including diseases and other health issues, and using these models to identify new drugs and drug combinations.

Examples of this work include models of angiogenesis and antibiotic action. Researchers have identified peptides that interrupt angiogenesis, the formation of blood vessels that allow cancerous tumors to grow and spread and ultimately, may lead to vision loss in age-related macular degeneration. Researchers have also discovered a small molecule that can increase the effectiveness of antibiotics up to 1,000-fold.

Modeling Angiogenesis

Aleksander Popel's research group (Popel is a professor of biomedical engineering with a joint appointment as professor of oncology at the Johns Hopkins University School of Medicine) created a computer model of angiogenesis to learn more about the process and to assist in computer-aided drug discovery (Figures S1 and S2). The group pored through the scientific literature, used different techniques to pull together molecular and cellular disease information on angiogenesis, and extracted the information in the form of mathematical submodels.

To generate the computational model of that mass of information, his group combined two techniques. One is data-driven bioinformatics, which establishes statistical relationships between molecular changes (such as gene mutations or gene expression) and phenotypic changes (such as cell behavior and disease processes). The second is knowledge-based mechanistic computational modeling, which draws on experimental information about biochemical reactions, signaling networks, tissue geometry, and transport processes, and recasts this information using mathematical and computational tools.

Other research groups are also beginning to combine the two techniques in their modeling efforts, Popel said. "Until recently, the development of data-driven and knowledge-driven models had proceeded in parallel, without much interaction between them. We now have begun to see the important convergence between the two fields of modeling."

For the angiogenesis model, Popel's group explicitly represented a wide range of molecular entities, including growth factors, matrix metalloproteinases (zinc- or calcium-dependent enzymes), and receptors. "And as we go up the scale from molecules to cells to tissues, we preserve all of the molecular information in the model." Such multiscale models are important because angiogenesis, as well as other biological processes and systems, function at and have consequences at various levels [S1]. "Multiscale modeling of complex biological systems is at the core of modern computational modeling," he noted.

Through the angiogenesis bioinformatics-based model, Popel's group has already identified a number of peptides that interrupt angiogenesis [S2]. His lab is currently testing these peptides, which are mimetic and, therefore, do not occur in nature, in animal models. "We are now optimizing these peptides for therapeutic applications in both cancer and in age-related macular degeneration," he said.

Modeling Antibiotic Resistance

A research group at Boston University (BU), Massachusetts, is also using computational modeling to develop drugs, but its focus is on antibiotics.

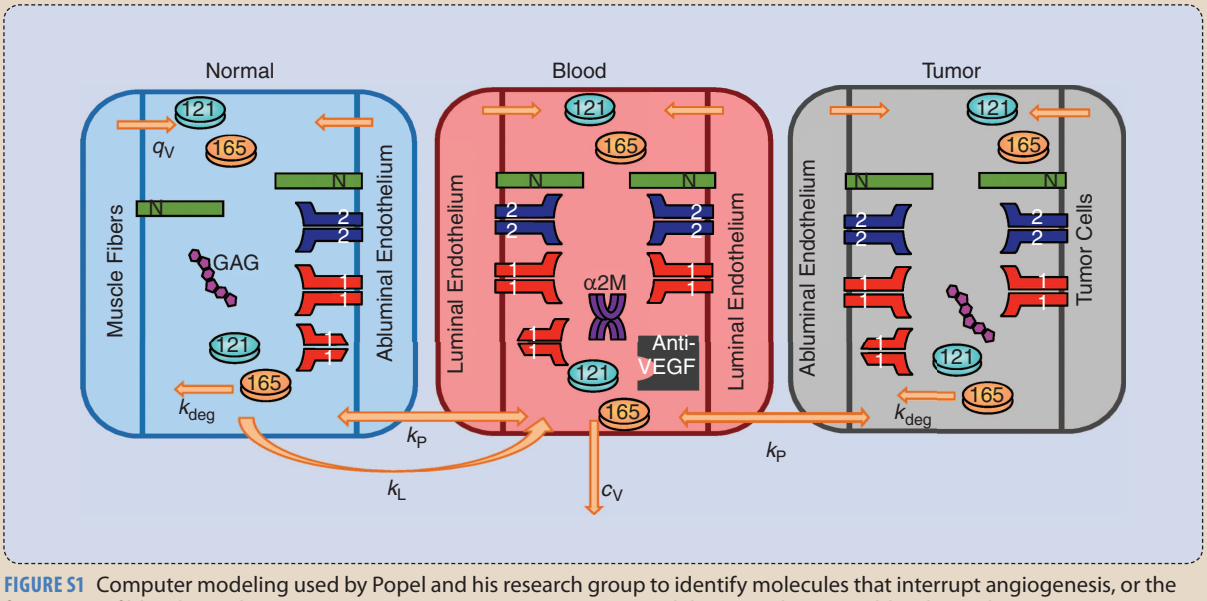

FIGURE S1 Computer modeling used by Popel and his research group to identify molecules that interrupt angiogenesis, or the formation of blood vessels. Angiogenesis is important in cancer research because these new blood vessels can support cancerous tumors, causing them to grow and spread. In this three-compartment model, Popel and his group illustrate how the angiogenesis-stimulating protein called vascular endothelial growth factor (VEGF) is transported between normal tissue, blood, and tumors. Here, VEGF is neutralized with an anti-VEGF therapeutic macromolecule. The image shows VEGF isoforms VEGF121 and VEGF165, which are secreted by normal cells (e.g., skeletal muscle myocytes), cancer cells, and endothelial cells; VEGF receptors (VEGFR1 and VEGFR2) and coreceptors neuropilin-1/2 (NRP), which are localized on parenchymal and endothelial cells; soluble VEGFR1 and glycosaminoglycan (GAG) chains, which are present in the interstitial space; and alpha-2-macroglobulin (a2M), which is present in the blood. Molecular species are transported between compartments via microvascular permeability (k_P) and lymphatic drainage (k_L). Unbound VEGF in the tissue compartments is subject to proteolytic degradation and is removed from the blood via plasma clearance (c_V). (Image courtesy of Aleksander S. Popel.)

