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Computational insight to observed collective phenomena of lipid membrane permeation

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The permeation of a substance through the phospholipid bilayer is a key factor in drug transport to its site of action. This ability is quantitatively expressed as a permeability coefficient and can be experimentally determined using various methods. One such is a liposomal leakage assay.

In previous experiments[1], this assay was used to measure the permeability of 5(6)-carboxyfluorescein (CF), taking advantage of its self-quenching properties at high concentrations. However, when another drug molecule was encapsulated in liposomes alongside the CF, its permeation profile changed. This was unexpected, as permeability of a molecule was so far determined solely by the phospholipid bilayer and the molecule itself.

These results indicate that the presence of an additional molecule type alters the permeability of CF, potentially due to interactions between the drug and CF or between the drug and the phospholipid membrane. Such interactions may either facilitate or hinder the passive transport of CF, thereby influencing the overall permeability profile. To gain deeper insight into the molecular mechanisms underlying these observations, we employed molecular dynamics (MD) simulations, which are widely used in contexts where understanding atomic-level interactions is crucial, such as in molecular docking.

Our MD simulations have so far explored interactions between the drug and the lipid membrane or CF and the lipid membrane. These simulations were conducted under a heating and cooling protocol designed to mimic conditions during molecular loading. The results have provided insights into the tendency of the drug molecule to incorporate into the lipid bilayer and its propensity for molecular clustering—both of which will help explain experimentally observed phenomena.

[1] Odehnalová, K.; Balouch, M.; et al. Liposomal Copermeation Assay Reveals Unexpected Membrane Interactions of Commonly Prescribed Drugs. *Molecular Pharmaceutics* **2024**, *21/6*, 2673–2683. DOI: 10.1021/acs.molpharmaceut.3c00766.