Innovations

Virtual cures

Entelos, Inc.

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For a brief period, supplying the data was enough. More genes meant more potential drug targets. But now the victims of the data flood are crying for help. Companies like Entelos, Inc. (Menlo Park, California) are coming to the rescue, by building models that integrate all those data into a single, homeostatic, interconnected whole. The models allow researchers to run virtual drug trials to determine the best drug targets, treatment regimens, and patient populations.

Entelos is approaching the problem one disease at a time, but building such models is still "not trivial," says Bernhard Palsson, a modeler from the University of California, San Diego, who has founded the company Genomatica to provide models of single-celled organisms. "This is not going to be as easy as people think," he says. Facing such a task, it won't hurt having chief scientific officer Tom Paterson on board. As one Entelos employee notes, "he really is a rocket scientist."

Rockets, business models, and biology

Paterson's experience ranges from aeronautics design to business strategizing, and Entelos' modeling methods are culled from both worlds. The aerospace industry has used simulation for years. As in this industry, Paterson prefers a top-down approach in which larger properties are examined first (Figure 1). "The top-down approach gives you a context for how the pieces fit together," he says. "It makes you less sensitive to how much data you have than you would really think."

"Let's say I start with the basics of fuel–air mixture and hydraulics, and eventually work my way up to how an airplane works," he continues. "The amount of detail you need is huge, and you lack the concept of how the pieces fit together. So you step back and ask how the airplane achieves flight. What are the high level functional properties that let an airplane do what it does? Then you work down into the details until you run out of data."

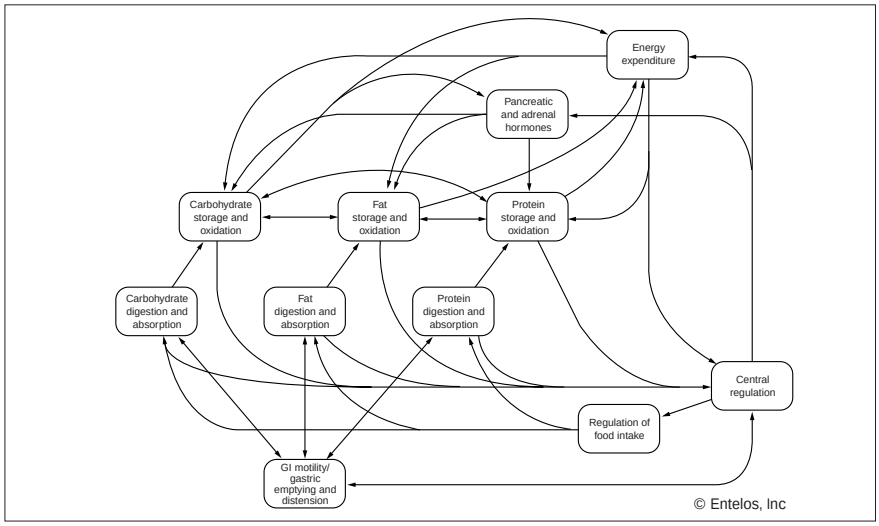
Curing real diseases by creating virtual diseases.

For the Entelos models, dubbed PhysioLabs, the first step is to simulate a healthy version of a particular corner of physiology. "Modeling a disease is pretty easy — there are many ways that you can build a skyscraper that falls down," says Paterson. "A healthy system is a much tougher design problem." The model must simultaneously satisfy many criteria, with more constraints being added as the model is refined. Once again biologists are borrowing from industry, says Paterson. "There are a tremendous number of parallels between air or space vehicles and biology. Both systems are self-contained, there are tremendous numbers of feedback pathways, and there are tremendous numbers of concurrent design constraints."

The constraints make model building more difficult, but give researchers more faith in the result. "It is truly amazing how effective a mathematically tight model is in focusing your attention, because you cannot get away with hand-waving," says Entelos CEO Sam Holtzman. "The math is a very harsh critic."

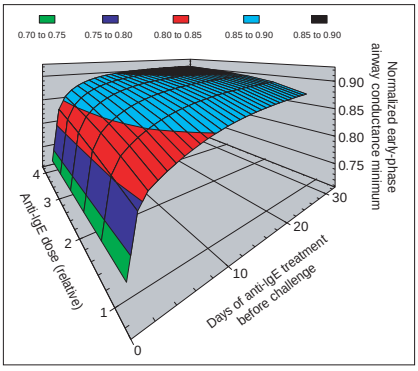
The critic may be arriving just in time. "It's become easy for an isolated biologist to propose a hypothesis that works in their own small area, but that doesn't make sense outside their area," says Paterson. The hypotheses may be falling victim to the simplicity of cause-and-effect reasoning. "Once

Figure 1



The top level of the Entelos obesity disease model, as it is depicted on-screen by the PhysioLab program. Clicking on one of the bubbles can take the user to the next level of detail (e.g., to a series of bubbles that represent all the interconversions that determine levels of protein storage and oxidation). At the lower levels, mathematics and literature references that support each interconversion are accessed by clicking on arrows or bubbles. Individual rate constants or starting values can be changed to modify the model or to simulate a disease state. When a disease or treatment simulation is run, many individual variables can be tracked (see Figure 2).

