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PHD THESIS PROPOSAL

MODELING THE FLEXIBILITY OF PROTEINS

Context. Protein functions are often associated with large amplitude - low frequency conformational changes, since such changes allow them to switch between active and inactive conformations. From a modeling perspective, predicting these changes requires addressing two problems. The first one is concerned with the exploration of the energy landscape of the system under scrutiny, for which various methods, typically based on molecular dynamics or Monte Carlo based simulations, have been developed [Wal03, JCPC11]. The second one, given a collection of conformations generated by one of these exploration methods, consists of modeling the kinetics and dynamics of the system studied, which account for the aforementioned large amplitude conformational changes [Wal03, RZMC11, NAKH14]. Both problems benefit from the ability to compare conformational ensembles and sampled energy landscape, a problem to which we recently contributed [CDM+15, CM15].

Goals. This PhD thesis will focus on two goals. First, we shall design novel algorithms to sample energy landscapes. The goal will be to improve state-of-the art algorithms such as basin hopping and transition based rapidly growing random trees. Second, we shall leverage the exploitation of sampled energy landscapes, with more accurate thermodynamic and kinetic descriptions (improved basin descriptions, improved collective coordinate designs). Validations will be carried out on simplified protein models, and on flexible antibody - antigen complexes.

Background. Master degree in Theoretical computer sciences or Applied mathematics or Biophysics or Structural bioinformatics.

References

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[NAKH14] L. Nedialkova, M. Amat, I. Kevrekidis, and G. Hummer. Diffusion maps, clustering and fuzzy markov modeling in peptide folding transitions. *J. Chem. Phys.*, 140, 2014.

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