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Adaptive Biasing Force Method for Vector Free Energy Calculations

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The adaptive biasing force method is an efficient technique to compute the potential of mean force along a reaction coordinate and for alchemical transformations. We present recent developments of the method for vector free energy calculations (i.e. for several reaction coordinates or for multiple alchemical transformations). General formulas are derived and their relative merit is discussed. In particular, many techniques require the ability to calculate second order derivatives and are therefore cumbersome to implement for complex reaction coordinates. We present new formulations requiring first derivatives only. Our approach will be compared with other popular techniques such as metadynamics. Application examples will be provided for simple examples, such as alanine dipeptide, and a more advanced one: the insertion of an amphipathic helix inside a cell membrane. For the latter, we will examine the stability of the inserted peptide relative to the interfacial configuration and its role in the association of individual peptides into larger multimeric structures, such as cellular channels. Our candidate for studies is the synthetic peptide $(LSLLLSL)_3$. It was shown experimentally that, in the presence of an electric field, the orientation changes from parallel to the membrane to perpendicular and the location of the center-of-mass (COM) changes from the membrane surface to the center of the lipid bilayer. Experimental results, however, provide no information about stability of individual helices in the transmembrane orientation. We will present results on the free energy surface of insertion of $(LSLLLSL)_3$ as a function of two coordinates: the distance of the COM of the peptide to the center of the membrane and the orientation of the helix relative to the membrane surface. Our results show that there is a global minimum corresponding to the parallel orientation at the water-membrane interface. The transmembrane arrangement of a single peptide is only metastable, i.e. it corresponds to a local minimum.