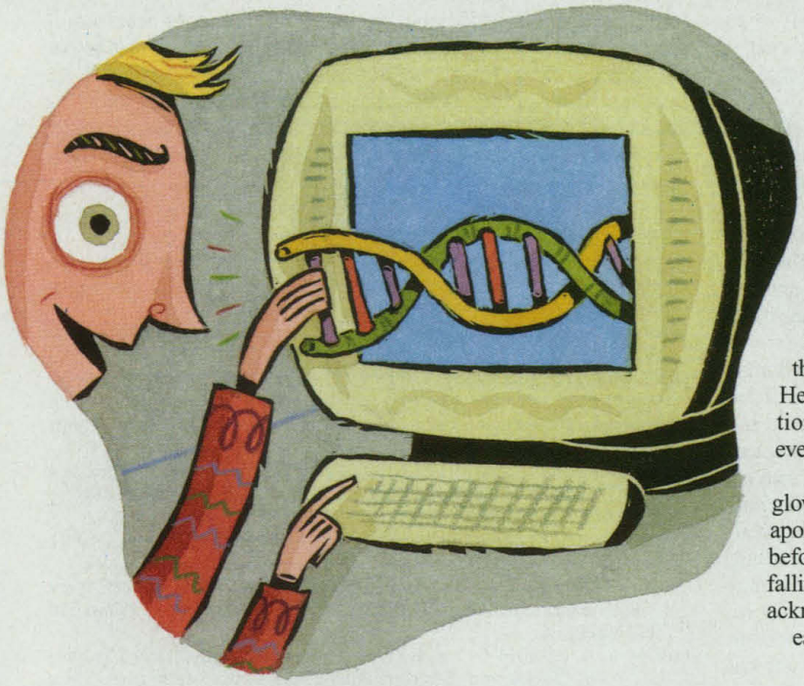

S(t)imulating Science

by MANJU M. HINGORANI

"Intruder alert! Intruder alert! All hands to battle stations. This will be a fight to the finish!"

Gert looked up from the controls and around the CellSim with pleasure and a lot of pride. It was a standard McPhage model that the laboratory had purchased from BioSimulations a couple of years ago. But there was nothing standard about the cell now. Gert had worked on it day and night (including weekends—she was, after all, a graduate student), to convert the McPhage to a microglial cell, a specialized macrophage specific to the central nervous system (CNS). Her baby was now ready to fly, and the first tests would involve her pet strategy for defense against myelin damage in multiple sclerosis.

Biomedical research had changed a lot from the time her grandmother had been a scientist at the National Institutes of Health. Gert was technically an immunobiopharmacologist studying CNS diseases, but she hadn't come within sneezing distance of a cell culture in years. That certainly wasn't a problem in her opinion. She thought the traditional methods of measuring whole-cell response to stimuli were about as scientifically valid as crystal ball viewing for understanding cellular function. How could one understand the intricate processes of life with experiments that examined only one phenomenon at a time? Such methods had been adequate 50 years ago when the human genome was incomplete and advanced statistical methods were not available. Now, new techniques were being developed every day to measure the probability continuum precisely under complex and rapidly changing conditions. Soon, researchers would be able to examine multiple interlinked biochemical processes simultaneously with the help of cell simulations.

That's why Gert worked in a computational statistics lab, although her primary interest lay in investigating multiple sclerosis (MS). She knew that to understand this complex disorder, and to develop an effective treatment, a comprehensive picture of the disease state was essential. In other words, she needed a good simulation of the pathology of MS. So she simulated. It was a risky Ph.D. project; there were no other biomedics in the lab, and her advisor, Dr. Emma Noether, didn't care much about anything other than theoretical statistics. Luckily, the university would provide funding for at least another year, and things were starting to look promising on the research front. Her system had not crashed during the last two mini simulations, and she was preparing to go for the whole deal this evening.

The door to the CellSim scraped open, and she turned to glower at Max, a new postdoctoral fellow in the lab. Without apology for the interruption, he said, "I'm hungry, let's get lunch before the cafeteria closes." She literally had to stop her jaw from falling open. She could count on one hand the times he had even acknowledged her existence in the past few months. What on earth did this abrupt invitation mean? Still, she hit the "pause" key and stepped out; she did remember that he had a very cute smile!

