Modeling Diffusion and Permeation Across the Stratum Corneum Lipid Barrier

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Human skin is a complex, multilayered organ of millimeter thickness. Its barrier function resides almost completely in the topmost layer, the stratum corneum (SC).[1] We investigate the barrier against chemical permeation in the SC lipid matrix by employing atomistic, force-field-based molecular dynamics (MD) simulations.

We carried out our study on the short periodicity phase (SPP)[2] of the SC lipid bilayer. As conventional MD simulations cannot sample permeation through lipid bilayers due to high free-energy barriers, we employ a range of enhanced sampling techniques, including umbrella sampling and metadynamics. Nevertheless, extensive sampling on microsecond timescales is necessary to converge potentials of mean force in all of these techniques.[3]

We present various structural and dynamical metrics that require long-timescale sampling, such as lipid flip-flop events that lead to long-lived asymmetries. We determine position-dependent diffusivities using two complementary analyses based on the same set of simulations and evaluate their accuracy through propagator analysis. [4] The two approaches provide upper and lower bounds for the true diffusivity, which, when combined with free-energy profiles, yield permeabilities relevant for modeling macroscopic skin transport.

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