## Poster E-12

# A Hierarchical Approach to Predict Protein Conformational Changes in terms of Localized Rearrangements using Temporal and Spatial Constraints


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**Short Abstract:** Stability and fluctuations of non-covalent contacts (hydrogen bonds and hydrophobic contacts) within a protein play an important role in stabilizing its structure, defining its flexibility and, hence, function. Based on dynamical behavior of non-covalent contacts extracted from molecular dynamics we present an approach to predict global conformational motions.

**Long Abstract:**

Proteins are held together in the native state by hydrophobic interactions, hydrogen bonds and interactions with the surrounding solvent, whose strength as well as temporal distribution affects protein flexibility and hence its function. Typically these non-covalent interactions flicker on and off over nanoseconds, and with molecular dynamics (MD) it is possible to obtain good statistics about the variations in non-covalent interactions. Using this information from MD, we define the duty cycle for non-covalent interactions as the percentage of time for which a given interaction is present. The duty cycle can then be used as a metric for defining a topological network of rigid bonds as a graph to analyze flexibility/ rigidity patterns [1] using graph theoretical algorithm implemented in a program FIRST [2] and termed rigid cluster decomposition.

However, it is not clear to what extent the dynamics of a folded protein is facilitated by these flickering bonds and how such small-scale perturbations in the system (flickering on and off) influence the long-time-scale flexibility of the protein. In this work, we systematically analyze non-covalent bond time-dependence and the dependence of stability of such bonds on the chosen geometric criteria, and, hence, their effect on analyzing the flexibility of the protein structure using rigid cluster decomposition. We conducted our analysis by varying the duty cycle cut-offs for both hydrogen bonds and hydrophobic tethers. We observe that at longer distance cut-offs, the hydrophobic interactions tend to be fairly stable, holding the protein together, while with the shorter distance cut-off criteria hydrophobic tethers fluctuate more than hydrogen bonds.

We have also analyzed relations between energetic and geometric criteria for non-bonded contacts definitions and their respective importance for predicting allowed conformational rearrangements in proteins. Based on gathering statistics from MD simulations from different ensembles (e.g. one stable conformation of a protein) and our analyses of non-covalent interactions, we are able to correlate structural changes that are observed between different ensembles with the stability of fluctuations of a small number of non-covalent contacts. This

hierarchical modeling, where observation of localized perturbations are used to explain propagation of global changes within protein structure taking into account both geometric and energy constraints promises to be a novel approach towards coarse grain modeling. We present our approach using several proteins of different sizes as examples.

References:

1. Mamonova T., Hespenheide B., Straub R., Thorpe M. F., Kurnikova M., Phys. Biol. 2 S137-S147.
2. Thorpe M. F., Lei M., Rader A. J., Jacobs D. J., Kuhn L., 2001, J. Mol. Graph. Model, 19 60-9.