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Replica Ornstein–Zernike Theory Applied for Studying the Equilibrium Distribution of Electrolytes across Model Membranes

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Abstract

By means of replica Ornstein–Zernike theory (supplemented in a few cases by Monte Carlo simulations) we examined the distribution of an annealed primitive model +1:–1 electrolyte in a mixture with uncharged hard spheres, or another model +1:–1 or +2:–1 electrolyte inside and outside the quenched vesicles, decorated by a model membrane, and across the membrane phase. We explored the influence of the size and charge of the annealed fluid on the partition equilibrium, as well as the effect of the vesicle size and membrane interaction parameters (repulsive barrier height, attractive depth, and membrane width). A hydrophobic cation, present in the mixture with NaCl, slightly enhanced the concentration of sodium ions inside the model vesicle, compared to pure NaCl solution. The replica theory was in good agreement with computer simulations and as such adequate for studying partitioning of small and hydrophobic ions or hydrophobic solutes across model membranes.

Graphical Abstract

INTRODUCTION

The transport of substances across lipid membranes is of vital importance for the biological processes.¹ In a living cell, membranes separate different areas and allow for selective permeability of various substances in a passively or actively regulated transport within and

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across the membrane. A membrane therefore represents a barrier, separating the interior of a given cell from its surroundings, or within the cell between different vesicles and organelles, and the separation/transport capability is responsible for many cellular processes.^{2,3} Membranes are of great technological interest as well, in particular the synthetic membranes with chemically tailored pores are being prepared with the purpose of protein separation and water transport.^{4–8} They are of tremendous importance in separation processes, such as reverse osmosis in the water desalination technology.^{9–11} The mechanism for molecular transport across membranes can be either active or passive. Although the active transport requires an input of energy, the passive transport is entropy-driven and is simply nonspecific diffusion process of the molecules across a membrane.¹

Due to low dielectric constant of the lipid bilayer (most oils and hydrocarbons have dielectric constant in the range 2–5)¹² the free energy barrier for small ions like sodium or potassium to diffuse across such a membrane is as high as 40 kcal/mol.¹² Their transport across the membrane is therefore facilitated by the ion channels, special proteins that are responsible for ion, as well as water, trans-membrane conductivity.^{8,13} The properties of lipids and membrane proteins are mutually adjusted to perform specific functions, one of them being to maintain the asymmetric profile of sodium and potassium ions inside and outside the cell regulating diverse physiological phenomena of our nerve system.^{13,14} Special cases of charged species penetrating through the lipid membrane are hydrophobic (organic, lipophilic) ions, such as uncouplers of oxidative phosphorylation, valinomycin, nonactin, triphenylalkylphosphonium nitroxides, and similar species.¹⁵ The membrane conductivity for these ions is several orders of magnitude larger than that of small ions. These lipid-soluble ions further increase the conductivity of the small ions across the membrane as well.¹⁶ To explain the transport mechanism of ions and other small molecules across the membrane is one of the more important questions concerning the biological, as well as synthetic, membranes. Several experimental as well as computer simulation studies of the phenomena have been performed, the exact process still not being completely understood.^{1,4–8,13,14,16–18}

One of the possibilities to study the membrane equilibrium is to consider the equilibrium between outside and inside aqueous environment of the membrane, taking into account the membrane–solute interaction potential.^{12,15,16,19–22} In the case of charged species, this interaction combines a repulsive electrostatic energy term with an attractive hydrophobic energy term, to give potential wells (binding sites) near the membrane interface and a potential barrier in the interior of the membrane^{12,23} (Figure 1). The energy barrier depends on the solute species and can be estimated using simple electrostatic models.¹² Such an approach, although not giving an insight into the mechanism of the transport through the membrane, enables the application of various theories of inhomogeneous fluids to be applied to study this phenomena, the results of which are much faster to be obtained than those of computer simulations. The results of such calculations, however, provide useful information about how different membrane potentials influence the composition of the solution inside the cell or a vesicle, compared to the one in the bulk. Because the advances in technology allow the synthetic membranes to be custom-made to have an appropriate permeability for a particular solute this information is crucial.^{1,6,8,17}

An analytical function mimicking the membrane–solute potential has been proposed by Bracamontes et al. in 1999.²³ The authors used replica Ornstein–Zernike (ROZ) theory to study the distribution of neutral species inside a spherical vesicle surrounded by a membrane-like wall. They have shown that the results critically depend on the membrane width, as well as on the chemical potential in the system. A similar method was later applied to study the membrane equilibria of a single primitive model electrolyte.²⁴ In neither case was the membrane selectivity considered. Here we propose to systematically study the influence of the membrane parameters on the distribution of solute species in a multicomponent systems (electrolyte mixtures or electrolyte in a mixture with uncharged component) across the membrane. As before, we use the ROZ method, applying it to the membrane model of Bracamontes et al.²³ The methodology is first tested by comparing the results with those from new computer simulations, whereas in the second part of the paper we present the results for different systems studied.