He didn't speak until she started chewing on a stale piece of pound cake after finishing her ham sandwich. Then suddenly he said, "Okay Gertrude, tell me about your new hypothesis."

Gert gritted her teeth, "I'll present it at group meeting next month, and my name is Gert." Ooh she hated his arrogance! And she hated being called Gertrude! Her grandmother had named her in honor of Dr. Gertrude Elion, the phenomenal Nobel Prize–winning scientist of the 20th century, who had discovered many life-saving drugs, including acyclovir, which was even now used to treat MS. So, technically the name was perfect, given Gert's career, but she had not appreciated being called "Gertrude Hellion" all her life!

Max exhaled heavily, trying to control his own temper. "This is not easy for me, Gert. I don't like working with a partner, but Emma wants me to help develop your MS CellSim in time for the WHO conference on human disease. She thinks your simulation is a good model system for our new probability continuum calculations."

This time Gert's mouth did fall open. So many thoughts swirled in her head, she couldn't speak. Dr. Noether had a good opinion of her CellSim? She had an opinion of it at all? The WHO conference? That was even beyond her wildest dreams! And then, the last thought, work with Max? Oh my goodness!! Finally, she asked, "What would you like to know?" This time he replied with a smile, "You haven't presented a group meeting since I joined the lab. Why don't you start at the beginning?"

"All right," she paused and thought a bit. Then stated, "Multiple sclerosis progressively disables the central nervous system. The disease begins with sporadic episodes of neurological dysfunction that worsen over time. My mom was paralyzed by the time she was 55. But—ah—that's not important here." Max said quietly, "I'm sorry." "It's okay," she replied, "She died 2 years ago, and I'm kind of over it now. Anyway, MS degrades the CNS through inflammation and demyelination of nerve fibers. It's an autoimmune disease with multiple origins. Essentially any combination of genetic or environmental factors, such as viral infections, may trigger an abnormal immune response in which neurons are targeted."

ILLUSTRATION BY ADAM MCCAULEY

Max looked at her intently, "That sounds complicated," he said, "And you're trying to simulate what the neuron goes through as the disease progresses?"

Gert let a shaky laugh escape her. "No," she said, "I'm a little smarter or stupider than that. See, several labs are trying to determine what changes in a neuron to make it susceptible—perhaps some difference in the outer membrane protein character. Essentially we're all looking for ways to fortify the neuron against attack, at the right time." She paused for a moment before presenting her idea, "I think we should focus just as much on the microglia as on the neuron."

"Microglia?" Max inquired.

Gert frowned at the interruption. She continued briskly, "Microglia are macrophages of the CNS. Normally, they defend against pathogens by amplifying the inflammatory response and aid cleanup by phagocytosis. In MS, microglia mistakenly identify neurons as invaders and damage them directly by phagocytosis and via inflammation." Max had a glazed look in his eyes, and she realized she was losing him. She got up and said, "Come, I'll show you the CellSim. I was going to run it after lunch anyway."

As they went to the lab, Gert explained hurriedly, "I've simulated microglia because I think these cells go through significant changes in character before they attack neurons. I also think we can manipulate these changes through gene therapy, which will be easier in microglia than in neurons, because macrophages are perfectly designed to take up foreign substances, such as viral vectors." She opened the CellSim door and stepped aside to let him in. It was cramped, with just enough room for her processing unit, two chairs, and a receptor bodysuit. Gert had invested a ton of funds into the bodysuit. Even though the computer stored all the data, she wanted her senses to be fully active inside the simulation so that she didn't miss anything. She offered the suit to Max and put on a headset herself.

"I'm going to run a mini-program that simulates a nerve cell under attack by microglia. We'll be inside the microglia, to the right of the nucleus. A large portal ahead will show the neuron. You'll see various signal transduction processes within the microglia and the inflammatory activity outside it. Your control panel will indicate changing levels of interferons, free radicals, nitric oxide, etc. Don't try to take in everything at once; I'll present important data in graphs later. I just want to give you an idea of how dynamic the situation is, and how difficult it will be to devise a therapy with no undesired effects."

