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Plenary Invited | Invited Talk

Systematic Identification of Order Parameters in Biophysical Systems

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Cooperative couplings between degrees of freedom in biophysical systems lead to effective dimensionalities far less than the $3N$-dimensional coordinate space of the N constituent atoms , suggesting that the underlying dynamics of the system may be characterized by a relatively small number of order parameters. This effective reduction in dimensioanlity has been framed as a separation of timescales, whereby the fundamental dynamics reside in a "slow subspace" to which the other degrees of freedom are slaved . Geometrically, the slow subspace may be considered a - possibly highly convoluted - low-dimensional hypersurface, termed the "intrinsic manifold", to which the dynamics are effectively constrained. In this work, we apply a nonlinear dimensionality reduction technique known as the *diffusion map* [1] to systematically extract the intrinsic manifolds, and good order parameters with which to parameterize them, for a variety of systems of biophysical relevance.

N-Alkane chains in water are well-studied systems of interest to the biophysical community as models for the role of hydrophobicity in protein folding . We have conducted solvated and ideal-gas phase simulations of C_8, C_{16} and C_{24} n-alkane chains, and applied diffusion maps to the simulation trajectories to extract approximately three-dimensional intrinsic manifolds. In the case of C_8, we find the dihedral angles to be good order parameters with which to describe transitions between local free energy basins. For the longer chains, we extract three global order parameters describing the underlying dynamics: the degree of chain collapse, the location of a bend in the chain and the handedness of the chain helicity. The dynamic relevance of the intrinsic manifolds furnished by the diffusion map approach allowed us to determine the low-free energy collapse pathway for solvated n-alkanes to proceed by a "kink and slide" mechanism.

Over 100ns of replica exchange molecular dynamics simulations of the linearized form of the 21-residue antimicrobial "lasso" peptide MicrocinJ25 (proMccJ25) in explicit solvent were conducted, and diffusion maps applied. We determined two global order parameters for the dynamics, well-correlated with the Glu8 Ψ angle and the identity of the residue at the β-hairpin turn, and identified three distinct folding pathways from the global free energy minimum: hydrophobic collapse, folding into a left-handed lasso, or formation of an "unwrapped lasso". Interestingly, although the peptide spontaneously adopts a left-handed lasso conformation, the native peptide - in which the lasso is covalently "sealed" in place by a post-translational modification enzyme - has a right-handed topology. These results suggest a role for the maturation enzymes, or leader sequence of the peptide precursor, in facilitating the folding process.

[1] Coifman, R. R., et. al., *Proc. Natl. Acad. USA* **102**, 7426 (2005).