Scientists develop new, innovative methods for characterizing proteins

October 11 2010, By Barry Ray

Using a combination of high-powered computers and advanced experimental magnetic resonance data, a Florida State University biophysical chemist has developed techniques that improve the way scientists can study and predict the structure and dynamics of proteins found in the human body. His innovations could ultimately shorten the time it takes researchers to develop new, more effective drugs and better understand biomedical processes that underlie a variety of health conditions.

The new techniques “allow us to more accurately understand protein behavior and function at all levels, how enzymes work, and how to develop drugs that bind to certain proteins,” said Rafael Brüschweiler, the George Mathew Edgar Professor in Florida State’s Department of Chemistry and Biochemistry and associate director for biophysics at the National High Magnetic Field Laboratory.

Given that there are hundreds of thousands of different proteins found in the human body, innovations such as Brüschweiler’s that can streamline their analysis and understanding are viewed as most desirable in the scientific community.

Over the past several years, Brüschweiler and his colleagues have integrated a pair of complementary but powerful tools, both of which provide detailed information about the structure and dynamics of proteins at the atomic level. Nuclear magnetic resonance (NMR) data are first collected for a particular protein that is being analyzed. (NMR is a

research tool that utilizes high magnetic fields to measure the strengths, directions and temporary fluctuations of magnetic interactions between the atoms in a protein fragment.)

Next, in a technique Brüschweiler has pioneered, high-powered computers are used to validate the NMR data in terms of their realistic representation of protein structure and dynamics, as well as to make additional predictions of those characteristics.

The computational results critically rely on the shape of the protein's "energy landscape" — the conformational space available to that protein under physiological conditions. However, due to its complexity, improving characterizations of the energy landscape is a difficult and time-consuming undertaking. In fact, until recently, a computer simulation of a single protein that represented just a microsecond took several months. Now, with the aid of the powerful computer array at Florida State's High Performance Computing Center, it takes Brüschweiler and his group only a fraction of the time it once did.

Working with a postdoctoral associate, Da-Wei Li, Brüschweiler has found a highly efficient way to directly use the NMR information for improving the protein potential. The basic idea is to "recycle" an existing simulation of an intact protein, using methods borrowed from statistical physics, for many trial potentials until the one is found that yields the best agreement with experiment. This leads to an increase in speed by a factor of 100,000 or more over previous methods. The approach is not only efficient but also permits the improvement of the protein potential directly on intact proteins, rather than on small fragments, as was the case in the past.

"This has opened up a new way of becoming increasingly quantitative in our computations, which is key in developing a predictive understanding of the functions of proteins," Brüschweiler said.

"As computers continue to become ever more powerful, 'in silico' approaches to the understanding of proteins will play in increasingly important role. However, these approaches need to be calibrated first against quantitative experimental data, which makes the combination with NMR so powerful."

A paper describing the research was recently published in the German publication *Angewandte Chemie* (Applied Chemistry), one of the world's leading peer-reviewed chemistry journals. That paper, "NMR-Based Protein Potentials," is available here.

"This is the culmination of a number of years of research on our part, so obviously we're excited about the progress we have made," Brüschweiler said. "While this is fairly basic research designed to develop a greater understanding of life at a molecular level, it opens up a range of possibilities for future advances by scientists all over the world."

"For example, it might be possible to develop and refine new drugs that target specific proteins in a certain way," he said. "Or to design new proteins that act as 'molecular machines' to perform specific functions in response to chemical stimuli."

Brüschweiler is currently in the second year of a four-year, $608,782 grant from the National Science Foundation that is helping to fund his research.

Provided by Florida State University