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Molecular simulation of nonfacilitated membrane permeation

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ABSTRACT

This is a review.
Non-electrolytic compounds typically cross cell membranes by passive diffusion. The rate of permeation is dependent on the chemical properties of the solute and the composition of the lipid bilayer membrane. Predicting the permeability coefficient of a solute is important in pharmaceutical chemistry and toxicology. Molecular simulation has proven to be a valuable tool for modeling permeation of solutes through a lipid bilayer. In particular, the solubility-diffusion model has allowed for the quantitative calculation of permeability coefficients. The underlying theory and computational methods used to calculate membrane permeability are reviewed. We also discuss applications of these methods to examine the permeability of solutes and the effect of membrane composition on permeability. The application of coarse grain and polarizable models is discussed. This article is part of a Special Issue entitled: Membrane Proteins edited by J.C. Gumbart and Sergei Noskov.

1. Introduction

One function of a biological membrane is to serve as a barrier between the cytosol and extracellular environment [1–3]. Intracellular compartments like mitochondria, the nucleus, etc., are also enclosed by membranes. The primary component of these membranes is amphiphilic lipids. These lipids consist of a polar or ionic headgroup and a tail that is comprised of one or more hydrocarbon chains. The hydrophilicity of the headgroups and the hydrophobicity of the tails cause the lipids to spontaneously self-assemble into planar bilayers where the headgroups face the solution and the tails form a hydrophobic interior layer.

Solutes crossing the membrane must pass through the nonpolar lipid tail region of the membrane. Compounds that are more soluble in bulk water than they are in the nonpolar membrane interior will tend not to partition into the membrane. This simple mechanism allows these thin bilayers (~40–50 Å thick) to provide an effective barrier for highly water-soluble compounds like ions and sugars. In pure lipid bilayers, the rates of permeation of these species are very low. In biological membranes, rapid permeation of these compounds can be facilitated by membrane proteins like channels or transporters [4–6].

Two distinct mechanisms have been proposed for permeation in the absence of a protein facilitator: passage through a transient water pore and direct permeation through the membrane [7]. Rare fluctuations in the bilayer structure can form transient water pores that allow ionic compounds to cross the bilayer while still solvated by water. This avoids the high thermodynamic penalty for dehydrating the ion. The second mechanism applies to non-electrolytic solutes, which can permeate directly through the membrane. This review will focus on molecular simulations of this second mechanism.

Many non-electrolytic compounds can permeate directly through the membrane because there is a significant probability for them to partition into the interior of the membrane. These compounds are generally only moderately soluble in aqueous solutions due to the lack of strong electrostatic interactions with water molecules. The London dispersion attractions between these solutes and the lipid tails can be competitive to their interactions with water, so the thermodynamic penalty for these compounds to enter the interior of the membrane is attenuated or even eliminated. To varying degrees, these compounds can undergo direct permeation without facilitation by a transmembrane protein.

The rate of permeation of a solute across a membrane is defined by its flux (J), which gives the number of molecules that cross a unit area of the membrane per unit time (e.g., μmol/s/cm^2). The flux is the product of the concentration gradient of the solute across the membrane (ΔC) and the permeability coefficient (P_m),

$$J = P_m \cdot \Delta C. \quad (1)$$

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P_m depends on the type of permeating solute, the membrane composition, and the conditions of permeation that occurs under e.g., temperature. It has units of distance per unit time and is commonly reported in cm/s. For a constant set of conditions and membrane composition, the permeability coefficient provides a measure of the intrinsic membrane permeability of a solute. P_m is therefore the standard experimental and computational measure of the permeability of a solute.

1.1. Experimental determination of permeability

A variety of experimental techniques are used to determine permeability coefficients. One of the most general techniques uses a planar bilayer separating two cells. A concentration gradient is created between the two cells and the change in concentration is measured after a time interval. Several techniques have been used to measure the solution concentrations, including radiolabeling [8], UV–vis spectroscopy [9], and LC–MS [10].

The concentration of electrochemically-active species can be measured by selective microelectrodes near the surface of the membrane. In some cases, the electrode measures the permeating species directly (e.g., the permeation of K^+ [11]). Weak acids and bases typically permeate in their neutral, conjugate form, but their permeation can be measured by microelectrodes that detect the ionic forms that are formed in the solution at the surface of the membrane. For example, the permeability of ammonia has been measured by ammonium-selective electrodes [12]. Similarly, the permeation of many weak acids has been measured by pH-sensitive microelectrodes that detect the small changes in pH at the surface of the membrane [13,14]. H_2O_2 permeability has been determined by an O_2-selective electrode by measuring concentrations of O_2 formed by the reduction of H_2O_2 inside the cell [15,16].

