Membranes, Ions, and Water at the Molecular Level

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The function of biomembranes is not restrict-
ed to surrounding a cell and its various com-
partments as inert separation layers. By
facilitating transport of molecules from one
side to the other, they play also an active
role. Membranes are composed of a complex
mixture of various lipids and proteins, with the
lipids forming a bilayer. Our aim is to understand
biomembranes in terms of the self-organization of
these constituents. The experimentally accessible informa-
tion about the molecular architecture of membranes is very
limited. Therefore, we use molecular dynamics simulation
techniques to study the cooperative processes underlying the
mesoscopic properties of membranes. As a first step, we
model membranes as lipid bilayers.

Membranes and Ions

A biomembrane in vivo is surrounded by an aqueous solution
containing ions. The most abundant atomic monovalent ions
are potassium (K^+), sodium (Na^+), and chloride (Cl^-). Sodium
and potassium can be specifically adsorbed at membranes as
indicated from various experimental and simulation studies,
the membrane affinity being somewhat higher for Na^+ than
for K^+. In order to model interactions of ions with a mem-
brane, a reliable force field is required but a force field for K^+
in conjunction with the widely used simple point charge (SPC)
model for water has not been available.

We have derived a force field for K^+ matching activity
coefficients of aqueous KCl solutions for a wide range of con-
centrations, as shown in **Fig. 1 [1]**. The figure also shows that
the solution activities of other force fields significantly devi-
ate from the experimental values. Our force field for KCl is
shown to also reproduce the experimental binding constant
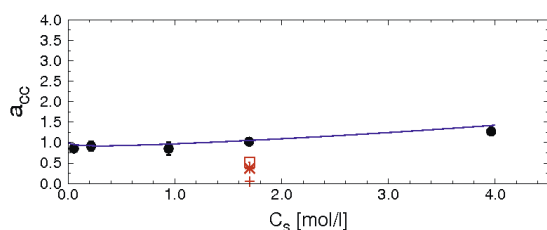for the adsorption of K^+ at a POPC bilayer as shown in **Fig. 2 [2, 3]**.

Fig. 1: Activity derivative of aqueous KCl solutions as a function of the
molar KCl concentration **[1]**. The line shows a fit to the experimental
data, the black circles indicate the results for our KCl force field with
simple point charge (SPC) water, and the red symbols show the results
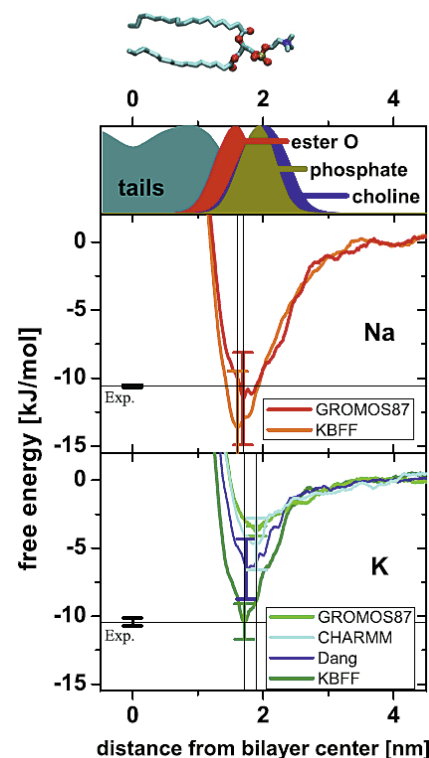for force fields from the literature.

Fig. 2: Free energy as a function of the distance of sodium or potassium
from the center of a POPC bilayer for different ion force fields **[2]**. The
horizontal lines show the experimental adsorption free energies (Exp.)
[3] for the respective cation chloride. The distribution of various atomic
groups normal to the bilayer and a representative lipid configuration are
shown as a reference.

In contrast, models used in previous simulation studies are
found to underestimate the membrane affinity of K^+, thus
exaggerating the difference between Na^+ and K^+. Our simula-
tions support the view that ion adsorption at PC membranes
is driven by an entropy gain due to the release of hydration
water from the ions and the lipids.