THE MODEL

A porous system, composed of a random disordered matrix of quenched particles within which an annealed fluid can be distributed, is called a quenched–annealed system. The quenched and the annealed phase are the two subsystems that are for a given temperature, size of the system, and the total number of particles in a given state of equilibrium. We used such a model system to study the partitioning of a model annealed electrolyte or uncharged particles across the membrane of the quenched model vesicles.

A primitive model electrolyte was used to describe the annealed salt solution. The ions were modeled as hard spheres (diameters of cations and of anions being $\sigma_+^{(1)}$ and $\sigma_-^{(1)}$, respectively) having a nominal charge of $z_+^{(1)}$ or $z_-^{(1)}$ in their centers. The solvent was a dielectric continuum with relative permittivity ϵ_r . The pair interaction potential between two ions i and j separated by a distance r was

$$\beta U_{ij}^{(11)}(r) = \begin{cases} \infty & \text{for } r < (\sigma_i^{(1)} + \sigma_j^{(1)})/2 \\ \frac{z_i^{(1)} z_j^{(1)} \lambda_B}{r} & \text{for } r \geq (\sigma_i^{(1)} + \sigma_j^{(1)})/2 \end{cases} \quad (1)$$

where $\beta = 1/(k_B T)$ (k_B is Boltzmann constant and T is temperature of the system) and $\lambda_B = e_0^2 / (4\pi\epsilon_r\epsilon_0 k_B T)$ is the Bjerrum length. Considering electrolyte mixtures, the two electrolytes had the same type of anions and different cations.

The neutral annealed component was modeled as an uncharged ($z_n^{(1)} = 0$) hard-sphere particle with the diameter $\sigma_n^{(1)}$. Interaction pair potential between two such particles or between the uncharged particle and an annealed ion was that of a hard-sphere fluid, i.e., ∞ for $r < (\sigma_i^{(1)} + \sigma_n^{(1)})/2$ and 0 elsewhere ($i = +, -, \text{ or } n$).

The quenched phase was a random disordered hard-sphere subsystem, composed of spherical particles of diameter $\sigma^{(0)}$. The pair interaction potential used to generate such subsystem was $U^{(00)}(r) = \infty$ for $r < \sigma^{(0)}$ and 0 elsewhere.

The quenched phase particles served as a model vesicles. A model membrane potential was used to describe the interaction between the annealed ions or neutral component and the particles of the quenched disordered phase. The pair potential between particle i of the annealed phase ($i = +, -, \text{ or } n$) and the particle of the quenched phase, $U_i^{(10)}$, was given by

$$U_i^{(10)}(r) = 4\epsilon_i \frac{U_0^i - (U_0^i + \epsilon_i) \left(\frac{\sigma^{(0)}/2 - r}{w_i} \right)^6}{4\epsilon_i + (U_0^i + \epsilon_i) \left(\frac{\sigma^{(0)}/2 - r}{w_i} \right)^{12}} \quad (2)$$

Here, ϵ_i represents the depth of the attractive part of the potential, U_0^i is the height of the barrier, and w_i is the half-width of the barrier (Figure 1).

In the present work, we examined a size symmetric case of the annealed fluid ($\sigma_+^{(1)} = \sigma_-^{(1)} = \sigma_n^{(1)} = 4.25 \text{ \AA}$), and size asymmetric cases (model hydrophobic cation with $\sigma_+^{(1)} = 8.5 \text{ \AA}$, model Na^+ with $\sigma_{\text{Na}^+}^{(1)} = 3.87 \text{ \AA}$, model Ca^{2+} with $\sigma_{\text{Ca}^{2+}}^{(1)} = 7.03 \text{ \AA}$, and model Cl^- with $\sigma_{\text{Cl}^-}^{(1)} = 3.62 \text{ \AA}$. Nominal charges of cations were $z_+^{(1)} = +1$ or $+2$ and of anions $z_-^{(1)} = -1$. The neutral component was uncharged $z_n^{(1)} = -1$. Two different vesicle sizes were examined with hard-sphere diameters of $\sigma^{(0)} = 26$ and $120 \text{ \AA}$. The parameters of the potential function (2) were $\beta U_0^+ = 65, 4.5, 1.6$, or 0.5 , $\beta U_0^- = 45$ or 3.2 , and $\beta U_0^n = 4.5$ $\beta \epsilon_+ = 0.03$ or 0.001 , $\beta \epsilon_- = 3.0$ or 0.1 , and $\beta \epsilon_n = 0.001$, $w_+ = 3$ or $9 \text{ \AA}$, $w_- = 2$ or $6 \text{ \AA}$, and $w_n = 3 \text{ \AA}$.

