Jeffrey Skolnick is a professor in the Georgia Institute of Technology’s School of Biology, director of the Center for the Study of Systems Biology and a Georgia Research Alliance Eminent Scholar in computational systems biology. He joined the faculty of Georgia Tech in January 2006. He was previously director of the Buffalo Center of Excellence in Bioinformatics at the State University of New York in Buffalo.

**Q:** What is computational systems biology?

**A:** The traditional way people study biological systems is a very reductionist approach. You have a very complicated system and you want to take it apart and study one molecule at a time. You study one molecule or family of molecules and become a world expert on it. That's very powerful, but it's like taking a car apart, dropping the parts on a desk and looking at one nut. You pick it up and have no clue where it fits in the car. It has some interesting properties, but the context in which it appears, its function, is lost if you study this one nut.

In systems biology, the goal is to study how the parts interact. If you look inside an individual cell, it's like a crowded party on New Year’s Eve, rather than an isolated person on a deserted island. The reductionist approach to biology tells us about the isolated person, but it misses the collective behavior. Systems biology attempts to understand and use the collective behavior of molecules to gain greater biological insight.

The long-term goal, whether it's reached experimentally or computationally, is to understand how things work synergistically.

We develop and apply computational algorithms to predict and understand the function of proteins — the molecular machines of the body. It’s estimated that in the human genome there are 20,000 or so types of proteins. The function of less than half of these proteins is known. If I'm an experimentalist, I want to know which of these proteins to study first because I want to study something interesting and potentially important. So we develop computational methods to prioritize these things.

On a practical level, we’re developing approaches to increase the efficiency of drug discovery. We want to adapt the systems biology approach to figure out, first of all, what makes a protein an interesting target of a drug. Then we’ll use this insight and systems approach to accelerate drug discovery.

**Q:** What is the potential scientific impact of this field of study?

**A:** We want to understand on a functional level what are the key issues of life that could be controlled or manipulated to allow us to do a lot of engineering once we understand the design principles. Then the implications are better diagnostics and treatment of diseases like cancer and diabetes. It's like mom, dad and apple pie. It sounds very good, but it’s not happening tomorrow. In the long-term horizon, systems biology is where the revolution in biology is occurring.

**Q:** How will the center you are building lead to better and healthier lives for people?

**A:** You have to take the long-term horizon. It's not happening tomorrow. It could happen in five to 10 years. We're developing more powerful diagnostics, particularly for ovarian cancer in collaboration with Professor John.
about the unknown ones? There are only 500 or so proteins that are known drug targets. In this field, you proceed by analogy because the systems are so complicated.

Q: A systems biologist takes a non-traditional approach to creating new drugs. Describe that process and how it differs from the typical approach.
A: By one means or another in the traditional process, you identify a protein target believed to be responsible for a disease. Then you screen it against a large library of small-molecule compounds to identify binders. Basically, there is a functional region that you want to plug up like a cork. It fits. Then you do medicinal chemistry to optimize it because you want it to fit tightly. You want to enhance the specificity. You don’t want it to bind to something it doesn’t belong with....

Then you feed the drug to an animal model, and it may work in the animal model, but not in humans. You have to deal with absorption and toxicity. There may be side effects. You may have to go back and optimize again, maybe make a subtle change that can have a big biological effect.

Systems biology wants to design in drug specificity to look at the biological context, the cellular pathways, the processes that the drug target is associated with. For example, imagine yourself McDonald (chair of the School of Biology). We’re developing an approach for diagnosis of ovarian cancer that could be used for detecting other types of cancer.

With regard to drug discovery, if we succeed, we will produce robust predictions for drug targets and reduce the current failure rate of 99 percent in drug discovery. The failure rate is so high because the human system is very complicated. If we’re very lucky, we’ll discover a new drug. If we’re not as lucky, but still lucky enough, we’ll develop a diagnostic.

Q: What are some research milestones you and your team have recently reached?
A: We’re very interested in proteins — their structure and biologically active shape. We’ve been curious about how many protein structures exist. We’ve recently published a paper in the Proceedings of the National Academy of Sciences (PNAS) that shows these structures arise from some remarkably simple design principles.

In another study with a talented graduate student named Jake Boggan, we’ve looked at the uniqueness of cellular pathways, which are like assembly lines. Our work shows that these pathways are not as uniquely defined as people thought.

We’re also asking what makes a protein a drug target. What characteristics can we learn from known drug targets that we can use to generalize...
in a city that is separated by a river. There is one bridge across the river. The best way to inhibit traffic out of the city is to blow up the bridge. But if there are 500 bridges, you’ve blown up one. So what? The traffic works around the bridge that is blown up. Is it at a critical point like the single bridge in the city, or are there many interconnected ways? Is it a unique molecule in an organism? Is it used only in this pathway, or are there 50 others? You have to look at the context in which it occurs. The goal and hope — it remains to be demonstrated — is that we can minimize the side effects and enhance the specificity of the drug. The burden of proof is on the field to prove this approach is a better mousetrap.

Q: Describe the capabilities of the supercomputing power — funded by the Georgia Research Alliance and IBM — available in your lab.
A: Our supercomputer can perform 15 trillion operations per second on a good day. As an example of the kind of calculations this supercomputer can do, we study a large class of molecules that are a major class of drug targets. We have an algorithm that seems to be among the world’s most accurate at predicting the structures and features of these molecules. With one computer, it would take 70,000 days — that’s 200 years — to do this one calculation. On the other hand, with the equivalent of 4,000 computers working on this calculation, it takes just 18 days.

There are thousands of protein sequences and hundreds of genomes we want to understand.

Q: How did your interests and opportunities lead to where you are today?
A: I don’t like to work on what everybody else is working on. You have to have a new and original idea. If you don’t have one in a field that’s already established, why bother? If I have an idea, I’m fearless to pursue it.

As a child, my parents were very nurturing. I remember my father coming home with tube experiments for me to do and those how-and-why science books. My mother encouraged us to be curious. There was nothing we couldn’t do if we tried hard enough. My parents took us to museums such as the Smithsonian. They always encouraged us to be creative and think outside the box.

Read more at: gtresearchnews.gatech.edu/reshor/rh-w07/skolnick.html