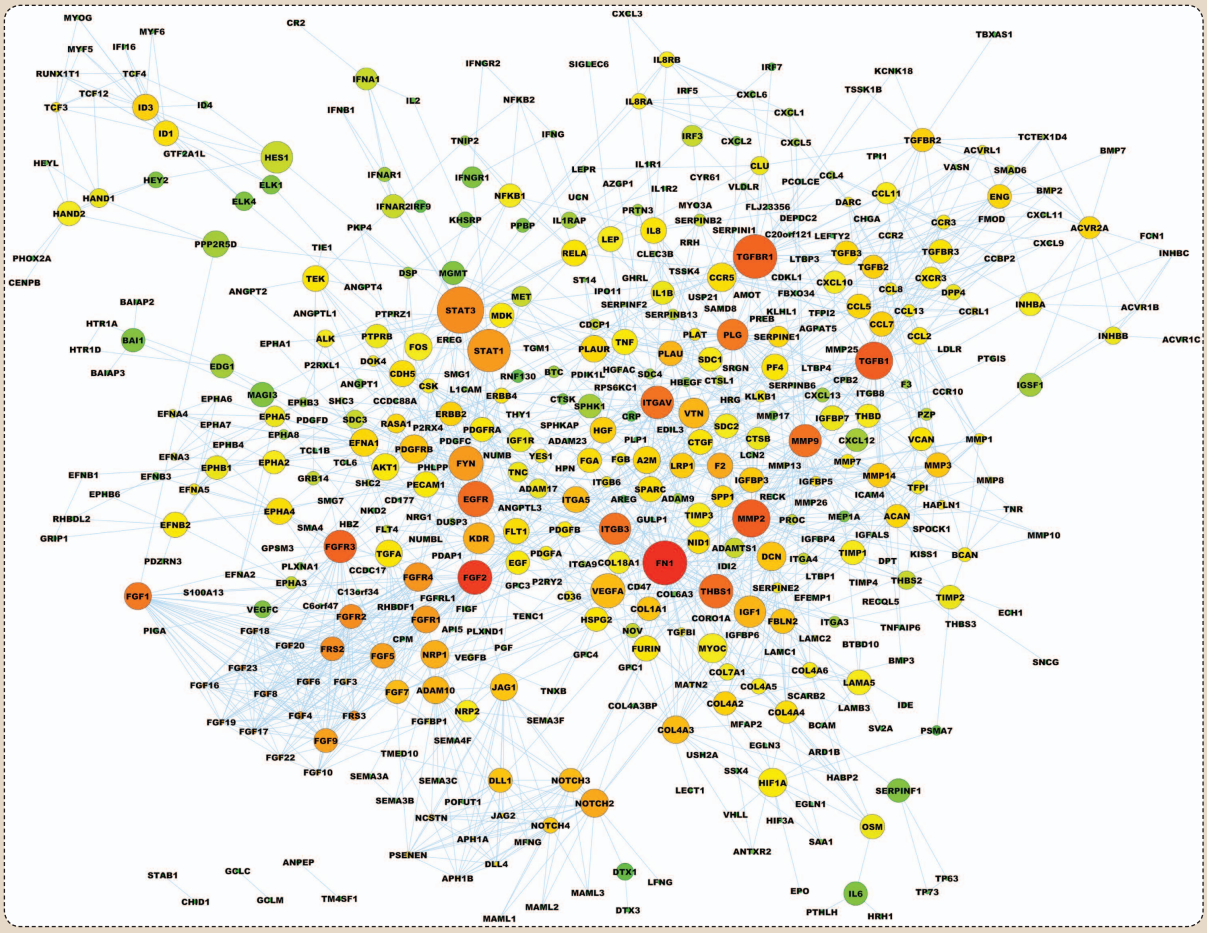

FIGURE S2 Graphic representation of the network of interactions between angiogenesis-associated proteins. Larger nodes (the red circles) indicate higher betweenness centrality, or greater interaction with other proteins and heightened importance to the network overall. Information like this is important for the generation of computer models of angiogenesis as well as the development of antiangiogenesis therapies. Popel uses computer models to identify molecules that might be used to improve antiangiogenic therapies. (Image courtesy of Aleksander S. Popel.)

"We're very interested in enhancing our antibiotic arsenal because the number of resistant strains in our communities and in our hospitals is growing, while the number of antibiotics being developed and approved is diminishing," said James Collins, Ph.D., professor of biomedical engineering at BU and investigator for Howard Hughes Medical Institute (Figure S3).

FIGURE S3 Photo of James Collins. He and his research group hope to use computer modeling to further antibiotic development. (Photo courtesy of Robert E. Klein/AP, HHMI.)

Their work actually goes back to 2007 when they published their findings on the mechanism behind bactericidal antibiotics [S3]. "In doing this bioinformatics and computer-based work, we discovered that bactericidal antibiotics, that is, antibiotics that kill bacteria, act in part via a common mechanism that involves the generation of reactive oxygen species (chemically reactive molecules containing oxygen) in the bacteria." When given at high enough dosage, the antibiotics trigger the production of sufficient reactive oxygen species (ROS) to kill all the bacteria. At lower doses, however, some bacteria are able to survive the less-severe ROS onslaught, and these bacteria and their progeny become antibiotic resistant.