REPLICA ORNSTEIN–ZERNIKE THEORY

The distribution of particles of the quenched subsystem is given by the radial distribution function (RDF), $g^{(00)}(r)$, of a system of hard spheres with diameter $\sigma^{(0)}$ and molar concentration $c^{(0)}$. The RDF was obtained by solving the one-component Ornstein–Zernike integral equation²⁵

$$h^{(00)}(r_{12}) = c^{(00)}(r_{12}) + \int c^{(00)}(r_{13}) \rho^{(0)} h^{(00)}(r_{32}) d\mathbf{r}_3 \quad (3)$$

in the Percus–Yevick (PY) closure.^{25,26} In eq 3 $h^{(00)}(r) = g^{(00)}(r) - 1$ is the total correlation function, $c^{(00)}(r)$ is the direct correlation function, and $\rho^{(0)}$ is the number density of the quenched particles ($\rho^{(0)} = c^{(0)} N_A$, where N_A is the Avogadro number).

Function $h^{(00)}(r)$ is an input parameter for the replica Ornstein–Zernike theory, used here to describe our quenched–annealed system. The so-called replica Ornstein–Zernike (ROZ) equations are in the k -space written as^{27,28}

$$\mathbf{H}^{(10)} = \mathbf{C}^{(10)} + \mathbf{C}^{(10)} * \boldsymbol{\rho}^{(0)} \mathbf{H}^{(00)} + \mathbf{C}^{(11)} * \boldsymbol{\rho}^{(1)} \mathbf{H}^{(10)} - \mathbf{C}^{(12)} * \boldsymbol{\rho}^{(1)} \mathbf{H}^{(10)} \quad (4)$$

$$\mathbf{H}^{(11)} = \mathbf{C}^{(11)} + \mathbf{C}^{(10)} * \boldsymbol{\rho}^{(0)} \mathbf{H}^{(01)} + \mathbf{C}^{(11)} * \boldsymbol{\rho}^{(1)} \mathbf{H}^{(11)} - \mathbf{C}^{(12)} * \boldsymbol{\rho}^{(1)} \mathbf{H}^{(21)} \quad (5)$$

$$\mathbf{H}^{(12)} = \mathbf{C}^{(12)} + \mathbf{C}^{(10)} * \boldsymbol{\rho}^{(0)} \mathbf{H}^{(01)} + \mathbf{C}^{(11)} * \boldsymbol{\rho}^{(1)} \mathbf{H}^{(12)} + \mathbf{C}^{(12)} * \boldsymbol{\rho}^{(1)} \mathbf{H}^{(11)} - 2\mathbf{C}^{(12)} * \boldsymbol{\rho}^{(1)} \mathbf{H}^{(21)} \quad (6)$$

where the symbol $*$ is used to denote the convolution. For an annealed subsystem with three different particle types the functions $\mathbf{H}^{(\alpha\beta)}$ and $\mathbf{C}^{(\alpha\beta)}$ are 3×3 matrices of the total $\left(h_{ij}^{(\alpha\beta)}\right)$ and direct $\left(c_{ij}^{(\alpha\beta)}\right)$ correlation functions, respectively, and have the general form

$$\mathbf{F}^{(\alpha\beta)} = \begin{bmatrix} f_{ii}^{(\alpha\beta)} & f_{ij}^{(\alpha\beta)} & f_{ik}^{(\alpha\beta)} \\ f_{ji}^{(\alpha\beta)} & f_{jj}^{(\alpha\beta)} & f_{jk}^{(\alpha\beta)} \\ f_{ki}^{(\alpha\beta)} & f_{kj}^{(\alpha\beta)} & f_{kk}^{(\alpha\beta)} \end{bmatrix} \quad (i, j, k = +, -, \text{ or } n \text{ for } \alpha, \beta = 1 \text{ or } 2) \quad (7)$$

whereas $\mathbf{H}^{(00)}$ is a 3×3 single-entry matrix with the element $h^{(00)}$ at position (1, 1), and $\mathbf{H}^{(10)}$ ($\mathbf{C}^{(10)}$) is a 3×3 matrix with a nonzero first column with elements $h_i^{(10)}$ ($c_i^{(10)}$).

Similarly, the matrix $\mathbf{H}^{(01)}$ has a nonzero first row with row elements $h_i^{(01)}$ ($i = +, -, \text{ or } n$). In eqs 4–6 $\boldsymbol{\rho}^{(1)}$ is the number density diagonal matrix of the annealed phase particles

$$\boldsymbol{\rho}^{(1)} = \begin{bmatrix} \rho_i^{(1)} & 0 & 0 \\ 0 & \rho_j^{(1)} & 0 \\ 0 & 0 & \rho_k^{(1)} \end{bmatrix} \quad (i, j, k = +, -, \text{ or } n) \quad (8)$$

and $\boldsymbol{\rho}^{(0)}$ is the number density single-entry matrix with the element $\rho^{(0)}$ at position (1, 1).