Figure 2



An experimental result from the asthma PhysioLab. Higher anti-IgE dose and longer anti-IgE treatment both lead to a better result (higher airway conductance), but it is clear that the duration of treatment is far more important than the dose. This should be taken into account in the design of any trial with this therapy.

you start looking at the degree of feedback, when you ask if it's cause or effect, you recognize that it's both," says Paterson. "We encourage our customers to get away from this idea of cause and effect. Cause and effect is like dominoes, and dominoes is the wrong way to think about disease."

The models yield some surprising new properties. "As you put together a complex system you see principles emerge that you would not get from a simpler representation," says James Bassingthwaighte (University of Washington, Seattle). Stuart Kauffman, now at Bios Group in Santa Fe, New Mexico, described such emergent properties in computer networks, but similar properties are what make the Entelos biological models truly useful. Emergent properties in biological simulation are perhaps not surprising. After all, says Bassingthwaighte, "you can regard life itself as an emergent property — you get a bunch of chemicals together and you get life."

The completed networks also show robustness — they tend to return to equilibrium even after certain parameters are changed. Theoretically this could make it difficult to detect errors in the models, but Adam Arkin of the University of California at Berkeley says that "robustness is such a strong constraint on the model space that it will be more of a help than a hindrance." Because only a few models will be robust, the property "reduces the feasible space that you have to search experimentally."

The construction process

The biggest challenge in building a model is converting biology to mathematics. "There's no place in the literature, save for a few systems like electrophysiology, where you can actually look up the equations," says Paterson. With non-linearity, errors and different levels of abstraction, Arkin says that, "the math, I don't think, is straightforward. There are major theoretical holes in simulation mathematics. There are issues that I don't know how they are addressing." But Paterson says he can get significant insights into complex systems with relatively simple mathematics, using non-linear ordinary differential equations.

On another strategy, Arkin says that Paterson "is absolutely right — the idea of modeling every atom in the cell is just stupidity. You have to go to a higher level." But, he says, "you have to choose the higher level carefully. You have to be very careful about what you are throwing out."

To make these decisions for each new disease, the model builders at Entelos immerse themselves in the literature and grill a different panel of advisers. Inevitably there are conflicts. In the future, some of these may be resolved by university researchers funded by Entelos, although the company itself has no plans for wet labs. Individual customers can pick and choose amongst competing hypotheses by changing parameters.

So far those customers are large pharma companies who subscribe to the PhysioLabs for use in the discovery phase. Holtzman predicts that PhysioLabs will be used to help with clinical trials, and that new customers may use them after buying consulting services for a single project.

What is it for?

A particular protein in a model may be of primary interest only to the one company that holds the patent defining that protein as a drug target (Figure 2). But Holtzman says that other companies will still have an interest. "A PhysioLab is a way to understand your therapeutic targets: what it is they do; how they achieve the clinical outcomes," he says. "You can look at alternate or combinatorial therapies, what competitors are doing, in-licensing opportunities, and out-licensing opportunities."

PhysioLabs have been used, for example, to show that a particular anti-asthma therapy would have positive initial effects, but then cause a disastrous compensatory reaction. An early version of a PhysioLab (before Entelos officially existed) was used to reverse a negative FDA decision, by showing that some of the phase III trials of a drug were disappointing because of an unseen patient bias: the patients were at university hospitals and therefore a greater number had a more serious version of the disease. Holtzman says the company involved "had an abundance of data, but no ability to integrate the data."

Having it all

Entelos are not the only ones with grand plans. Bassingthwaighte is an originator of the Physiome Project — a loose consortium of researchers who are simulating the body, one organ system at a time. Similarly, Physiome, Inc. (Princeton, New Jersey) has designed an *in silico* heart and is moving on to the immune system.

Modelers feel that their time has come. "Leaders in the genomics field are all coming to this realization that model building is becoming the rate-limiting step," says Palsson. "There's a major shift taking place in the biological sciences." Math is back, he says, and "biology is going to become quantitative."

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