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Multi-scale modelling of macromolecular conformational changes

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Modelling protein flexibility and plasticity is computationally challenging but important for understanding the function of biological systems. Furthermore, it has great implications for the prediction of (macro) molecular complex formation. Recently, coarse-grained normal mode approaches have emerged as efficient alternatives for investigating large-scale conformational changes for which more accurate methods like MD simulation are limited due to their computational burden.

We have developed a Normal Mode based Simulation (NMSim) approach for efficient conformation generation of macromolecules. Combinations of low energy normal modes [1] are used to guide a simulation pathway, whereas an efficient constraints correction approach is applied to generate stereochemically allowed conformations. Non-covalent bonds like hydrogen bonds and hydrophobic tethers and phi-psi favourable regions are also modelled as constraints.

Conformations from our approach were compared with a 10 ns MD trajectory of lysozyme. A 2-D RMSD plot shows a good overlap of conformational space, and rms fluctuations of residues show a correlation coefficient of 0.78 between the two sets of conformations. Furthermore, a comparison of NMSim simulations starting from *apo* structures of different proteins show that ligand-bound conformations can be sampled for those cases where conformational changes are mainly correlated, e.g., domain-like motion in adenylate kinase. Efforts are currently being made to also model localized but functionally important motions for protein binding pockets and protein-protein interfaces using relevant normal mode selection criteria and implicit rotamer basin creation.

References

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