The HNC closure was used when eqs 4–6 were solved, i.e.

$$c^{(\alpha\beta)}(r) = \exp[-\beta U^{(\alpha\beta)}(r) + t^{(\alpha\beta)}(r)] - 1 - t^{(\alpha\beta)}(r) \quad (\alpha, \beta = 0 \text{ or } 1) \quad (9)$$

$$c^{(12)}(r) = \exp[t^{(12)}(r)] - 1 - t^{(12)}(r) \quad (10)$$

where $t^{(\alpha\beta)} = H^{(\alpha\beta)} - c^{(\alpha\beta)}$. For the ion-ion correlation terms, a renormalization of the total and direct correlation function into a short and long-ranged terms is required and was described elsewhere.^{29–31}

When the ROZ equations were solved numerically, a direct iteration on a equidistant grid of 2^{15} points was used (real space interval $r = 0.005 \text{ \AA}$ for $\sigma^{(0)} = 26 \text{ \AA}$, and $r = 0.01 \text{ \AA}$ for $\sigma^{(0)} = 120 \text{ \AA}$).

MONTE CARLO SIMULATIONS

To obtain the RDFs for a given system, we used Monte Carlo (MC) computer simulations in the canonical ensemble. A standard Metropolis sampling algorithm was applied.³² We implemented the periodic boundary condition, and the electrostatic interactions were treated by the Ewald summation technique.^{32,33}

First, the quenched subsystem was generated in a separate run. Twelve (12) hard spheres with hard-sphere diameter $\sigma^{(0)} = 26 \text{ \AA}$ were randomly (no overlap) inserted one by one into a cubic simulation box with edge length $L = 99.878 \text{ \AA}$. The molar concentration of the particles was therefore $c^{(0)} = 0.02 \text{ mol dm}^{-3}$. Next, 3×10^8 canonical MC particle displacements were performed, and the final distribution was taken as a quenched matrix.

Into such a matrix, particles of the annealed fluid were inserted one by one into random positions (no overlap) of the simulation box of volume L^3 . For a +1:–1 electrolyte the number of cations and anions was 60, respectively, and for a +2:–1 electrolyte it was 60 and 120, respectively. The number of uncharged particles was 60. The molar concentration of a given salt or of the uncharged component was therefore $c^{(1)} = 0.1 \text{ mol dm}^{-3}$. The system was equilibrated over 5×10^7 MC displacement moves, and the statistics was afterward collected over $(3–5) \times 10^8$ moves.

Several different realizations of the quenched phase were tested, but the RDFs were same within the statistical error.

RESULTS AND DISCUSSION

All presented results apply to model aqueous solutions, characterized by the dielectric permittivity of water at $25 \text{ }^\circ\text{C}$, resulting in a Bjerrum length being equal to $\lambda_B = 7.14 \text{ \AA}$. The concentration of the electrolyte(s) and of the uncharged hard-sphere component, comprising the annealed fluid mixture, were equal to 0.1 mol dm^{-3} . In all cases the concentration of the

quenched particles with hard-sphere diameter of $\sigma^{(0)} = 26$ was 0.02 mol dm^{-3} and for $\sigma^{(0)} = 120 \text{ Å}$ it was $2 \times 10^{-4} \text{ mol dm}^{-3}$.

Comparison of the ROZ Theory with Computer Simulations.

We begin our discussion by comparing the results of the replica Ornstein–Zernike (ROZ) theory with the canonical Monte Carlo (MC) computer simulation results. We considered two different compositions of the annealed fluid: (i) The annealed fluid was a mixture of a restricted primitive model (RPM) +1:–1 electrolyte with uncharged hard spheres, and (ii) a +1:–1 RPM electrolyte was in a mixture with a +2:–1 RPM electrolyte. The concentration of each annealed component (electrolyte(s) and uncharged) was 0.1 mol dm^{-3} . All annealed particles had the same diameters ($\sigma_+^{(1)} = \sigma_-^{(1)} = \sigma_n^{(1)} = 4.25 \text{ Å}$) and were equilibrated at 25 °C ($\lambda_B = 7.14 \text{ Å}$) with a random disordered quenched subsystem of hard spheres ($\sigma^{(0)} = 26 \text{ Å}$, $\rho^{(0)} = 0.02 \text{ mol dm}^{-3}$). In Figure 2 we present the distribution of the annealed fluid species within the spherical vesicle surrounded by the model membrane (cf. eq 2). The width and depth of the membrane barrier were the same for the cations and for the uncharged component ($\beta U_0^+ = \beta U_0^n = 4.5$, $w_+ = w_n = 3 \text{ Å}$, and $\beta \epsilon_+ = \beta \epsilon_n = 0.001$, respectively) whereas for the anions it was $\beta U_0^- = 3.2$, $w_- = 2 \text{ Å}$, and $\beta \epsilon_- = 0.1$.

