

TACKLING THE MYSTERY: THE MONO VIRUS

Many people know infectious mononucleosis (mono) as the disease of fevers, sore throats, and fatigue that can rob students of entire semesters. Medical researchers know mono as the disease caused by the Epstein-Barr virus (EBV)—one of the oldest, most common human viruses.

By age 45, about 95 percent of all adults have been infected, according to the U.S. National Center for Infectious Diseases. EBV is a tenacious virus that can maintain a life-long, persistent infection in healthy people. Researchers know it 'hides out' in healthy people, but what triggers it to go from 'sleeper agent' to an infection that spreads to other individuals is still unknown. (*Continued on p. 12.*)

ECE's Paul Plassmann—along with Mark Jones and a team of graduate students—is working with researchers from Tufts University to understand the dynamics of EBV; how it interacts with human cells and organs over time. Using supercomputers, they are developing a simulation that researchers hope to use to model the behavior of the virus at the cellular level in a human body.

“We just can't watch cells interacting over time in a human body,” Plassmann says. Given the impossibility of observing the virus infecting people, a simulation testbed is the only solution for such situations, he says, adding that biologists have coined a term for it. “They call experiments in living tissue ‘in vivo,’ experiments in the laboratory ‘in vitro,’ and now, experiments using computer simulations, ‘in silico.’”

“The more we can do with simulation, the more we can help to find ways to improve people’s health.”

The mystery

Viruses typically target certain kinds of cells and particular organs, he explains. “EBV hangs out in the tonsils.” Specifically, EBV targets naïve B-cells, which are part of the body’s adaptive immune response system. An EBV-infected naïve B-cell then goes through the “germinal center process” and fools the body’s immune system into thinking that the infected cell is real memory B-cell. “It then hides out in the adaptive immune system’s memory compartment. For unknown reasons, these infected B-cells occasionally are activated and become ‘lytic.’ In the lytic phase, the virus reproduces, destroying the original cell and producing free virus, which can infect other B-cells or leave in the saliva to infect other people.”

After the initial acute phase of the infection, EBV survives in the body at a constant rate of about 5 in a million cells. The mystery, Plassmann says, is how EBV cells remain at a constant population under the radar of the body’s immune system. “Biologists do not know how long an infected B-cell lives,” he explains. “It could be as short as a week. At some point, the cell has to reproduce or go lytic and infect other cells.” When people develop mono, as much as 50 percent of their memory B-cells become infected and destroyed by the immune system, causing the familiar symptoms.

Simulating extraordinary complexity

Simulating a live biological process is extraordinarily complex. The simulation models cells, viruses, and other biological objects as agents and simulates their motion and interaction through the solu-

tion of stochastic differential equations. Each agent has an internal state, which can be modeled as a finite state machine or ultimately by chemical pathways that will involve hundreds of states and thousands of transitions. The real computational challenge, however, is with the number of cells. “We are modeling hundreds of millions to billions of cells,” Plassmann explains. “The time step for the simulations is on the order of minutes, but we want to see what happens over a span of months or years.” The simulations easily get into the teraflop to petaflop range (greater than 10^{12} to 10^{15} floating point operations per second), which is the edge of what is possible with today’s fastest machines, he says.

Such simulations typically require supercomputers, or parallel computers, he says. Plassmann uses machines with between 200 and 400 processors. An interesting new development in computer engineering is that number of cores per chip is rising quickly, “so we will have to develop the algorithms and software that can take advantage of these massively multi-core architectures,” he says.