The research group built on these findings, and, in a February 2013 paper [S4], described how they used computer modeling to figure out how to promote ROS production in bacteria, specifically *Escherichia coli* (*E. coli*). "We constructed a computer-based model of the metabolic network of *E. coli* and analyzed the different genes in *E. coli* to see which ones, when inhibited, would boost the natural levels of reactive oxygen species in the bacteria," Collins said (Figure S4).

Their model was based on work pioneered by bioengineer Bernhard Palsson of the University of California, San Diego, and other groups, Collins said. "I think what makes our approach unique is that we extended these models by including several

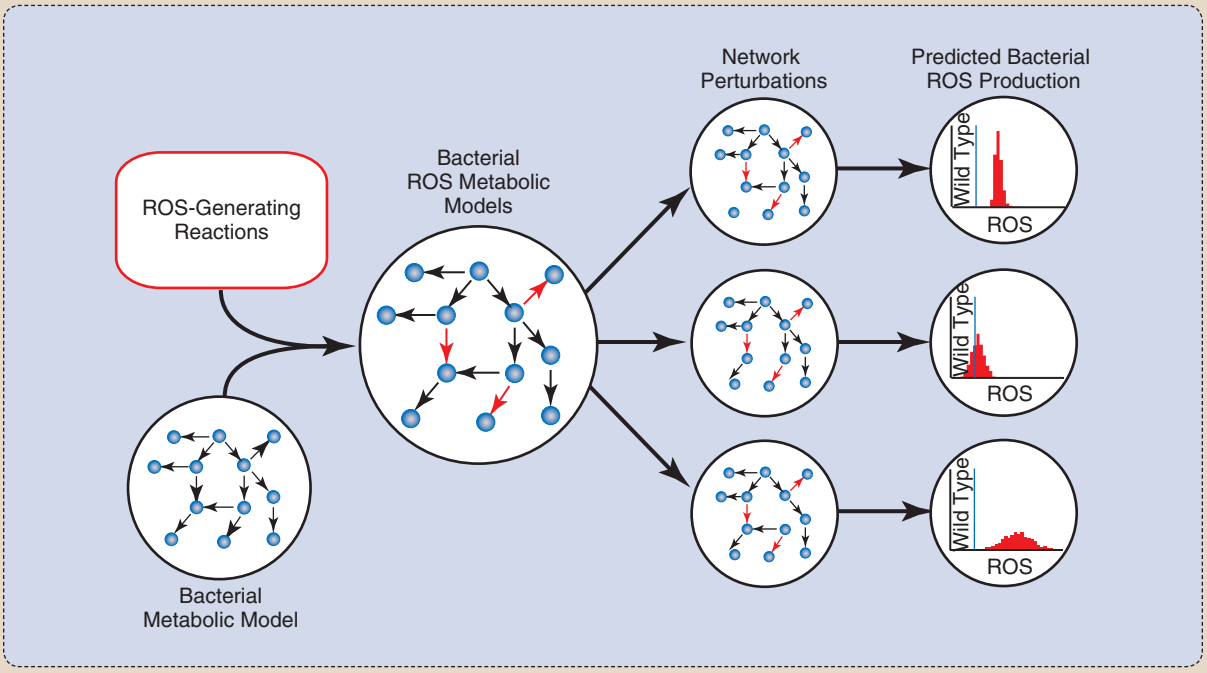

FIGURE S4 A computer-based model of the metabolic network of the bacterium *E. coli*. Collins and his research group constructed the model to predict which bacterial genes, when inhibited, would boost the natural levels of ROS in the bacteria. Antibiotics kill bacteria, in part, by way of a common mechanism that involves the generation of ROS, which are chemically reactive molecules containing oxygen in the bacteria. (Image courtesy of James Collins and Jonathan Winkler.)

hundred additional reactions to account for possible reactions that could produce reactive oxygen species." In addition, his research group took the idea of one of its members, Mark Brynildsen, postdoctoral researcher (now assistant professor of chemical engineering at Princeton University, New Jersey), and extended Palsson's models to not only conduct infectious-disease research but also to identify targets that could enhance the killing actions of antibiotics.

By following up with laboratory experiments, Collins and his research group showed that their validated targets could enhance the killing efficacy of antibacterials ten- to 1,000-fold. They also used their findings to identify a small molecule that inhibited one of the predicted, validated target genes. When administered in combination with an antibiotic, that small molecule (which was just for proof-of-principle demonstrations) improved the killing efficacy ten- to 100-fold. "In principle, with a small molecule that acts as such, you could take a lower concentration of antibiotics but achieve similar levels of killing," Collins said. From a patient standpoint, that means a lower dose of an antibiotic and fewer potential side effects.

Collins' research team, which includes about 30 undergraduate students, graduate students, and postdocs, is extremely pleased with the results they have achieved so far, especially in applications for improving health care, Collins said. "It's very motivating. Young people today are particularly driven by context, so they can see why they're doing what they're doing and that they can make a difference."

Future of Computational Modeling

The contributions and potential of computational systems biology, including multiscale modeling, are just emerging and "will be in the forefront of the transformation of medicine," Popel said.

He noted, "Computational modeling of biological systems is making real headway in the United States and around the world. Important discoveries are being made using computational modeling. Modeling is used in designing new therapeutics, and new biocomputational tools are being developed." One measure of this quickly advancing field is the growing number of computational-biology publications in major biological and general science journals as well as the creation of new journals devoted to computational modeling, Popel explained. At universities, too, students are flocking to computational biology programs.

The excitement is deserved. Popel remarked, "The field is young and quickly developing, and its full potential is yet to be explored. We are still at the beginning of the road."