In Figure 2a the radial distribution functions between such a vesicle and an ion (cation and anion) and uncharged species are shown. The ROZ theory results are shown with lines, and the MC computer simulations results are shown as symbols. We see that ROZ results are in excellent agreement with the exact MC results for this case. In Figure 2a we see that cations (red) and uncharged component (black) are almost completely excluded from the membrane (centered at $\sigma^{(0)}/2 = 13 \text{ Å}$), whereas a very small portion of anions (blue) can reside inside the membrane phase. The parameters for the membrane barrier height of cations and anions were selected to resemble the ratio given in ref 12 for small ions (Figure 2C therein). The fact that the energetic barrier is approximately 1.4 times larger for cations than for anions is reflected in a small probability to find anions inside the vesicle membrane. Small anions exhibit an attractive well at the boundaries of the membrane (i.e., interior and exterior membrane interfaces), whereas for cations this well is extremely shallow (Figure 2C of ref 12). For this reason the parameters of eq 2 were selected so that $\epsilon_-/\epsilon_+ = 100$. We see that the model lipid barrier has a higher probability for adsorption of anions than cations and/or uncharged component representing the solvent. Going away from the membrane interface, the RDF values for anion–vesicle get lower than those for cations/uncharged component. The profiles of RDFs for cations and uncharged component are very similar. A somewhat higher probability for the uncharged component close to the membrane interface is observed compared to the case for the cations. At equilibrium the concentrations of all the annealed fluid components are increased compared to the exterior of the vesicles.

A more stringent test for the theory is in the case where an +1:–1 electrolyte was mixed with a divalent salt. In Figure 2b we therefore compare the matrix-annealed component RDFs for both cation types ($z_+^{(1)} = +1$ or $+2$) and for the anions ($z_-^{(1)} = -1$). Again, all particles were of equal sizes (diameter of 4.25 Å) and the concentration of both electrolytes was 0.1 mol dm^{-3} . We see that even for divalent ions the theory gives good results compared to the MC

simulations. Changing the uncharged component for a +2:−1 electrolyte does not affect the distribution of the +1:−1 electrolyte significantly; the RDFs for the anions are somewhat higher in the case where uncharged component is present because the uncharged component does not screen the ion–ion interactions. As a result, the RDFs of the +1 charged cations in systems with uncharged component are somewhat lower than in the presence of a +2:−1 electrolyte.

The quality of the agreement was similar for other cases studied, and the comparison will be hereafter omitted due to clarity of presentation. We have to stress that numerical convergence of the ROZ equations is much faster than the simulation time needed to obtain good statistics (especially in the interior of the model vesicle). Also, ROZ theory is appropriate for studying the cases of larger vesicles where simulations are difficult to carry out, because larger simulation boxes are required. The advantage of the theory is also when higher concentrations of the annealed and/or quenched components are studied.

Influence of the Ion Charge and Size and of the Barrier Height and Width on the Membrane Partitioning.

We ask ourselves next how the charge of the annealed particle influences the distribution of that particle with respect to the model membrane. We show in Figure 3 the RDFs for a system of annealed +1:−1 RPM electrolyte ($\sigma_+^{(1)} = \sigma_-^{(1)} = 4.25 \text{ \AA}$) in a mixture with (i) uncharged hard-sphere component ($\sigma_h^{(1)} = 4.25 \text{ \AA}$), (ii) same +1:−1 RPM electrolyte, and (iii) +2:−1 RPM electrolyte. The ROZ results for the distribution of uncharged component and of +1 and +2 charged cations with the vesicles are presented, and namely for three different model membranes. In Figure 3a the membrane potential interaction parameters were the same as described above (the barrier height, width, and depth were equal for all cations and uncharged components). As seen in Figure 2, anions ($z_-^{(1)} = -1$) are preferentially distributed on both sides of the membrane interfaces. Increasing the charge of the species that is in a mixture with that +1:−1 RPM electrolyte from 0 to +2 decreases the height of the RDF peak corresponding to the membrane interfaces. Comparing the uncharged and +1 charged particles shows this difference in RDFs is small, but quite more expressed in the case of +2 charged cations. Note, however, that the y -axis scale is enlarged in Figure 3 compared to that in Figure 2. The probability to find a +2 charged cation in the center of the vesicle is larger from the probability to find +1 charged ion or uncharged component. The presence of the vesicles has a rather long-ranged influence on the annealed fluid—the RDFs approach unity only after approximately 40 Å away from the vesicle center (i.e., 24 Å away from the outer membrane surface).