Gert threw the switch, and instantly she and Max were cocooned inside a purple and pink environment with a blazing light up ahead. That was the portal which looked onto the battleground. Literally.

Max jerked beside her and yelled, "Hai!! What the...?!" She held his hand and laughed, "Don't worry, they're not real droid starfighters, just activated T-cells. I got bored of simulating blobby cells, so I gave them character. It doesn't affect the data though." She added with a smile, "Those blazing guns represent heavy secretion of TNF-α, TNF-β, and γ-interferon. They won't hurt you."

Max pulled his hand away and said in a clipped voice, "I'm fine. It's very interesting." The simulation played out, and ended with the myelin sheath on the neuron tattered and torn, the neuron dead, and the microglia exhausted. They stepped out of the CellSim and went to the coffee room. She waited for him to speak.

"I understand why you need probability continuum to create all these dynamic immune response pathways and to examine how they change through interactive and feedback loops as the attack progresses. But your data can be presented in graphs and illustrations, so why make a CellSim?"

Gert smiled, "Do you think it is possible to process so much information using only the sense of vision? People tried that, early this century, when immense amounts of data were generated by DNA chip technology. It became impossible for individuals to keep track of relevant information and think coherently about it, which was essential for advancement of biomedical science. The breakthrough came in the thirties when scientists realized that the human brain could process all that information, and much more, and that the rate-limiting step was at the data input level. Using just our eyes was not enough. Since then, researchers studying complex systems, such as the human body or the universe, try to utilize simulators that input data through all five senses. My bodysuit does that very well, which is why you experienced such a deep shock initially."

"I'm impressed." Max smiled and held out his hand. "What do you intend to do next?" Gert shook his hand and flushed at the compliment. She shook her head and said, "I'll simulate the effects of current drugs used to treat MS. Once I've established that baseline, I will test my treatment strategy."

Max asked, "What is that?"

She hesitated before replying, "I want to modify the microglial cell so that when it changes to attack a neuron, it will also start secreting large quantities of antiphagocytic proteins that will coat the neuron and protect it from digestion." Max glanced at her with a skeptical look, "That's sounds like a good idea, but what about...?"

And so their discussion continued—for 5 hours. Finally, when Gert almost fell off her chair, Max stopped asking questions. He told her he would finish his new algorithm for faster probability calculations by next week. He hoped it would allow her to add more reaction pathways into her CellSim without overloading the processor. On that note, they got up, closed the lab, and walked back to university housing.

Gert wished Max good-night and floated inside her room. And landed back on the ground with a thump. She had been so excited about the idea of her CellSim at the WHO conference, she hadn't thought about anything else. Now, a small voice in her head was asking nasty questions and she couldn't ignore it. Would Dr. Noether and Max allow her to exhibit her work as a breakthrough in CellSim technology? Or would it just be a vehicle to show off their novel mathematical techniques? Who would be the primary presenter at the conference? For that matter, how would the paper be written and who would be first author? She didn't like thinking about these things, but she knew they were part of the reality she had to face. Still, if it weren't for the math, her research couldn't have come this far. Anyway, the conference was 6 months away and there was so much work to be done, she'd worry about the political stuff later. At this time, other than the CellSim, her feelings about Max seemed much more important.

He had caught her off guard. She enjoyed his company and really liked the idea of working with him. Obviously he was smart; he had surprised her with his suggestion about accounting for the placebo effect in the treatment phase. The more she thought about it, the more she knew she had to factor it into her simulation somehow. After all, placebo effects were known to be responsible for almost 30% of the cures in several diseases, including those with neurological origins. Perhaps she could introduce a loop that increased anti-inflammatory cytokines more than expected from conventional drug treatment. A quick scan of the literature would provide enough information to make a guesstimate.

She knew what she had to do next, and the first chore was to get a good night's sleep. She switched off the light, closed her eyes, and dreamed of her heroine, Dr. Elion, with a small smile on her face.

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