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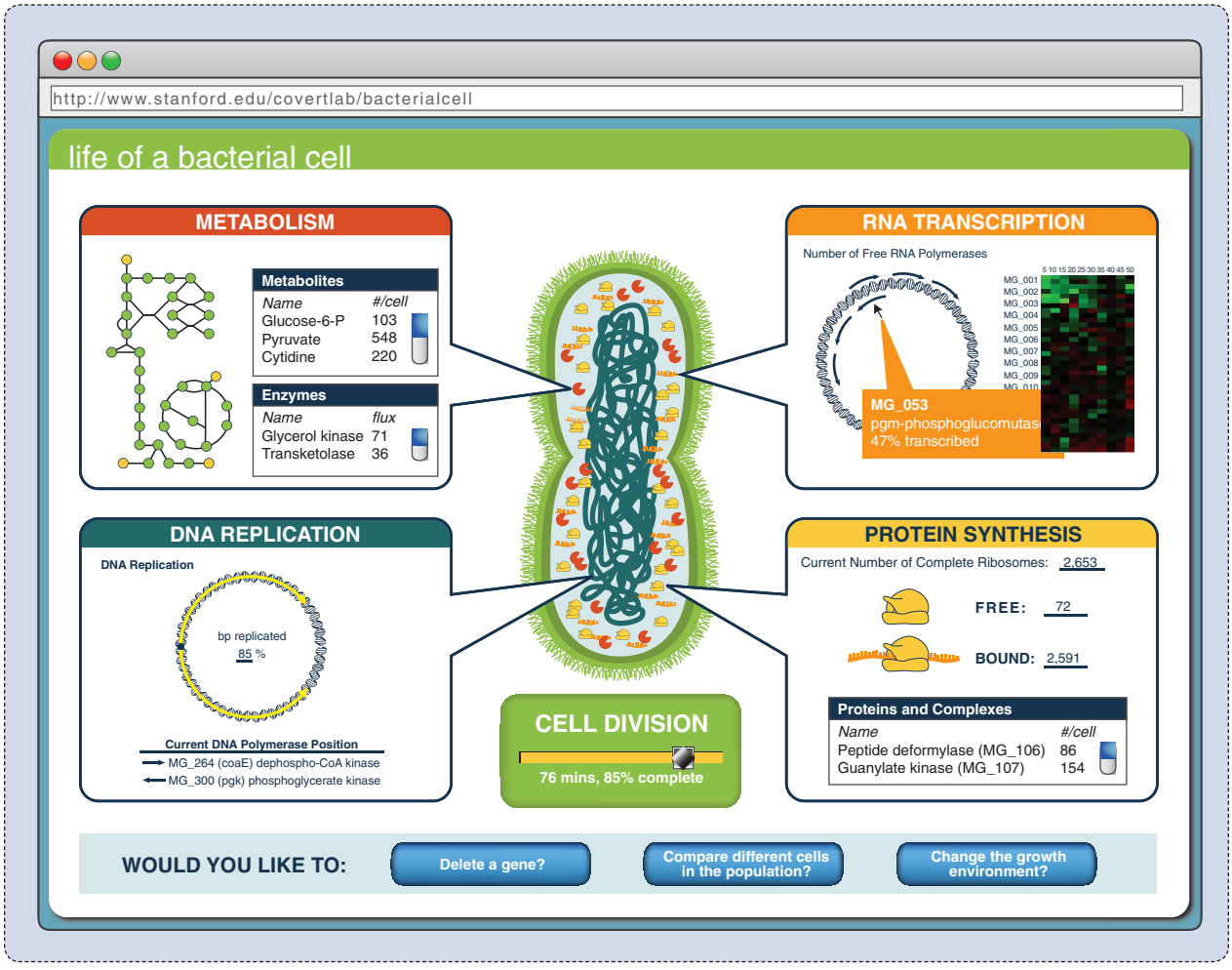

FIGURE 3 Stanford's computer model that accounts for the many aspects of the bacterial cell's life cycle. (Image courtesy of Jane Maynard, Jane Maynard Design.)

interaction that takes place in the cell's life cycle (Figure 3). Combined with additional recent advances in computational biology, Covert's work represents a turning point in computer modeling of biological systems.

The speeds at which new advances in computer modeling are occurring have surprised many scientists, including Covert. "If you would have asked me even five or six years ago when we would be able to model a whole cell, I would have said, 'not for decades.' Yet, here we are."

How did this happen? How are researchers today generating computer models that were thought impossible just a few years ago? A good part of the answer lies in new computational approaches.

Channeling the Information

Computer models of biological systems require the compilation of information gleaned from scientific literature; since so much data exists, gleaning takes time. "Basically, three of us went through about a thousand papers by hand, reading them, talking about them, and trying to extract data in order to understand the organism better," said Covert about his group's model of *M. genitalium* (Figure 4).

It is not enough to just collect the information. To make it useful, it has to be combined, compared, overlaid, and interrelated to generate a true simulation of life. Covert's group approached the task with an overarching recognition. "We realized that no single mathematical method is sufficient to model a cell; because all the properties are so different, our understanding of each of them is so different, and the data that's associated with them is different," he said.

So, rather than bending the heterogeneous data to suit one method, Covert's group selected various methods that were good fits for the diverse modules and their data sets, and integrated the different methods. "We broke the cell's functionality into 28 modules (Figure 5), such as metabolism and transcriptional regulation, and then asked: What is the best way to reproduce this? What's the data that's out there? What would we expect to be modeling, and what would that look like? Is the data largely qualitative or quantitative? Based on that, we just chose the best methods," he said.

The next job was to bring those molecular-pathway models, or submodels, together into one large working computer model. "That was what I would call the hard part," Covert said.