Figure 3b shows the distribution of the same particles, but in the case where the model vesicles were much larger, i.e., $\sigma^{(0)} = 120 \text{ \AA}$ ($c^{(0)} = 2 \times 10^{-4} \text{ mol dm}^{-3}$). Although the distributions of the particles at the membrane interfaces are qualitatively similar as in the case of smaller vesicles, the inhomogeneity is less pronounced, and the concentration of the species inside the vesicles does not depend on its charge. The distribution of the differently charged species becomes even smoother if the membrane width increases (Figure 3c: $w_+ = 9$

Å and $w_- = 6$ Å). In this particular case the humps showing the increased concentration of divalent cations at the membrane interfaces disappear completely.

To test the influences of the particle size, we show in Figure 4 the matrix-annealed fluid RDFs for an annealed +1:−1 RPM electrolyte ($\sigma_+^{(1)} = \sigma_-^{(1)} = 4.25$ Å) in a mixture with (i) same +1:−1 RPM electrolyte (continuous line) or (ii) an +1:−1 electrolyte having twice larger cations, i.e., $\sigma_+^{(1)} = 8.50$ Å (dashed line). Such ions can be considered hydrophobic.^{15,34} Both electrolytes have the concentration of 0.1 mol dm^{-3} and anions with diameter $\sigma_-^{(1)} = 4.25$ Å. RDFs for the cations are shown in Figure 4. Here, as in the case of different charge, the same three different membrane cases were examined. We see that there is a larger probability for larger cations to be distributed closer to the membrane interfaces. Far away from the membrane, the probability of finding larger cations in small vesicles becomes smaller than the probability of finding smaller cations (Figure 4a). Larger cations have smaller surface charge densities than smaller cations with the same nominal charge ($z_+^{(1)} = +1$ in our case). Decreasing the surface charge density of the ion results in a higher probability to find its place closer to the membrane interface (cf. Figure 3). In the case of larger vesicles (Figure 4b,c), there is no pronounced influence of the cation size to its concentration within the vesicles, suggesting that the confinement plays an important role defining the concentration profile.

For a mixture of two +1:−1 RPM electrolytes with a common anion, we tested the influence of the membrane barrier height, U_0^+ , on the distribution of cations. Here, all annealed particles were of equal sizes ($\sigma_i^{(1)} = 4.25$ Å), and the concentration of the electrolyte components was 0.1 mol dm^{-3} . In Figure 5 we show the RDFs for the case where $\beta U_0^+ = 4.5$ or 1.6. Other membrane parameters were the same as already described. Lowering the energetic barrier of the ion increases the probability to find that ions within the membrane (dashed line). Because a part of that component is distributed within the barrier, the equilibrium concentration of it inside the vesicle (and close to the outer side of the membrane interface) gets lower compared to the case where the membrane-ion barrier height is larger.

Influence of the Hydrophobic Ions on the Distribution of a Model NaCl Solution across the Membrane.

As already stated in the Introduction, the membrane conductivity for hydrophobic ions is several orders of magnitude larger than that of small ions, and their presence further increases the conductivity of the small ions across the membrane as well.¹⁶ To test the ability of our model to describe this phenomena, we calculated the distribution of sodium and chloride model ions across the model membrane with and without the hydrophobic ions being present. Hydrophobic (lipophilic) ions such as, for example, tetraphenylboron anion (TPB[−]) or tetraphenylphosphonium cation (TPP⁺) are rather bulky. Estimates for the diameter of TPB[−] and TPP⁺ range from 8.4 Å¹⁵ up to almost 11 Å.³⁴ Our model for a hydrophobic cation was therefore a +1 charged hard sphere with a diameter of $\sigma_{h,t}^{(1)} = 8.5$ Å.

For model Na^+ and Cl^- the ion diameters that produce results in good agreement with the experimental thermodynamics properties (osmotic and mean activity coefficient) of aqueous NaCl solutions were selected,^{35–37} namely, $\sigma_{\text{Na}^+}^{(1)} = 3.87 \text{ \AA} \left(z_{\text{Na}^+}^{(1)} = +1 \right)$ and $\sigma_{\text{Cl}^-}^{(1)} = 3.62 \text{ \AA} \left(z_{\text{Cl}^-}^{(1)} = -1 \right)$. The parameters for the membrane potential (eq 2) were chosen with approximate accordance to data given in ref 12: for sodium and chloride ions (small ions) the parameters were $\beta U_0^{\text{Na}^+} = 65$, $\beta U_0^{\text{Cl}^-} = 45$; $\beta \epsilon_{\text{Na}^+} = 0.03$, $\beta \epsilon_{\text{Cl}^-} = 3.0$; and $w_{\text{Na}^+} = 20 \text{ \AA}$, $w_{\text{Cl}^-} = 15 \text{ \AA}$, and the parameters for the hydrophobic cation were $\beta U_0^{\text{h},+} = 0.5$, $\beta \epsilon_{\text{h},+} = 3.0$, and $w_{\text{h},+} = 15 \text{ \AA}$. Counterions to the hydrophobic cations were Cl^- . The concentrations of both electrolytes were 0.1 mol dm^{-3} and of the vesicles of diameter $\sigma^{(0)} = 120 \text{ \AA}$ it was $2 \times 10^{-4} \text{ mol dm}^{-3}$.