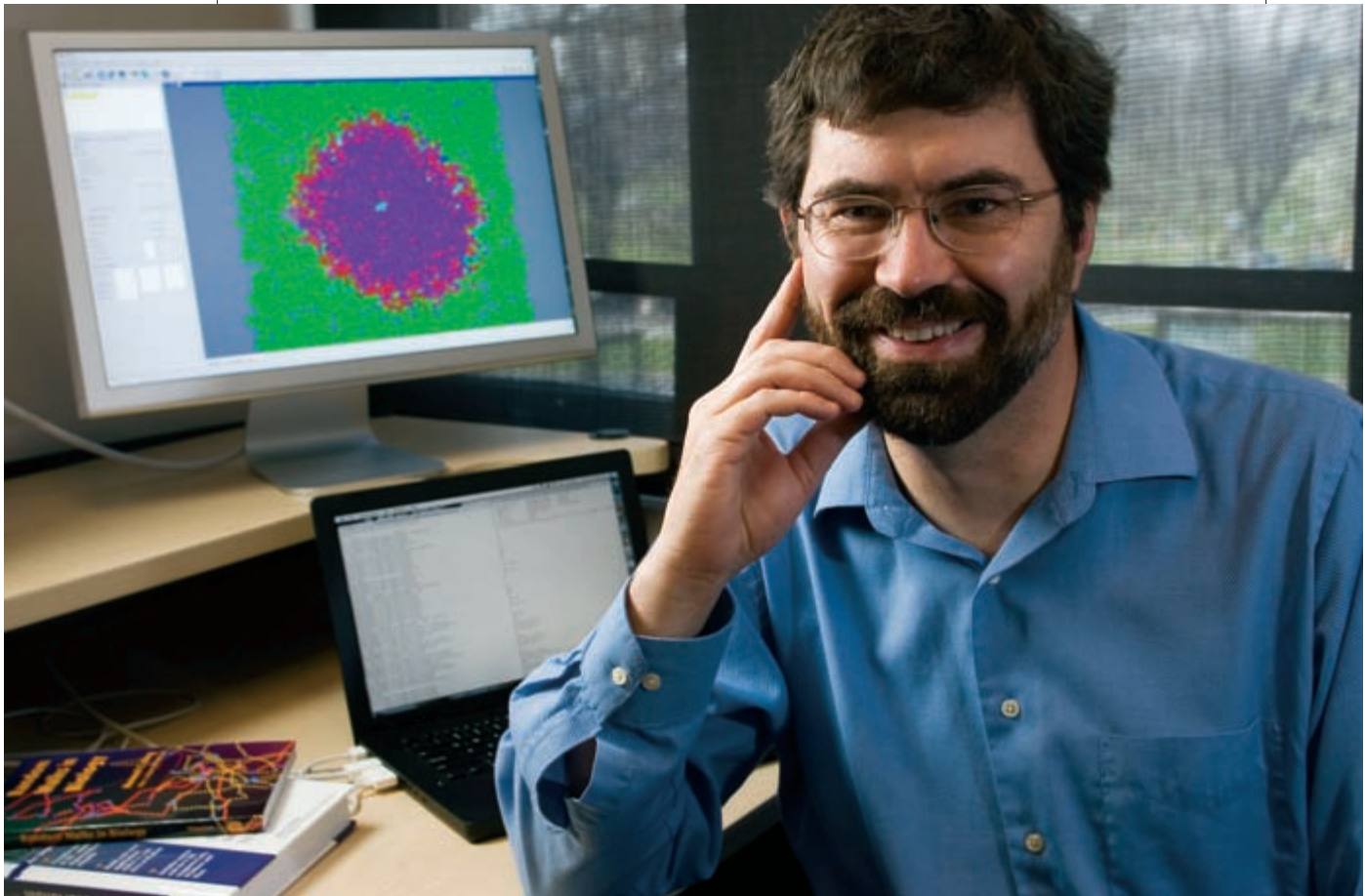
Another complicating factor is that the reactions and dynamics involve different time scales, creating a multi-scale problem. “There is a slower time scale where we model the motion and interaction between cells,” Plassmann explains. “However, where we model the chemical pathways inside a cell, things happen on a much faster time scale. The trick is to have the simulation move at the longer time scale of the cells, while accurately representing what is happening at the shorter time scales,” he says.

Borrowing from combustion

The team is using some ideas from their experience in combustion modeling. In combustion, the fluid mechanics happens at the slow time scale (millisecond time scale) and the chemistry happens at the fast time scale (nanoseconds). “The observation is that similar chemistry calculations are done repeatedly. So, rather than redoing them, we store the results of these calculations in a ‘scientific database’ and approximate subsequent chemistry calculations based queries to this database. This approach has enabled speedups in combustion simulations of 100 to 1000 times, Plassmann says.

While Plassmann enjoys the challenge of multi-scale simulations, he says the most fun is working with people in other fields on predictive capabilities. “In my work on EBV, I’m working with experimentalists. Their experiments look at understanding the specifics of particular cellular transitions, interactions, or properties. However, the simulation is the ‘whole picture’ and gives an experimental biologist a chance to see how these specific properties affect the

Paul Plassmann is developing simulations to help solve the mystery of the latent infection of the Epstein-Barr virus that causes mono. The screen behind him, and the image on page 11, show a cross section of a simulation of a germinal center—an active area of the tonsils used by the adaptive immune system to develop memory B-cells.



complete biological system. In the predictive mode, a biologist can now ask the question, ‘if I can experimentally change a specific interaction (by, for example the use of a drug) how will that affect the entire system?’”

The give-and-take between biologists and engineers is fun, he says. “There are many things we discover that they don’t know, but are necessary for an accurate simulation. For example, how long does a memory B-cell live? Where does it divide? They don’t know. And you can’t track a memory B-cell around the body in vivo. You might have a picture of the germinal center, but that’s just a snapshot.” Germinal centers are areas of activity that develop dynamically after the immune system activates B-cells. And ultimately one has to be able to understand these dynamics to get to the bottom of latent EBV infection.

“Together, we design experiments to get the information we

need. Then we see how the results map to what they already know ... The neat thing about this is once we figure out how the germinal center works, we have a model that can be used for predictive purposes. There is no way they can get that without our simulations.”

The team is discussing similar models for other biological systems, he says, such as modeling influenza infections of the lungs. They are in discussions with one group about developing models for H5N1, the bird-flu virus. Another potential project involves modeling the T-cell response to dioxin in the environment.

Plassmann says the hope is to develop a general simulation framework that can make big contributions to research in systems biology. In biology, for example, “the more we can do with simulation, the more we can help to find ways to improve people’s health.”