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MemCross, a robust computational tool to evaluate membrane permeation coefficients of drug-like molecules

Membrane crossing events are key in the pharmacokinetics of xenobiotics. Among them, passive permeation is the most ubiquitous. Therefore, an accurate and cost-effective prediction of permeation coefficient (logP_{erm}) is highly valuable. Among the theoretical methods to predict logP_{erm}, all-atom molecular dynamics simulations are versatile and can provide an accurate description of all intermolecular interactions. However, the cost associated with the required sampling often limits to the study of a few small permeants.
Here, we present MemCross, a tool based on the inhomogeneous solubility-diffusion model and the Accelerated Weight Histogram (AWH) method, and which takes subdiffusion into account. We report the first use of AWH on all-atom membrane simulations. The ease of use of MemCross and its relatively fast convergence allowed to benchmark it on more than 350 xenobiotics (mostly drugs) for which experimental logP_{erm} are available. We believe this is the largest study performed with drug-like database, while performing all-atom MD simulations, totaling more than 1.2 millisecond of simulation time. A very good correlation was obtained with experimental logP_{erm} of PC-based liposomes (R^2 = 0.83). Thus, MemCross is a flexible and affordable tool to evaluate logP_{erm} of xenobiotics, while providing an atomistic description of the permeation process.

Session

Computational methods

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