It’s All About Geometry: Protein Contact Surfaces Hold Key to Cures

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Your mother always told you to do your geometry homework, and for scientists seeking new treatments for diseases like Parkinson’s and Alzheimer’s, this advice turns out to be right on the mark.

In the atomic-level landscape of proteins, shape determines the all-important function of these molecules of life. For example, when a protein molecule responsible for Parkinson’s binds with the cell membrane, will a new drug candidate interrupt this interaction -- preventing disease progression and protecting the patient? It all depends on the precise geometry and energy of the protein structures.

Researcher Igor Tsigelny and colleagues at the San Diego Supercomputer Center (SDSC) and UC San Diego have developed a new tool known as MAPAS (Membrane-Associated Protein Assessments) which harnesses the power of supercomputers at SDSC and Argonne National Laboratory to study how proteins contact cell membranes. It turns out that this three-dimensional “virtual molecular world” is very good at letting researchers zoom in on key details of this all-important contact process, holding out the promise of new treatments for a wide range of devastating diseases, from Parkinson's and Alzheimer's to kidney disease and cancer.

“It’s extremely important to explore the structural details of the zone where the protein contacts the membrane so that we can understand the molecular mechanisms of disease development,” said Tsigelny. “This knowledge gives crucial guidance in selecting which among many possible compounds are most likely to do well in tests to intervene in such protein-membrane interactions and help treat these diseases.”

The researchers describe the new MAPAS tool in the February 2008 (vol. 5 no. 2) online edition of *Nature Methods*. In addition to Tsigelny, the other authors, who are all at UCSD, include Yuriy Sharikov, Ross Walker, Jerry Greenberg, Valentina Kouznetsova, Sanjay Nigam, Mark Miller, and Eliezer Masliah.

In studying a protein, the traditional approach is to crystallize it and then illuminate it with X-rays, which yields information about its three-dimensional geometry, or “protein structure.” But this method has great difficulty in identifying the key parts of a protein that will participate in membrane contact.

“That’s why it’s very important to be able to predict these protein contact surfaces theoretically, using a computer program like we’ve developed,” said Tsigelny.

In making its predictions, MAPAS starts with a simple idea from geometry. Because an individual protein molecule is so much smaller than a round cell, the cell membrane looks like a flat surface as the protein approaches it -- just as the spherical earth appears flat to a person walking on it. This approach allows the researchers to more efficiently compute the structural information they are seeking.

The MAPAS tool takes as a starting point a protein’s known three-dimensional shape, and then applies a set of scoring methods based on comprehensive Steered Molecular Dynamics calculations to predict whether this protein structure can form strong contacts with the cell membrane. If so, MAPAS goes on to identify all the flat faces or planes that make up this protein. It is these planar protein surfaces that can attach to the cell membrane, and MAPAS predicts which of these regions are most likely to bind to the membrane, based on specific protein contacts with the lipids or fats that make up the membrane.

The team has validated the performance of MAPAS by confirming that it correctly models a number of membrane-contacting proteins that are already

known.

The powerful MAPAS program with its virtual protein world is already providing important benefits in both extending basic scientific understanding of proteins and fighting disease.

“For example, without the MAPAS program we wouldn’t have been able to develop the important new model we found for Parkinson’s disease,” Tsigelny explained. He and his colleagues have already published an important advance in understanding this disease, based on computations using MAPAS. These new insights can in turn open important avenues for developing new treatments.

Added Tsigelny, “We’re also currently using MAPAS to study Alzheimer's disease mechanisms as well as molecular models of the processes involved in kidney disease and some cancers.”

The importance of the work has been recognized by a prestigious Department of Energy (DOE) Innovative and Novel Computational Impact on Theory and Experiment (INCITE) award of 1.2 million processor hours, which will allow the team to run their programs on a supercomputer at Argonne National Laboratory and extend their research on Parkinson’s disease.

The researchers are also working to create a supercomputer-powered system that unites multiple programs, including MAPAS with multiple data sources, to carry out comprehensive studies of the mechanisms in diseases involving membrane-protein connections.

Source: University of California, San Diego