He and his team recognized full well that the 28 cell-functionality modules were "very interdependent and integrated,"

but for their purposes, they made the assumption that for a tiny enough period of time, the modules each acted independently. For example, one module may produce certain compounds that affect a second module. That second module may produce different compounds that, in turn, affect the first module as well as a third module. Instead of constantly trying to capture all of those inputs and outputs, Covert's model accounts for those changing inputs and outputs at one-second intervals and only at those intervals, and in the meantime, each simulation runs independently. "The general idea is that we just run each module individually, yet they're all dependent on the results of the previous time step and they

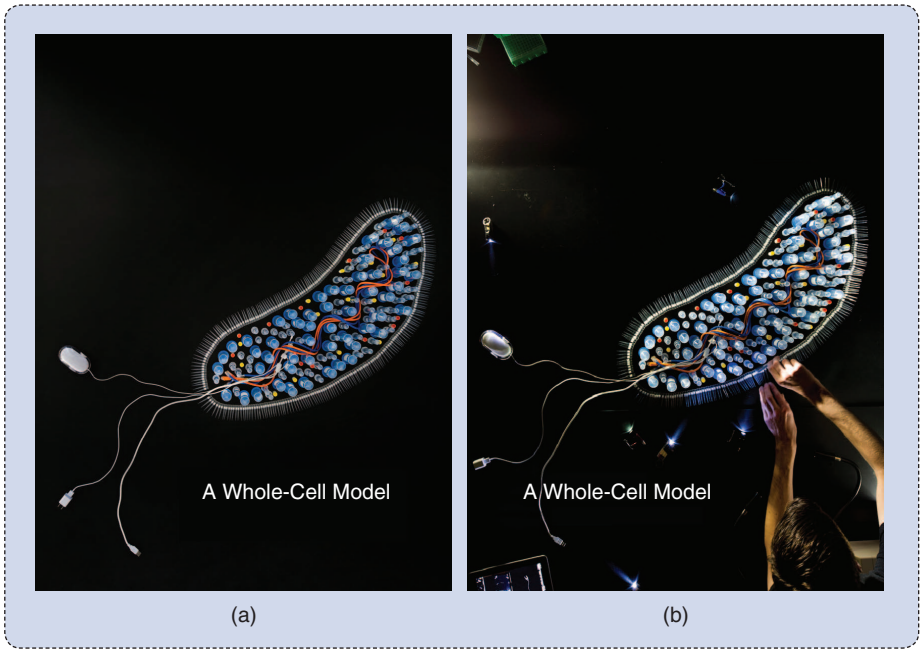

FIGURE 4 (a) and (b) Simulation of an organism's life cycle generated by Covert's research group. (Images courtesy of Erik Jacobsen, Threestory Studio, Inc., and Bernhard André, Bernhard André Photography, San Francisco, California.)