The results for the equilibrium distribution of Na^+ in solutions with pure annealed NaCl (dashed line) and when NaCl was in a mixture with a +1:–1 electrolyte having a hydrophobic cation (continuous line) are shown in Figure 6a, whereas the distribution of Cl^- is given in Figure 6b. Shown with dotted lines is the RDF for the vesicle–hydrophobic cation interaction. Although our model cannot mimic the transport through the membrane (the concentration of a certain species within the membrane is determined mostly by its potential barrier), one can see the influence of the presence of the hydrophobic cation on the concentration of the sodium chloride within the vesicle. The hydrophobic cation causes the concentration of the sodium cation within the vesicle to slightly increase (the value of the RDF for Na^+ close to the vesicle center is larger when the hydrophobic ion is present in the annealed electrolyte solution; Figure 6a). Within our model, this can be explained as follows: due to the much smaller potential barriers of hydrophobic ions compared to those of small ions, the hydrophobic cations get adsorbed within the membrane (the RDF is approximately 0.5 within the membrane; see dashed line), causing the chloride counterions to adsorb on both membrane interfaces to partially neutralize the positive charge of the membrane (Figure 6b). These negatively charged chloride ions now electrostatically attract positively charged sodium ions, causing their concentration within the vesicles to increase.

CONCLUSIONS

We presented a simple model of membrane equilibrium that can be theoretically studied by replica Ornstein–Zernike integral equation theory which is, compared to computer simulations, relatively fast and free of statistical errors. At the same time, the theory gives excellent agreement with the Monte Carlo computer simulations. We showed that by adjusting the membrane potential parameters, one can regulate the relative concentrations of different annealed species within the membrane surrounded vesicles and across the membrane itself. As such, the model combined with the presented theory can serve as a guide for tuning the parameters for synthetic membranes. Unfortunately, the model itself does not provide the direct link to the experimental factors that would actually results in the appropriate membrane potential.

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Figure 1.

Schematic representation of the annealed-quenched fluid potential function, eq 2, centered at $\sigma^{(0)}/2$, and the meaning of parameters ϵ_i , U_0^i , and w_i . Index i designates the identity of the annealed fluid particle $i = +, -, \text{ or } n$.

Figure 2.

Vesicle-annealed fluid RDFs for a system with +1:-1 RPM electrolyte in a mixture with (a) uncharged component or (b) +2:-1 RPM electrolyte. Lines denote the ROZ results, and symbols show MC data: circles denote +1 cations, squares -1 anions, and triangles uncharged component or +2 cations. All particles of the annealed phase were of equal size, $\sigma_i^{(1)} = 4.25 \text{ \AA}$, and the concentrations of electrolyte and uncharged component were 0.1 mol dm^{-3} . The concentration of the quenched phase ($\sigma^{(0)} = 26 \text{ \AA}$) was $c^{(0)} = 0.02 \text{ mol dm}^{-3}$. Membrane potential parameters were $\beta U_0^+ = \beta U_0^n = 4.5$, $\beta U_0^- = 3.2$; $w_+ = w_n = 3 \text{ \AA}$, $w_- = 2 \text{ \AA}$; $\beta \epsilon_+ = \beta \epsilon_n = 0.001$, $\beta \epsilon_- = 0.1$ (Schematic representation of the annealed-quenched fluid

potential function, eq 2, centered at $\sigma^{(0)}/2$, and the meaning of parameters U_0^i , w_B and ϵ_i are given in Figure 1.) All apply to the aqueous solution at 25 °C ($\lambda_B = 7.14$ Å).

Figure 3.

Vesicle-annealed fluid RDFs for a system with +1:−1 electrolyte in a mixture with uncharged (dotted line) component, +1:−1 (dashed line) or +2:−1 (continuous line) RPM electrolyte ($c_n^{(1)} = c_{el}^{(1)} = 0.1 \text{ mol dm}^{-3}$). All particles of the annealed phase were of equal size, $\sigma_+^{(1)} = \sigma_-^{(1)} = \sigma_n^{(1)} = 4.25 \text{ Å}$. The concentration of the quenched phase was $c^{(0)} = 0.02 \text{ mol dm}^{-3}$, and the vesicle sizes were $\sigma^{(0)} = 26 \text{ Å}$ (panel a), or the concentration was $2 \times 10^{-4} \text{ mol dm}^{-3}$ for $c^{(0)} = 120 \text{ Å}$ (panels b and c). $\beta U_0^+ = 4.5, \beta U_0^- = 3.2$; $\beta \epsilon_+ = 0.001, \beta \epsilon_- = 0.1$. Panels a and b: $w_+ = 3 \text{ Å}, w_- = 2 \text{ Å}$. Panel c: $w_+ = 9 \text{ Å}, w_- = 6 \text{ Å}$. All apply to aqueous solution at 25 °C ($\lambda_B = 7.14 \text{ Å}$).

