biomedical and health informatics

Biomedical and Health Informatics Lecture Series

Tuesday, October 27, 2009
12:00-12:50 p.m., Room T-739

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"Dynameomics"

The goal of Dynameomics is to perform atomistic molecular dynamics (MD) simulations of representative proteins from all known folds in explicit water in their native state and along their thermal unfolding pathways. Here we present 188 fold representatives and their native state simulations and analyses. These 188 targets represent 67% of all the structures in the Protein Data Bank. Aggregate statistics are presented that show the simulation results are unbiased by fold topology or experimental origin of the structure. The behavior of several specific targets is highlighted to illustrate some of the general properties in the full data set and to demonstrate the role of MD in understanding protein function and stability. As an example of what can be learned from mining the Dynameomics database, we identified a protein fold with heightened localized dynamics. In one member of this fold family the motion affects the exposure of its phosphorylation site and acts as an entropy sink to offset another portion of the protein that is relatively immobile in order to present a consistent interface for protein docking. In another member of this family, a polymorphism in the highly mobile region leads to a host of disease phenotypes. To encourage understanding of the relationships between protein dynamics, function and disease, we have constructed a web site, complementary to the PDB, which allows access to a novel hybrid relational/multidimensional database to view and interrogate simulations of the top 30 targets: http://www.dynameomics.org. The dynameomics database should also be useful for determining the rules governing protein folding and kinetic stability, which should aid in deciphering genomic information and for protein engineering and design. This database contains both the largest collection of protein simulations and protein structures in the world.

Dr. Daggett has 23 years of experience performing simulations of proteins. She developed the approach of simulating protein unfolding to characterize the folding process. She also was the first to use simulation methods to map conformational changes associated with amyloidosis. At UW she was a founding member, and is now the Director, of the Biomolecular Structure and Design Program. She is PI of NIH, Human Frontiers of Science, Microsoft, DOE and other grants. Until very recently she was a charter member of the NIH Macro-molecular Structure and Function B Study Section. She has also evaluated grants for many other sponsors, including DOE, NAS/NRC, BBSRC, MRC, The Wellcome Trust, the Hereditary Disease Foundation and various NIH projects. Dr. Daggett is the Senior Editor of Protein Engineering Design and Selection (PEDS) and she is on several editorial boards: Biochemistry, Structure, and Biomedical Computation Review (BCR). She is co-editor of the Current Opinion in Structural Biology issues on Folding and Binding, 2007 and 2009. She was elected to the Biophysical Society Council (2007-2010), and she has organized several international meetings. Dr. Daggett has published ~160 scientific papers, which have garnered over 6000 citations.