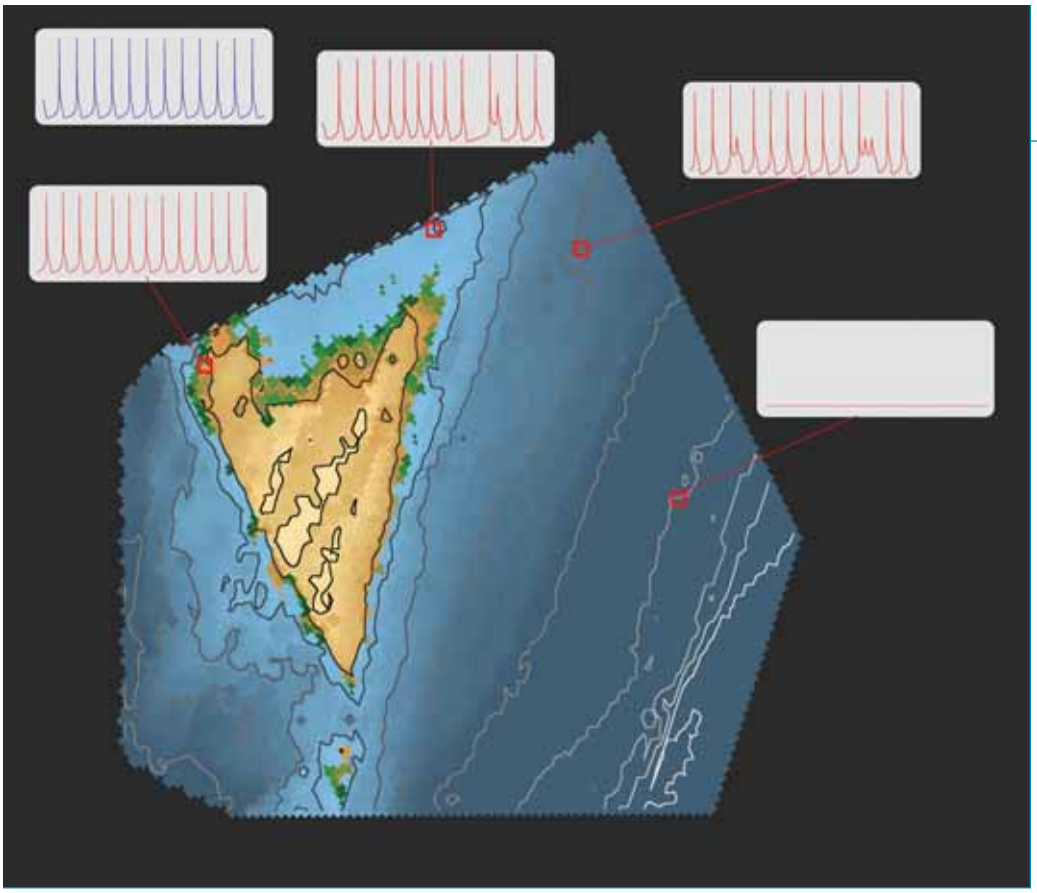

One neuron firing pattern can be produced in a variety of ways. Here, typical voltage traces of different computational models (red) have to be compared with the experimental data (blue). The image shows a view of a small slice of the complex landscape for which thousands of parameter sets have been tested. Fitness has been color coded: Good models form a brown island surrounded by a blue sea of bad models. In other parts of parameter space (not shown) similar isolated islands of good models can be found.

experimental error, clinging to the notion of a "platonic ideal" of a neuron with an unchangeable firing pattern.

To look at the problem more closely, De Schutter and **Pablo Achard, PhD**, a postdoc in his lab, computationally modeled the Purkinje cell, an especially complex type of neuron best known for forming as many as 200,000 synapses. The team's model specified 10 types of ion channels and broke the cell into four different regions that the channels could occupy. Using a mathematical approach called the phase-plane method, the model neurons were permitted to evolve their ion channel densities to produce all four firing patterns that Purkinje cells display. To the researchers' surprise, about 20 possible combinations of ion-channel densities fit the bill. The results were published in the July 2006 issue of *PloS Computational Biology*.

The work suggests, De Schutter says, that neurons are preprogrammed for a particular type of firing pattern. Each cell then decides locally how to distribute ion channels to achieve its signaling goal. How well the model predicts real biological properties is not clear and is difficult to test experimentally. Neurophysiologists can record impulses from just a few neurons at a time; the sheer quantity of recordings needed for a thorough comparison with the model doesn't yet exist. "My estimate is you'd need about two people working full time for a year for that data," De Schutter says.

> "This paper is a beautiful example showing that we shouldn't be thinking about a single solution to capture what a neuron is doing," says Eve Marder, "but a family of solutions."

Regardless, the model provides a more nuanced version of how physiologists should conceive of their cells, says **Eve Marder, PhD**, a professor of biology at Brandeis University who studies both physiology and modeling in neurons. "The assumption has been that there was a single solution and the variance was your fault," Marder says. "This paper is a beautiful example showing that we shouldn't be thinking about a single solution to capture what a neuron is doing, but a family of solutions."
—Alla Katsnelson

Two Ways to Merge

Cell membranes fuse with other membranes to allow material in and out. If incoming material includes invading viruses, that can be bad news for the cells. Until recently, the process of membrane fusion has been poorly understood. Now, a powerful computer model shows that neighboring membranes can merge in two distinct ways—a fact that was previously unknown. The work could help researchers clarify how viruses invade cells, and possibly lead to ways to fight viral infections.

