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Strategies for the exploration of free energy landscapes: unity in diversity and challenges ahead

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Computer simulations play an important role in the study of transformation processes of condensed matter, including phase transitions, chemical reactions, and conformational changes of biomolecules. In principle, atomic trajectories, such as those generated using the molecular dynamics approach, contain detailed structural, thermodynamic, and kinetic information about activated processes. In practice, due to free energy barriers, there is often a wide gap between the time scale of the transformation and the time scale accessible with simulations. This review offers a practical guide to the ingenious methods aimed to accelerate the exploration and reconstruction of free energy landscapes of complex systems. The focus is on basic unifying concepts, successful strategies, and pitfalls, illustrated with examples of application to scientific problems from different disciplines. The current challenges in the field consist mainly in the cumbersome identification of optimal reaction coordinates and in the extensive recourse to expert human supervision and fine tuning of the algorithms. The full achievement of wide-spectrum formulations and easy reproducibility of results would constitute the breakthrough necessary to enter the era of routine use of enhanced sampling simulations.

Keywords: activated processes, rare events, free energy landscapes, enhanced sampling, molecular dynamics