REGIONAL CENTRE FOR BIOTECHNOLOGY
Seminar series

Computing the relative stabilities and the per-residue components in protein conformational changes

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Abstract

Protein molecules often undergo conformational changes, say from A to B. In order to get insights about the forces that drive such changes, it would be useful to have a method that computes the per-residue contributions to the *conversion free energy* $\Delta G = G_B - G_A$. I will describe a method that I call ``Confine-Convert-Release (CCR), which imposes and releases constraints on a protein molecule using thermodynamic integration in molecular dynamics simulations. The method is applicable to large conformational changes, such as between completely different folds. As validation, I will show that CCR correctly predicts the stable states of several ``chameleon'' sequences, which are at cusps of conformational change and that have previously been challenging for molecular simulations. And, I will show using examples of Critical Assessment of Protein Structure Prediction (CASP) experiments that CCR can often discriminate the native protein structure from its non-native or misfolded states. The per-residue free-energy (PRFE) components of ΔG allow us to ``reverse-engineer'' the known design principles of the chameleon proteins, implying that PRFEs can also give insights into natural driving forces. This opens up the possibility for systematic improvements in structure-prediction scoring functions, in the design of protein conformational switches, and in interpreting protein mechanisms at the amino-acid level.