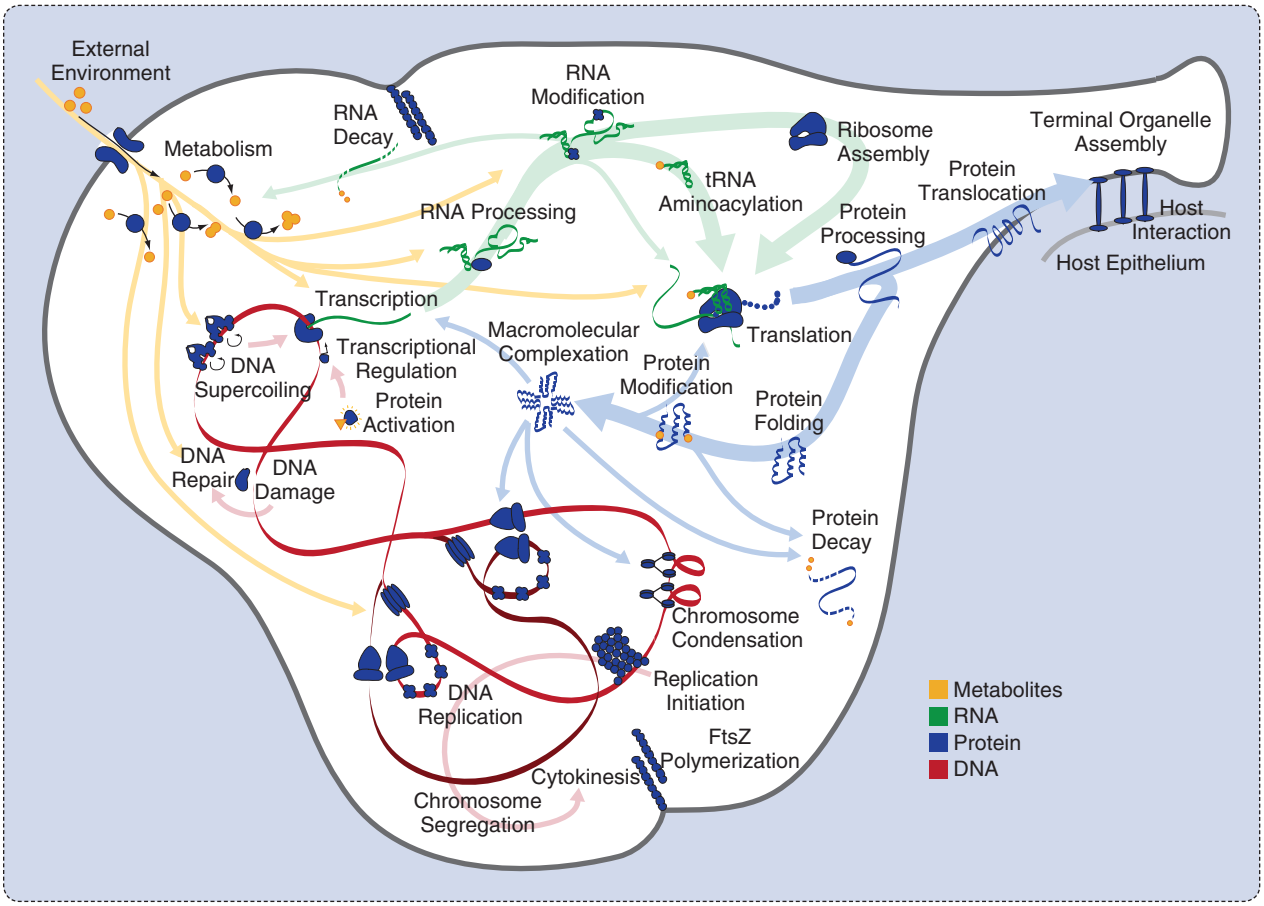

FIGURE 5 Model of *M. genitalium* generated by Covert's group. To generate the model, the group broke the functionality of the bacterial cell (shown here in its characteristic shape) into 28 modules, which are grouped by color: metabolic in orange, RNA in green, protein in blue, and DNA in red. Stanford's whole-cell model integrates the 28 modules. (Image courtesy of Markus Covert Lab, Stanford University.)

all contribute to the results of the next time step independently," he explained.

This approach allowed the Stanford researchers to coalesce all of the disparate information about *M. genitalium* into a working model of the organism.

On-the-Fly Scalability

The start-up company CytoSolve focuses on diseases instead of whole-cell modeling, but, like Covert's group, it relies on a meticulous review of scientific literature to draw together submodels that define various molecular pathways. "Right now, we have about 1,500 submodels that we've taken from or generated from public-domain, peer-reviewed research papers," said VA Shiva. Using the technology he invented as a core part of his research at MIT, he founded CytoSolve in 2011 and recruited his former advisor C. Forbes Dewey Jr., Ph.D., professor of mechanical and biological engineering at MIT.

"In 2003, I came back to MIT after working in building large-scale enterprise class systems for Global 2000 companies," VA Shiva said. "I realized that computational systems biologists needed a similar enterprise class platform to model the whole cell, and without such an enterprise systems approach, whole-cell modeling would always be a Holy Grail."

CytoSolve's researchers brought their backgrounds in distributed computing to the problem of coalescing the submodels and developed what it calls "the world's first computational platform for scalable integration of molecular-pathway models" [3].

"I think the advantage we had was that I and some of our team members had experience working for big organizations where you have to integrate large-scale computing systems that have underlying, constantly changing parts," VA Shiva said. "For example, a large company like CitiGroup has a financial system, a human-resources system, perhaps a sales-force system, a customer-database system, and those systems—which typically each have their own native file formats—all have to be integrated. On top of that, the data in each system is constantly being updated. You do that not by merging them into a monolithic code base, or into one singular system, but by creating a tiered architecture, a layer on top of the distributed models, that integrates these models on the fly while allowing them to be kept in their native formats," he said.

The same holds true in biology. Each research group does its work and presents its data in its own way. The resulting submodels are different, and they can change as new research is published, VA Shiva said. "If the rug is constantly being moved from beneath you, how do you handle that? Well, you have to have a distributed computational approach. Otherwise, you cannot scale to build any meaningful models and, more importantly, one cannot maintain the larger model since the rug is being pulled out all the time."

> **"What's fascinating about that is we're going from in silico modeling all the way to IND filing in 11 months, compared to the four years that's typical for traditional drug-development work."**

Many other computational modeling platforms require the various languages of the submodels—such as Matrix Laboratory (MATLAB), Systems Biology Markup Language (SBML), and Fortran—to be translated into one base language before they are aggregated into the overall model. "The problem with this approach is that a researcher may publish a new paper, which changes the rate constants, adds a new species (such as a protein), or otherwise alters the submodel. That means you have got to go back, download that paper again, and recode it up," VA Shiva said. "That's not going to scale if you've got another 20 pathways that are part of that computer model."

The CytoSolve platform solves that problem, because it not only integrates submodels in their native languages but also allows for changing information, VA Shiva said (Figures 6 and 7). "The submodels are like little jigsaw pieces that can change in real time as new information comes in, and CytoSolve is like the engine in the sky that lets you put the jigsaw puzzle together for different diseases. And if new information is published, it automatically integrates that in," he explained. "Otherwise, it's too complex of a problem. You can't do it."

Drug Development

CytoSolve is using its platform to identify and introduce new drug therapies (Figure 8). Compared with traditional drug-development practices that take about four years to go through laboratory, animal, and human testing, VA Shiva said,

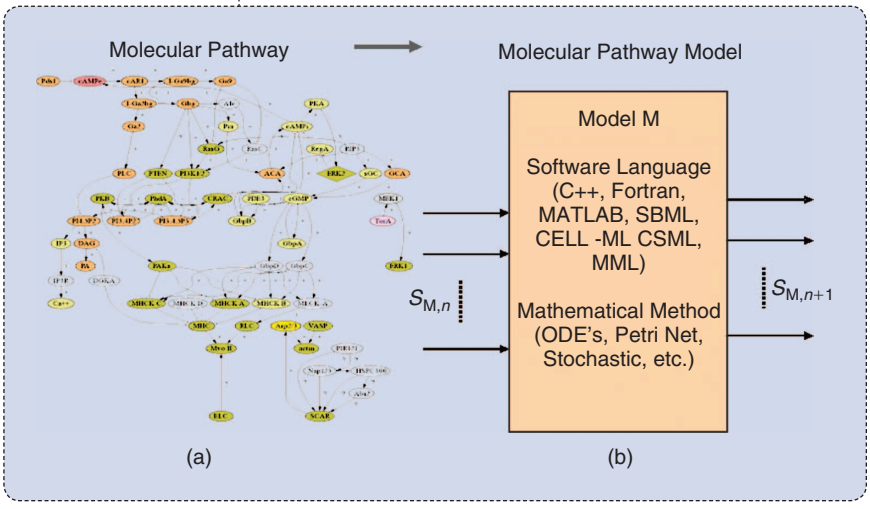

FIGURE 6 (a) Molecular pathway converted into (b) a molecular pathway model. The model receives inputs (*SM*,*n*) and evaluates outputs (*SM*,*n*+1). The model may be encoded in different programming languages and may utilize various mathematical approaches. (Image courtesy of VA Shiva Ayyadurai.)

