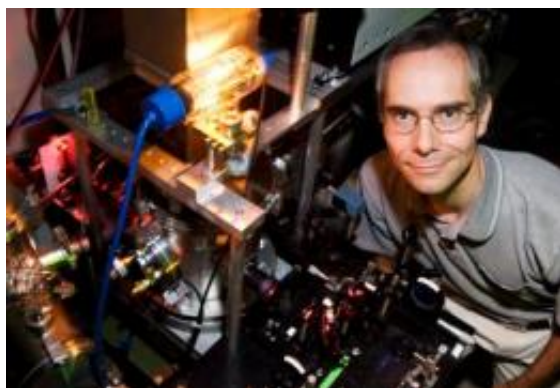


Faster protein folding achieved through nanosecond pressure jump

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Martin Gruebele, the James R. Eiszner Professor of Chemistry at the University of Illinois and corresponding author of the paper, says that prodding proteins to fold by suddenly removing high pressure (a technique also known as "pressure jumping") through electrical bursting makes for a "kindler, gentler way" of inducing proteins to fold. Credit: L. Brian Stauffer

A new method to induce protein folding by taking the pressure off of proteins is up to 100 times faster than previous methods, and could help guide more accurate computer simulations for how complex proteins fold, according to research by a team of University of Illinois scientists accepted for publication in the journal *Nature Methods* and posted on the journal's Web site May 31.

Martin Gruebele, the James R. Eiszner Professor of Chemistry at the U. of I. and corresponding author of the paper, says that prodding proteins to fold by suddenly removing high [pressure](#) (a technique also known as "pressure jumping") through electrical bursting makes for a "kindler, gentler way" of inducing proteins to fold.

"When you're increasing the pressure on something, you're squeezing the atoms and making them come closer to one another," Gruebele said, "but you're not necessarily causing the very complicated changes to the microscopic

motion that occur when you change the temperature. Pressure is a simpler variable than temperature."

In order to carry out their biomolecular functions, proteins fold from a chaotic, random coil that looks like spaghetti strands floating in boiling water to their native state as an orderly, well-defined but compact structure.

From the point-of-view of the [protein](#), Gruebele said, pressurizing it to about 2,500 atmospheres is much less disruptive than, say, cranking up the temperature by 30 degrees.

"Temperature is a pretty complicated variable in that it involves random motion at a microscopic level," Gruebele said. "When you perturb a protein by raising its temperature, its chains completely unravel, and it might take longer for it to collapse back down to the folded structure."

To induce [protein folding](#), a sample contained in a sapphire cube covered by a small steel diaphragm is pressurized to several thousand atmospheres, causing the [biomolecules](#) to unfold. A powerful electrical current then bursts the diaphragm, which releases the pressure and produces a sub-microsecond pressure drop. The proteins re-fold, and are monitored through laser-excited fluorescence.

Gruebele's electrical-bursting method also allowed for a miniaturization of the apparatus, which improved the speed and sample volume of the diaphragm design. That, in turn, allows for a better comparison between how proteins fold in vitro in the lab versus how a computer algorithm would predict how they would fold.

After the pressure is applied, the proteins were able to re-fold or "spring back" to their native-state structures "much more readily than if we had heated them and cooled them down," Gruebele

said.

Applying pressure to induce protein folding is not a novel laboratory technique. According to Gruebele, previous methods using electrically controlled valves, piezoelectric constriction and burst diaphragms weren't fast enough or didn't produce enough pressure to generate viable data on the microsecond timescale.

To reach the realm of simulation-worthy data, "you need hundreds of nanoseconds to a few microseconds worth of data-capture time," Gruebele said. With the previous methods, "we weren't close to the timeframe where you could perform computer simulations, right now or in the near future."

Ultimately, being able to feed experiment-generated data into a computer simulation will lead to better computer forecasts about how proteins fold, Gruebele said.

"By putting experiments and computer simulations together, we're going to be able to predict how proteins fold much more quickly and reliably," he said.

Gruebele, who is also a researcher at the Beckman Institute, believes that scientists will eventually be able to perform computer simulations of protein folding that are accurate enough predictors of folding so that "if you had a protein involved in a disease and its structure wasn't known, you could go to the computer and model how it behaves."

For example, when certain proteins in the brain mutate, that can lead to Alzheimer's disease, Gruebele said.

"The structures of proteins are ultimately what's responsible for their function," he said. "Changes to their structure often cause abnormal functions. That's why we want to understand protein structures, and be able to model how they change."

Gruebele said that computer simulations already yield a pretty accurate picture of a given small organic molecule. But with this new method that

breaks the microsecond barrier, "we've just opened up a whole new world of proteins for study," he said.

"There are only a handful of proteins that we know about that would fold by temperature jumps or other methods in a couple of microseconds," Gruebele said. "But there are many proteins that do it in hundreds of microseconds, and that could be sped up to a few microseconds by pressure jumps."

Gruebele said that if you want to improve computer simulations of protein folding so that they're 99.9 percent reliable - so reliable that a medical doctor could trust the results - you need many test cases. And if you need lots of test cases, you need to be able to run computer simulations quickly, Gruebele said.

"This experiment enables a greater number of proteins to be tested by simulations and experiments simultaneously, which will push forward the agenda of getting [computer simulations](#) that are more reliable and faster," Gruebele said.

Source: University of Illinois at Urbana-Champaign ([news](#) : [web](#))

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