The interaction of ions with membranes also affects the
tendency of membranes to fuse with one another, a key step
in intracellular traffic, viral infection, and liposome-mediated
drug delivery. The latter is achieved by pH-responsive lipo-
somes. One important component of such systems is choles-
teryl hemisuccinate (CHEMS) being negatively charged and
forming stable liposomes above pH 6 and being neutral
below pH 5 where it becomes fusogenic. Our MD simulations
explain this behavior showing strong binding of counterions
to anionic CHEMS and counterion release for neutral CHEMS

as shown in **Fig. 3**. Counter ion release is found to correlate with a decrease in the effective headgroup size known to promote fusion **[4]**.
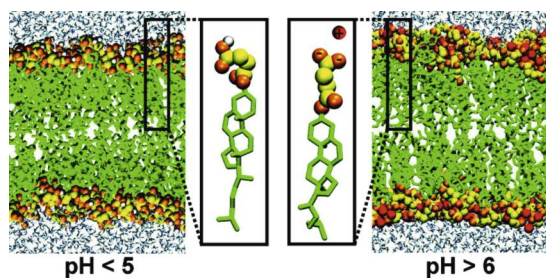

Fig. 3: Cutout cross sections of hydrated CHEMS bilayers in (left) proto-nated state and (right) deprotonated state with sodium, the insets show-ing individual CHEMS molecules **[4]**.

Membrane Fusion

The fusion of two membranes requires the approach of the membranes, the latter being hindered by strong repulsive hydration forces. We have computed the hydration forces between two POPC bilayers using a coarse grained model and get good agreement with experimental values. Our results suggest that, unlike suggested previously, the direc-tionality of hydrogen bonds between the lipids and water, not described in our model, is not essential for the occurrence of hydration forces **[5]**.

Once two membranes are close to each other, the hydra-tion forces can be circumvented by the formation of small defects which can lead to the formation of so-called "stalks" between the two bilayers formed by multiple lipids. Our sim-ulations show that such defects are related to the exposure of hydrophobic lipid tails to the water, as shown in **Fig. 4 [6]**. Peptides derived from the fusion hemagglutinin fusion pro-tein of the influenza virus and denoted as fusion peptides, known to induce membrane fusion in vitro, do not accelerate stalk formation and even increase the hydration forces, thus not facilitating fusion kinetically. However, they can stabilize stalk-pore complexes thermodynamically as shown by self-assembly, leading to a new, so-called simple cubic phase, induced by the peptides **[7]**. We do find that fusion peptides strongly stabilize membrane nanopores, in good correlation with experiments. Even in the absence, though, membrane nanopores are kinetically stabilized by a small energy barrier, as we have revealed from atomistic simulations **[8]**.
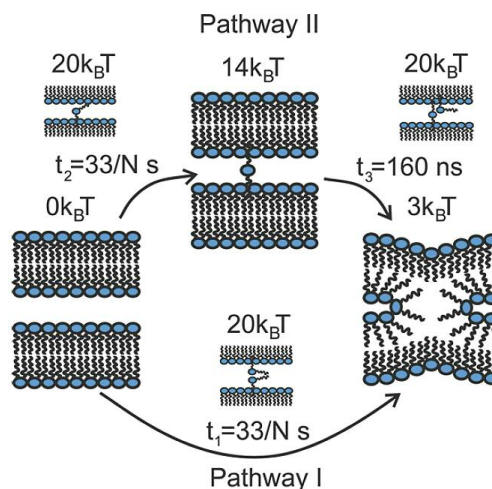

Fig. 4: Early membrane fusion energetics and kinetics for two POPC bilayers separated by five waters per lipid **[6]**. *The symbol N denotes the number of lipids in the proximate leaflets.*

Electrokinetic Phenomena

Hydrophobic surfaces in water are widely believed to adsorb hydroxide (OH^-) ions. This is suggested by the fact that oil droplets in water exposed to an electric field move as if they were negatively charged (i.e., they exhibit negative elec-trophoretic mobilities). However, we have performed MD simulations using an all-atom polarizable potential reproduc-ing the sign and the size of the electrophoretic mobilities of oil in water although ions were absent, as indicated in **Fig. 5 [9]**. The underlying mechanism is related to the polarization of the water and the oil at the interface. Our results may help to resolve a current controversy concerning the charge of hydrophobic surfaces in water. Interestingly, non-classical electrokinetic phenomena - in the form of charge inversion - also occur in biology, playing a role in the function of kidney and related diseases **[10]**.
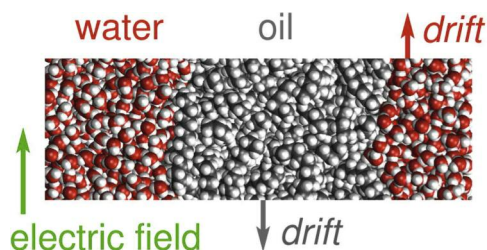

Fig. 5: An electric field applied parallel to a water/oil interface induces a tangential movement between the phases **[9]**. *The effect requires a suf-ficiently detailed model describing not only the water but also the oil in full atomic detail and using a polarizable interaction potential.*

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