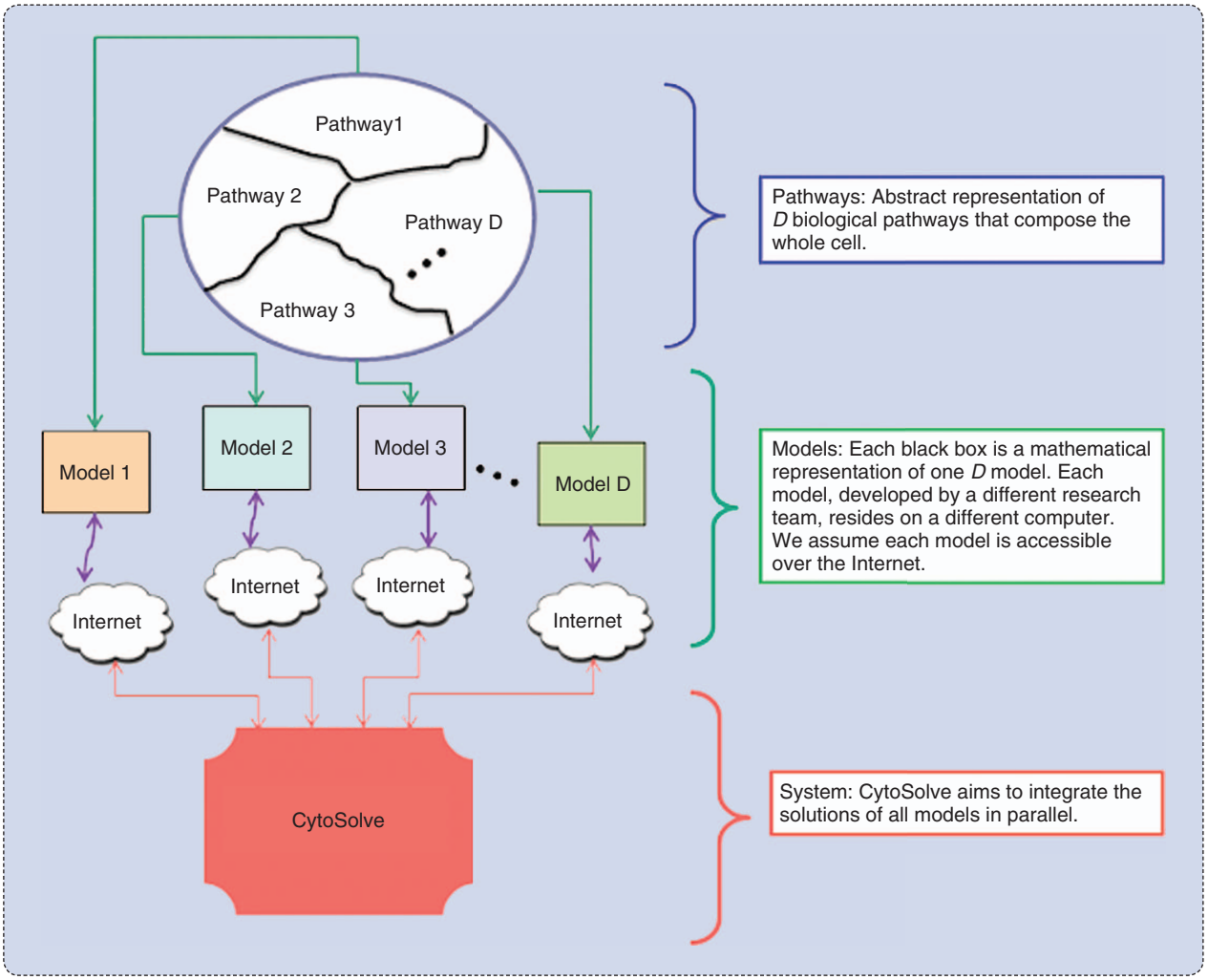

FIGURE 7 CytoSolve's approach involves viewing the cell as a collection of pathways, each represented as a dynamic model. The CytoSolve platform can couple and integrate those models. (Image courtesy of VA Shiva Ayyadurai.)

CytoSolve's modeling platform can bypass much of the preliminary testing and go straight to human trials in less than a year. Apart from time, this saves considerable money.

As the company moves forward, it will develop its own multicombination drug therapies and will license its computer-modeling platform to large pharmaceutical companies so they can use it to identify new drug therapies, especially drug combinations, VA Shiva said. "Right now, there are about 360 drug combinations out there that have been approved, and out of those, most are two-drug combinations. Only 15 are three-drug combinations, and just one is a combination of four." The reason for the low numbers of multidrug combinations is that each of the drugs can affect multiple molecular pathways, and the geometric progression of the interactions spiral out of control when the number reaches three, four, or more, he said. "With CytoSolve, we can combine not just two drugs, but seven, eight, or nine. And what's especially attractive about drug combinations is that you can reduce the dosage of each drug, which means we can lessen potential toxicity."

