Under TheHood

BY JENELLE BRAY, PhD

Normal Mode Analysis: Calculation of the Natural Motions of Proteins

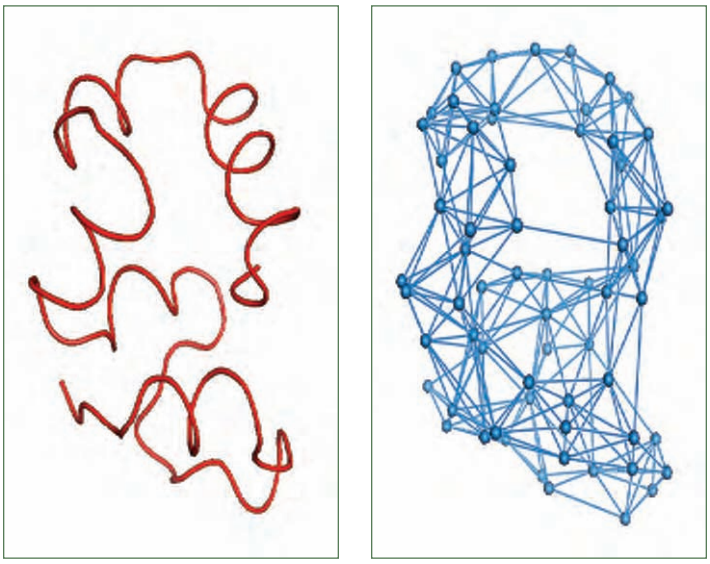
Advances in computational power and algorithms have led to longer and more accurate molecular dynamics simulations of protein folding. But these approaches, because they are computationally intensive, cannot yet be used to model conformational changes of large, already-folded proteins at biologically relevant time scales. Yet these kinds of movements are often biologically interesting: For example, understanding and predicting the conformational change a protein undergoes upon the binding of a small molecule—such as a drug—can lead to better rational drug design.

Normal mode analysis fills the gap: It can quickly reveal the overall change in the conformation of large proteins, without the need to calculate the specific molecular mechanism, such as the motion of specific bonds.

Normal mode analysis, also known as harmonic analysis, existed before the advent of computational biology and is applicable to many fields. It identifies the natural, resonant movements of a physical object, such as a building, bridge or molecule. In acoustics, a guitar string's harmonics (or overtones) are its normal modes, and the modes' corresponding frequencies are their pitches; in geology, normal mode analysis of low frequency normal seismic waves generated by large earthquakes leads to greater understanding of the deep substructures of the earth.

For proteins, normal mode analysis represents each amino acid as a bead. All pairs of beads less than a specified distance away from each other in 3-D space are connected by springs. The force constants of the springs are determined by fitting to experimental data. Once the spring constants and the masses of the atoms have been tabulated, the movement of the beads and springs can be described by a matrix version of Newton's second law of motion. Analytically solving this equation gives the protein's natural motions, called normal modes, and their associated frequencies.

A combination of the normal modes describes the motion of the protein. The biologically relevant modes are the low-frequency modes because they describe the large-scale, overall motion of the protein. Normal mode analysis does not specify which of the low-frequency modes describe most of the conformational change. However, with a small amount of experimental data, such as the change in pairwise distances between a few pairs of residues (derived from fluorescence resonance energy transfer or FRET) or in overall shape (derived from cryo-electron microscopy), the relevant modes can be determined. Then the conformational change of the protein can be predicted.



A protein shown on the left as a simple ribbon and at right in a beads and springs representation for normal mode analysis. Courtesy of Jenelle Bray.

In addition to predicting conformational changes of proteins, normal modes can be used to help solve x-ray crystallography structures or to improve protein-ligand docking calculations. Additionally, if there are two known conformations of a protein, the normal modes that contribute most to the conformational change can be calculated. Then we can use the modes to understand the pathway and to describe the conformational change in only a few degrees of freedom.

The application of normal mode analysis to proteins has given researchers an important tool for solving problems in computational biology. □

DETAILS

Jenelle Bray is a Simbios Distinguished Postdoctoral Fellow in Russ Altman's and Michael Levitt's labs. She works on the development and application of torsion angle normal mode analysis.

For more information about normal mode analysis, go to http://www.igs.cnrs-mrs.fr/elnemo

or check out a recent paper by Jenelle Bray and her colleagues: Optimized torsion-angle normal modes reproduce conformational changes more accurately than cartesian modes. Bray JK, Weiss DR, Levitt M. *Biophys J.* 2011; 101 (12): 2966-9