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From Biased Trajectories to Local Mobility: Residence Times as a Route to Diffusivity

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A molecular trajectory contains a detailed record of motion, but turning that record into a position-dependent diffusivity is far from straightforward. In heterogeneous systems, observed motion reflects both local mobility and free-energy-driven drift, which must be disentangled when the dynamics are reduced to a single transport coordinate. Established methods either alter the dynamics through harmonic confinement or introduce choices involving lag times, spatial discretization, regularization, parametrization, or the long-time limits of noisy correlation functions.
I will present a residence-time approach for determining position-dependent diffusivities directly from biased molecular trajectories [1]. Once an adaptive bias has approximately removed the free-energy gradient along the transport coordinate, local diffusivities can be inferred from mean first-exit times out of finite spatial intervals. The estimator requires no additional restrained simulations, kinetic model fitting, or correlation-function extrapolation. Because residence-time observations are strongly correlated, blocking analysis provides statistically consistent uncertainty estimates.
The method is assessed for systems of increasing complexity: oxygen diffusion in a liquid slab, water permeation through a fluid phospholipid bilayer, and transport of water and volatile organic compounds through a highly ordered skin-barrier model. The latter is particularly demanding because slow structural relaxation and long-lived membrane asymmetries complicate both free-energy and diffusivity calculations [2,3]. In the liquid slab, the inferred diffusivities recover independent bulk values within statistical uncertainty. In the membrane systems, they undergo a more stringent test through propagator-level validation: the diffusivity profiles are combined with the free-energy landscape to predict time-dependent probability distributions, which are compared directly with molecular trajectories.
These results show how residence-time statistics can turn enhanced-sampling trajectories into spatially resolved descriptions of molecular mobility. The talk will examine the assumptions behind this reduction, where it succeeds, and how its validity can be tested rather than presumed.

References

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