"Ultimately we'd like to be able to control fusion in biological systems and induce or inhibit it for therapeutic purposes," says **Peter Kasson, PhD**, a chemistry postdoctoral scholar at Stanford University and leader of the study. This paper takes steps in that direction. "Our model helps provide an explanation for how you get these two fusion processes," he says.

Previously, scientists debated whether membranes fuse by joining directly from

their initial contact or by going through a "hemifused" halfway point, where the outside layers have merged but the insides remain separate. "We show that both could happen," says Kasson. The work was published in the August 8, 2006, issue of the *Proceedings of the National Academy of Sciences*.

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Observing two membranes combining in a lab is difficult because it happens so quickly—on the order of microseconds. Earlier models haven't represented membranes in as much detail, over such long timescales, or with as many simulations as this one does, says Kasson.

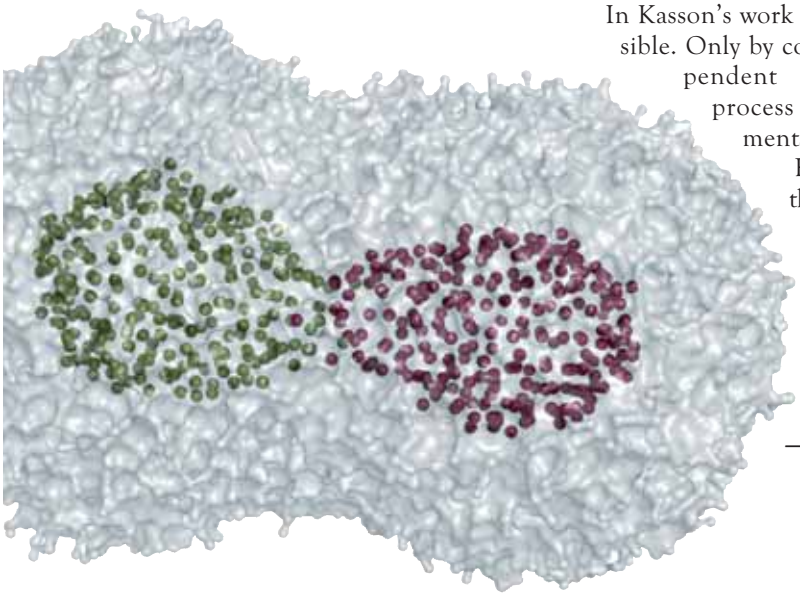
The team ran 10,000 separate simulations of membrane fusion using a distributed computing network called Folding@Home, in which people around the world donate screensaver time to biological research. In each simulation, the fusing membranes began with different starting conditions and evolved based on laws of physics and chemistry. The result: The simulated membranes merged through either of the two routes rather than exclusively through one or the other.

Erik Lindahl, **PhD**, professor of bioinformatics at Stockholm University, Sweden, thinks the project sets the pace for future work in the field. "The key thing is that they're not doing one simulation, they're doing many," he says. "In ten years nobody will publish a single simulation anymore."

Siewert-Jan Marrink, **PhD**, head of the molecular dynamics group at the University of Groningen, the Netherlands, and creator of a previous model of membrane fusion, agrees. "I do consider this work to be a significant step forward," he says. "In my original publication of the fusion process of the same system I was only able to look at a few events, but I could not tell how relevant these were. In Kasson's work this has become possible. Only by comparing many independent instances of the process can global assessments be made."

Kasson is delighted that his model explains experimental observations and can help in planning new experiments. "That's the most exciting part," he says, "when we can come full circle."

—Clara Moskowitz



As a pore forms between two vesicles, the phosphate groups from the membrane's outer leaflet (red from one vesicle, green from the other) mingle with one another in the pore region. Courtesy of Peter Kasson.

Cancer Proteins Show Off Their Networking Skills

New research suggests that cancer proteins, like influential people, have the most connections. These results, from an extensive study of how human proteins interact with one another, could help explain why cancer wreaks such havoc in cells.

"We haven't gotten to the bottom of what the increased connectivity really means, but perhaps highly connected proteins, once mutated, are more likely to cause disease," says coauthor **Paul Bates**, **PhD**, who heads the Biomolecular Modelling Laboratory at the Cancer Research UK London Research Institute. The research was published in the September 15, 2006, issue of *Bioinformatics*.

Bates and his graduate student **Pall Jonsson** built a model of the human proteome that contained more than 108,000 interactions using experimental information on proteins in other species, including yeast and worms. The typical protein can connect with a limited number of other proteins. The researchers scored the data and linked proteins known to interact, leading to a protein-protein interaction network, also known as the "interactome." Then, using information from a 2004 census of 346 human genes known to mutate in cancer, Bates and Jonsson mapped 509 human cancer proteins onto their network.

The average cancer protein was linked to 23 other proteins in the network, more than twice as many as the typical protein. By analyzing protein clusters, the researchers also found the proteins from cancer genes tend to occupy intersections between protein communities that govern crucial functions such as regulating cell growth and death. This makes sense, says Bates, as proteins that are changed by cancerous mutations tend to disrupt many cellular functions. Bates adds that understanding the network properties around these proteins could help researchers identify drug targets.

Shinichiro Wachi, a doctoral candi-