Figure 4.

Vesicle-annealed fluid RDFs for a system with +1:−1 RPM electrolyte in a mixture with the same +1:−1 RPM electrolyte (continuous lines) or with a size asymmetric +1:−1 primitive model electrolyte (dashed lines). The concentration of both electrolytes was $c_{\text{el}}^{(1)} = 0.1 \text{ mol dm}^{-3}$. All anions of the annealed phase were of equal size $\sigma_-^{(1)} = 4.25 \text{ Å}$, and the cations were $\sigma_+^{(1)} = 4.25$ (continuous lines) or 8.50 Å (dashed lines). The concentration of the quenched phase was $c^{(0)} = 0.02 \text{ mol dm}^{-3}$, and the vesicle sizes were $\sigma^{(0)} = 26 \text{ Å}$ (panel a), or the concentration was $2 \times 10^{-4} \text{ mol dm}^{-3}$ for $\sigma^{(0)} = 120 \text{ Å}$ (panels b and c). $\beta U_0^+ = 4.5$,

$\beta U_0^- = 3.2$; $\beta \epsilon_+ = 0.001$, $\beta \epsilon_- = 0.1$. Panels a and b: $w_+ = 3$ Å, $w_- = 2$ Å. Panel c: $w_+ = 9$ Å, $w_- = 6$ Å. All apply to aqueous solution at 25 °C ($\lambda_B = 7.14$ Å).

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Figure 5.

Vesicle-annealed fluid RDFs for a system with +1:−1 RPM electrolyte in a mixture with +1:−1 RPM electrolyte characterized by lower membrane barrier height for cations. The concentration of both electrolytes was $c_{\text{el}}^{(1)} = 0.1 \text{ mol dm}^{-3}$. All ions of the annealed phase were of equal size ($\sigma_+^{(1)} = \sigma_-^{(1)} = 4.25 \text{ Å}$). The concentration of the quenched phase ($\sigma^{(0)} = 26 \text{ Å}$) was $c^{(0)} = 0.02 \text{ mol dm}^{-3}$. For both electrolytes: $\beta U_0^- = 3.2$; $w_+ = 3 \text{ Å}$, $w_- = 2 \text{ Å}$; $\beta \epsilon_+ = 0.001$, $\beta \epsilon_- = 0.1$, with the difference being $\beta U_0^+ = 4.5$ for one cation type and $\beta U_0^+ = 1.6$ for the other cation. All apply to aqueous solution at 25 °C ($\lambda_B = 7.14 \text{ Å}$).

Figure 6.

Vesicle-annealed fluid RDFs for a system with pure NaCl and in a mixture with +1:−1 electrolyte having a hydrophobic cation. Dashed lines apply to pure NaCl, and continuous lines to NaCl in a mixture with hydrophobic ions. Dotted lines denote the vesicle/hydrophobic ion RDFs. Panel a gives the results for Na^+ and panel b for Cl^- . The concentration of both electrolytes was $c_{\text{el}}^{(1)} = 0.1 \text{ mol dm}^{-3}$, and of the quenched phase ($\sigma^{(0)} = 120 \text{ Å}$) it was $c^{(0)} = 2 \times 10^{-4} \text{ mol dm}^{-3}$. The diameters of ions were $\sigma_{\text{Na}^+}^{(1)} = 3.87 \text{ Å}$, $\sigma_{\text{Cl}^-}^{(1)} = 3.62 \text{ Å}$, and $\sigma_{\text{h},+}^{(1)} = 8.5 \text{ Å}$. Membrane potential parameters were for small ions:

$\beta U_0^{\text{Na}^+} = 65$, $\beta U_0^{\text{Cl}^-} = 45$; $\beta \epsilon_{\text{Na}^+} = 0.03$, $\beta \epsilon_{\text{Cl}^-} = 3.0$; and $w_{\text{Na}^+} = 20 \text{ \AA}$, $w_{\text{Cl}^-} = 15 \text{ \AA}$, whereas the parameters for the hydrophobic cation were $\beta U_0^{\text{h},+} = 0.5$, $\beta \epsilon_{\text{h},+} = 3.0$, and $w_{\text{h},+} = 15 \text{ \AA}$. All apply to aqueous solution at 25 °C ($\lambda_{\text{B}} = 7.14 \text{ \AA}$).