B-factor Prediction and Conformational Pathway Generation by Robust Elastic Network Model

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ABSTRACT

In computational structural biology, particularly in protein dynamics, there are two big issues: i) local thermal fluctuation represented by B-factor, which is a metric to indicate how much each atom vibrates under the assumption of harmonic oscillation, and ii) large conformational change leading biological function.

In this study, we propose a robust elastic network model (RENM) in order to better predict both B-factor and conformational pathway compared to the existing other ENMs which often fail to reproduce the experimentally observed B-factor due to their oversimplified force-fields. RENM considers not only inter-connections accused by surrounding molecules in a crystal unit cell, but also intra-connections by applying symmetric constraints based on crystal space group and mass-weighted spring constants depending on the types of amino acids and chemical bonds, respectively. Over 500 tested protein structures, RENM successfully predicts B-factors, without any additional computation burden, in better accuracy compared to those of traditional ENM.

We also apply RENM to generate conformational pathway between two metastable conformations of the same protein. Traditionally, intermediate conformations are incrementally generated by an optimization of RMSD value in the topological domain. However, in the proposed method, low-frequency normal modes, which are engaged in large conformational changes, are generated by RENM and utilized as bases of conformational change in each intermediate state. This remedy can endow the predicted pathway with better justification in terms of mechanics as well as topological constraints.

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