DRUG DISCOVERY THROUGH THE COMPUTATIONAL MICROCALORIMETER. EFFICIENT DETERMINATION OF STANDARD BINDING FREE ENERGIES AND MEMBRANE PERMEABILITIES.

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One of the grand challenges of rationale drug design is the prediction of the affinity of potential therapeutic agents for a given protein target. This challenge is in large measure rooted in the considerable changes in configurational entropy that accompanies the binding process, which atomistic simulations cannot easily sample. Two strategies relying upon alchemical transformations, on the one hand, and geometric transformations, notably potential of mean force calculations, on the other hand, are proposed, invoking a series of geometric restraints acting on collecting variables designed to alleviate sampling limitations inherent to classical molecular dynamics simulations. I will show through the example of a protein binding a small substrate, that both strategies, however of clearly different nature, can yield nearly identical standard binding free energies within chemical accuracy. I will further show how the methodology can be seamlessly transposed to protein-protein complexes. I will also outline current strategies to estimate binding entropies from such calculations. Downstream from the prediction of binding affinities is the challenging prediction of bioavailability. To estimate the permeability of the biological membrane to a drug candidate, an approach based upon Bayesian inferences, which reconciles thermodynamics and kinetics in molecular dynamics simulations with time-dependent biases, is put forth. Performance of the method is illustrated with prototypical permeants diffusing in a homogeneous lipid bilayer.

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