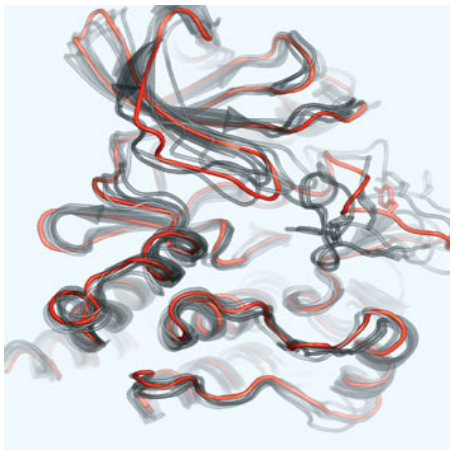
Protein Dynamics on the Supercomputer Big Screen

Now playing at a supercomputer near you: proteins in action. Scientists from Berkeley Lab and UC Berkeley are using NERSC's IBM supercomputer to simulate how protein molecules move, rotate, and fold as they carry out life's most fundamental tasks.

Although they only approximate real-life phenomena, the increasingly realistic movies are becoming useful complements to real-world experiments in helping scientists determine how proteins function. Using them, biologists can gain a better understanding of how incorrectly folded proteins lead to a range of diseases, or how other proteins synthesize adenosine triphosphate (ATP), the fuel that powers many biomolecular motors.



This simulation of a tyrosine kinase reveals how the protein changes shape.

"Proteins are very complex molecules with thousands of atoms, but they don't come with a user's manual," says John Kuriyan of Berkeley Lab's Physical Biosciences Division. "Fortunately, over the past few years, rapid increases in computing power and better simulation programs have made it possible to visualize protein dynamics like never before."

NERSC's IBM supercomputer boasts the raw power needed to develop simulations that are detailed enough to capture a protein's fastest movement, and long enough to portray their relatively infrequent but biologically important changes. In some cases, this means stringing together femtosecond-length, atom-scale snapshots of a 50,000-atom protein, frame by frame, into movies that span several nanoseconds. (A femtosecond is one-millionth of a nanosecond, and a nanosecond is one-billionth of a second.)

Although these high-resolution simulations take days to prepare even on a supercomputer, they enable Kuriyan and colleagues to test-drive proteins under a variety of conditions. They can see what happens when a protein is given just enough energy to teeter on the edge of a conformational change. Or they can prod a protein to change shape, and gauge how forcefully it resists or how readily it gives in.

So far, Kuriyan and colleagues have used NERSC simulations to learn how certain proteins, called Src tyrosine kinases, transmit signals initiated by growth factor receptors in human cells. Mutant forms of these proteins can trigger cancer. They've also simulated the conformational and energy changes that proteins involved in DNA replication must undergo in order to rapidly copy DNA strands.

In each case, the simulations furthered their understanding of protein dynamics and helped guide real-world experiments. They also underscored the need for powerful computers. The quickest motion in a protein is the stretch of the carbon-hydrogen bond, which occurs in about one femtosecond. This means that each frame of a simulation must depict a protein's movement femtosecond by femtosecond. If it doesn't, the simulation will skip over these carbon-hydrogen stretches and be as true to life as a jerky 1920s movie. But interesting changes in proteins, such as the rotation of a portion of the ATP-making enzyme, often occur in the microsecond to millisecond time scale — up to nine orders of scale slower than a femtosecond. In other words, a simulation must weave together billions of femtosecond-length snapshots in order to capture one or two rare but important changes.