Magnetic resonance techniques can be used to study the permeability of certain solutes. Electron paramagnetic resonance (EPR) can be used to measure the permeability of solutes with unpaired electrons, such as NO [17–19] and O_2 [20,21]. This technique is particularly powerful because the rate of diffusion at different depths within the membrane can be measured. ^1H and ^{17}O nuclear magnetic resonance (NMR) has also been used to measure the rate of water permeation. Water molecules that permeate into a liposome containing paramagnetic metal complexes (e.g., Mn(II), Ln(III), or Gd(III)) will undergo a rapid spin relaxation, allowing the rate at which water molecules cross the membrane to be determined [22].

Fluorescence spectroscopy can be used to measure the permeability of solutes that affect fluorophores loaded inside liposomes. The transmembrane permeation of protons was measured by the change in fluorescence of pyranine, a pH-sensitive dye [11]. Water permeability has been calculated from the increase in self-quenching of carboxyfluorescein as the volume of the liposome decreases in response to osmotic pressure [23]. The permeation of the fluorophore itself can also be measured if the fluorescence is affected by the contents of the liposome. For example, the permeation of tetracyclines was measured by the observation of the enhanced fluorescence of a Tet-repressor-bound tetracycline inside a liposome [24]. The rate of permeation of aromatic-containing acids, like salicylic acid, into liposomes has been measured by monitoring the fluorescence of Tb^{3+}-carboxylate complexes [25].

One limitation to permeability measurements using liposomes is that stopped-flow devices are often used to create the concentration gradient between the solution and the interior of the liposome. Pohl and coworkers noted that the mixing time associated with this technique means that they cannot be used to study very fast rates of permeation and are restricted to solutes where $P_m < 10^{-2}$ cm/s [26].

These techniques have a range of capabilities and limitations. Simple planar-bilayer cells can be used across a range of solutes, provided that permeation is slower than the solution mixing time. Liposomes loaded with fluorescent reporters can also be used with slowly-permeating solutes that can be measured by fluorescence spectroscopy. Microelectrode methods can be used when the concentration of the solute can be measured electrochemically or can be measured indirectly by a change in an equilibrium (e.g. pH), although this can involve complicated kinetic models due to multi-species equilibria and unstirred layers at the membrane–water interface [27,13,28]. Magnetic resonance methods, like EPR and NMR, can only be used for select solutes. The challenges associated with experimental permeability measurements have encouraged the development of molecular simulation methods that can support experimental results and provide insight into trends in permeability.

1.2. Permeability models

Understanding the relationship between the chemical properties of the solute and its permeability is important for predicting the toxicity and pharmacokinetics of a compound [29–31]. Models for predicting membrane permeability date back well over 100 years; publications by Meyer in 1899 and Overton in 1901 established the relationship between high rates of nonfacilitated membrane permeation and the hydrophobicity of the solute [32,33]. Walter and Gutknecht quantified this observation by showing that there is strong linear correlation between the log of the permeability coefficient and the log of water–alkane partition coefficients for a wide range of neutral solutes [34]. This supports the Meyer–Overton rule that the rate of permeation is proportional to the relative solubility of the solute in the apolar membrane interior vs an aqueous solution.

Several experimental and theoretical models have been developed to predict permeability [35–37,29,30], with varying degrees of success, but the advent of computer simulations have led to the most significant developments. Molecular simulation methods for lipid bilayers have made it possible to study the permeation of solutes without direct empirical inputs. These simulations have provided atomic-scale interpretations of these data and quantitative interpretations of permeability trends in terms of the solution thermodynamics and dynamics. Empirically-based principles of permeation like the Meyer–Overton rule can now be interpreted within a rigorous physical framework. This review presents some of the research on the simulation of nonfacilitated permeation over the last 20 years. Interested readers may also be interested in a recent review by MacCallum and Tieleman on simulations of small molecules interacting with lipid bilayers [38] and a review by Orsi and Essex on modeling permeability [39].

2. Development of the solubility-diffusion model

To develop a quantitative theory for nonfacilitated permeation, the membrane is described as a fluid environment that the permeant passes through by Brownian motion. This model is consistent with direct molecular dynamics simulations of membrane permeation. Fig. 1 shows the trajectory of a O_2 molecule permeating through a DPPC bilayer. The solute undergoes an effectively random walk along the z-axis before exiting the opposite side of the membrane. The solute also undergoes significant lateral motion inside the bilayer in the xy plane, but a rate theory can be developed based on the net flux (J) of the solute along the z-axis alone.

The dynamics of the solute are complicated by the inhomogeneity of the bilayer, which varies in chemical composition and density along the transmembrane axis, z. In the inhomogeneous solubility-diffusion model, both the solute diffusivity ($D(z)$) and potential of mean force (PMF, $w(z)$) vary as a function of the position of the solute along the z axis. $w(z)$ is related to the solubility of the solute at z, $K(z) = \exp(-w(z)/k_BT)$, so this model is commonly referred to as the solubility-diffusion model.

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