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All-Atom Simulation of Protein Folding and Direct Validation Against Time-Resolved Spectroscopy Experiments.

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The theoretical characterization of a protein folding process requires to overcome three main formidable challenges. First, the transition path ensemble for the folding reaction has to be accurately sampled. Next, the reactive trajectories generated by computer simulations have to be post-processed, in order to identify the kinetically relevant meta-stable states. Finally, this structural information needs to be translated into predictions for experimental observables, to enable experimental validation.

In this talk, I discuss how these three major steps can be tackled by means of a specific combination of path integral-based enhanced sampling algorithms and approximation schemes [1], Renormalization Group-based statistical analyses [2], and excited-state quantum chemical calculations (required to connect molecular dynamics with time-resolved spectroscopy experiment) [3].

For illustration purposes, we report on applications of this scheme to predict the time-resolved single-molecule FRET and ensemble near-UV CD signals for the folding of several proteins consisting of several hundreds of amino-acids, using a realistic all-atom force field. Depending on time availability, we will also report about the application on the same scheme to simulate the interconversion between the cellular prion protein PrP-C into aggregates of the pathogenic scrapie isoform PrP-Sc [4].

References

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[3] A. Ianeselli, S. Orioli, G. Spagnolli, P.Faccioli, L. Cupellini, S. Jurinovich, B.Mennucci, J. Am. Chem. Soc.140, 3674 (2018)

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