Run your fingertips across a tabletop. Is it hard? Can you feel texture? Our sense of touch gives us this information. But how? For that matter, how do we sense the gorgeous music of a symphony or the throb of an electric bass or cocktail conversation in the next room?

It may come as a surprise that for all of the above the answer is proteins. While it’s well known that hundreds of thousands of different proteins are ceaselessly busy in the body, there’s an important group we’re only recently learning about in detail. They’re called mechanosensitive channels, and they’re found in all living organisms, where they reside in the membranes that form cell walls. Like other membrane-channel proteins, MS channels open and close to provide a pathway for molecules to exit or enter the cell. The flow of ions — calcium, sodium and others — through membrane channels creates electrical signals that regulate neural and muscular activity. The special trait of MS channels, however, is their ability to open in response to mechanical stress — such as the pressure of a fingertip on a tabletop or vibrations in the air — and thereby trigger neural processes like touch and hearing.

An estimated 30 percent of the proteins in cells are membrane proteins, yet we’ve been slow to learn about them because it’s difficult to determine their structure. “While we know about 10,000 proteins,” explains biophysicist Klaus Schulten of the University of Illinois, Urbana-Champaign, “only about 20 of these are membrane proteins — a very small fraction.”

Until quite recently, none of these were MS channels. In 1998, however, structural biologists at Caltech determined the structure of a bacterial MS channel, called the bacterial large conductance mechanosensitive channel, or MscL. This groundbreaking work became the raw material that form the narrowest part of the channel is its stiffest part, in agreement with experiments. The simulation also showed that the helices that form the narrowest part of the channel are its stiffest part, in agreement with experiments measuring the flexibility of different parts of the protein.

For this first simulation of an MS channel residing in a hydrated membrane bilayer, the equilibration computation alone was so demanding that the researchers chose not to put strain on the channel-membrane system. Instead, they simulated the protein alone, applying surface tension directly to MscL. Results showed an opening of 30 Angstroms as the channel helices flattened in response to pressure, in good agreement with experimental measurements of the “conductance pore.”

Experiments have yielded valuable structure about MscL, but give no picture of how the molecular structure changes as strain on the membrane opens the channel. As a step in that direction, Schulten and his colleagues first constructed a computational model of a section of cellular membrane containing MscL. To realistically simulate the cellular environment, they “hydrated” the membrane — placing it within a bilayer of 7,387 water molecules — yielding a molecular system of 55,666 atoms.

Using the CRAY T3E, they first simulated this membrane-bilayer system with realistic conditions of temperature and pressure to allow it to “equilibrate,” to fluctuate and find its natural state. Results revealed that MscL is structurally stable in its closed state, in agreement with experiments. The simulation also showed that the helices that form the narrowest part of the channel are its stiffest part, in agreement with experiments measuring the flexibility of different parts of the protein.

“Of course, this isn’t totally satisfactory,” explains Schulten. “We wanted to do the same simulation but with stretching of the membrane.” For this, Schulten and Gullingsrud in early 2001 were among the first researchers to productively use the early model, 256-processor version of the Terascale Computing System. They rebuilt the membrane environment, to accommodate the dynamics of adding strain, with 242 lipids and 16,148 water molecules, a system of 88,097 atoms. Their pioneering, very large-scale simulation confirmed the earlier results and looked more closely at the process of channel opening. The new simulations show a staged process and show, further, that the narrowest part of the channel functions like a cork in a bottle.

“First you get the widening of the protein,” explains Schulten, “through the flattening of the helices, like an iris shutter on a camera, but the ‘cork’ is still sitting there. Then this opens up radially also, and the whole channel becomes accessible to the molecules that pass through it.” The simulations give a detailed picture of which parts of the protein move and how they move as the channel goes from open to closed, details that elaborate upon experimental data and enrich understanding of this nascent branch of protein research.

In early 2001, researchers used the prototype terascale computing system for a pioneering simulation of a mechanosensitive membrane protein.

Top and side view representation of MscL embedded in the hydrated cellular membrane. Colored rods represent helices of the ion channel, with colors corresponding to subunits of the channel’s pentameric structure. Lipid molecules (light blue strands) that form the membrane include “headgroups” (green spheres) where they meet surrounding water.

Klaus Schulten (left) and Justin Gullingsrud, University of Illinois at Urbana-Champaign. Schulten directs the Theoretical Biophysics Group at the University of Illinois Beckman Institute for Advanced Science and Technology.

This image represents the full structure of MscL, including the helices shown extending below the membrane, which form the narrowest part of the channel. Simulations show that this sub-structure functions like a cork in a bottle, blocking the channel even as strain opens other parts of the passage until the cork finally lets go and the channel fully opens.