Pharmaceutical companies that license the CytoSolve platform can point it at a disease of choice, let the system screen various combinations of generic and soon-to-be generic drugs, and spit out a marketable combination, VA Shiva said. In addition, the companies can contribute their own submodels to the CytoSolve database without revealing proprietary information. "We've done it in such a way that public models can be integrated with private models," he said. "A pharmaceutical company may not want to share the guts of their model—their rate constants or software codes—but they may want to share the inputs and the outputs in order to integrate with public models and engage in collaborative learning. This kind of opacity is possible with the platform," he said.

To prove the viability of its model, researchers at CytoSolve used it to identify a drug therapy. "We've taken the disease pancreatic cancer, found all of the pathways that were written on it in the scientific literature, and modeled it. From that model, we've actually found some combinatorial drugs for pancreatic cancer and are about to go to our first investigational-new-drug (IND) filing," he said. Once filed, the drug will undergo U.S. Food and Drug Administration (FDA) review, and if it gets the green light, the drug will proceed to Phase 1 clinical trials.

"What's fascinating about that is we're going from in silico modeling all the way to IND filing in 11 months, compared to

the four years that's typical for traditional drug-development work," VA Shiva said. "This shows that we can do the in silico testing, avoid a lot of the animal cell testing that takes time and money to do, and go right to human testing. That's possible because our model allows us to validate everything, and we can do that because the model comes from peer-reviewed papers, and each one of those papers is based on in vitro and in vivo testing." He added, "Moreover, experts have shared with us that the FDA will actually find our in silico data valuable in making their IND application assessments."

The company has created both the business methodology and the computational and scientific methodology, he said. It's also contributing its own information to the research pool. "Whenever we create a submodel, perhaps a submodel on some aspect of diabetes or whatever, we provide it to a public repository. That's how we give back to the research community."

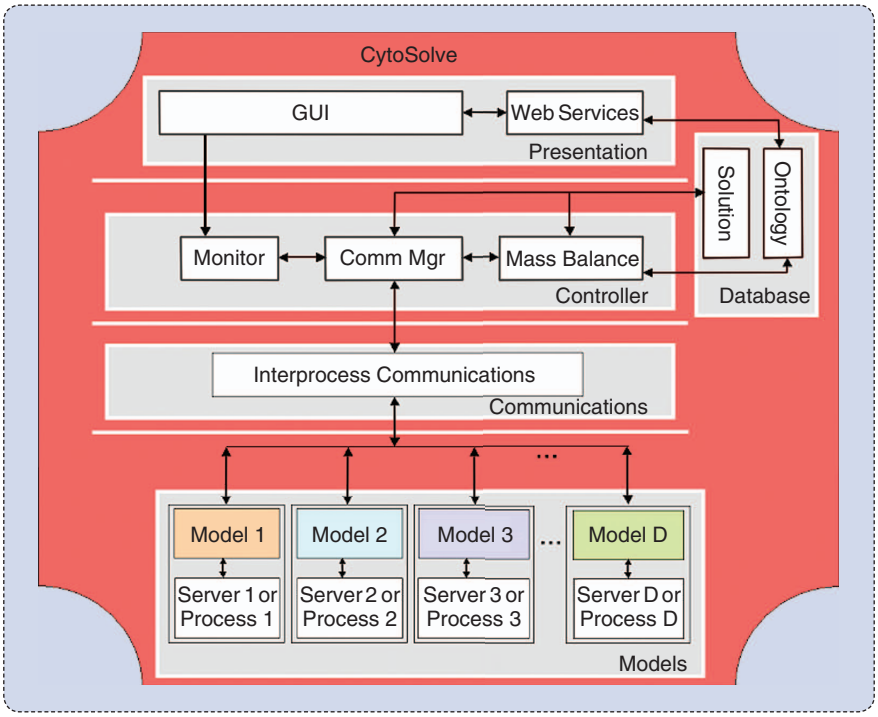

FIGURE 8 The tiered architecture of CytoSolve integrates submodels produced by diverse research groups, and does so on the fly by automatically incorporating updates to those submodels as well as new research. In so doing, the CytoSolve platform can produce scalable computational models of biological systems and disease processes, potentially leading to new drug therapies. (Image courtesy of VA Shiva Ayyadurai.)

From Bacterium to Human-Cell Models?

Although recent contributions to computer modeling of biological systems have catapulted the field forward over the last year, plenty of work remains to be done.

Stanford's work in modeling an organism is a good example. "There are definitely things that are beyond the scope of the model," Covert said. While his research group pinpointed the exact location of every protein that binds to the chromosome, they didn't explicitly model the position of every atom and molecule in the entire cell. "This is not a molecular-dynamics type of simulation," he said. In addition, the model presents a somewhat narrow view in that it focuses on one single cell and one cell cycle. "We didn't model the interactions between cells."

To make the leap to an organism with a larger genome, such as the intestinal bacterium *E. coli* or even a human cell, the model would require considerable modification. "You'd think it would be relatively similar, but it actually turns out that there are a lot of new functionalities that we would need to include, and there would be many conceptual leaps that would have to be made to go up to *E. coli* and eventually to human cells," Covert said. "Still, I think this is a great start."

His group's work, and that of others, has provided needed motivation. "Even five years ago when I was talking about a computer model of an organism, people weren't really buying it," he said with a chuckle. Publishing their model of an organism has helped change that. "Even though doing a human cell will be much harder, I know for a fact that there's already talk about it. I'm very hopeful that people will be coming into our field now and working with us or working in friendly competition with us to build these models."

Computer modeling can go even further, VA Shiva said. "Systems biology is a very experimentally focused field. It's not like in physics where we have ab initio or engineering laws from which we can derive things. With computer modeling, however, we can bring together all of this information we have amassed and potentially lead to some laws that will unify biology."

Popel added, "The computer revolution has certainly occurred in other fields of science and engineering, and now it is occurring in biology and medicine. It's tremendously exciting and very remarkable that it occurs in our time."

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