

# Water between Membrane and Colloidal Theories for Cells

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To incorporate water as a structural and thermodynamic component of biomembranes, the consideration of the membrane interphase as a bidimensional hydrated polar head group solution, coupled to the hydrocarbon region allows for the reconciliation of two theories on cells in dispute today: one considering the membrane as an essential part in terms of compartmentalization, and another in which lipid membranes are not necessary and cells can be treated as a colloidal system. The criterium followed is to describe the membrane state as an open, non-autonomous and responsive system using the approach of Thermodynamic of Irreversible Processes. The concept of an open/non-autonomous membrane system allows for the visualization of the interrelationship between metabolic events and membrane polymorphic changes. Therefore, the Association Induction Hypothesis (AIH) and lipid properties interplay should consider hydration in terms of free energy modulated by water activity and surface (lateral) pressure.

Keywords: lipid hydration ; water interphases ; crowded systems

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## 1. Membrane and Coacervate Theories

### 1.1. The Membrane Theory

The classical paradigms supporting the actual membrane models are resumed.

The lipid bilayer is the backbone of the membrane in which proteins can be inserted. In some conditions, non-lamellar aggregates can be formed as transient structures depending on the lipid composition <sup>[1]</sup>.

The lipid bilayer conformation is a selective permeability barrier in which water and non-polar solutes can cross driven by a concentration gradient. Permeability is evaluated as a partition-diffusion process in which the lamellar conformation is not altered. Under this paradigm, solutes dissolve in the membrane and water copermeates. On the other hand, ions and most polar solutes cannot permeate the lipid membrane, and therefore, it occurs due to the presence of specialized proteinaceous carriers or channels coupled to metabolism (active transport). The cell is filled with ordinary water with small solutes including  $K^+$  in solution. To compensate for the passive leaks, ion pumps located at the membrane continuously operate, a process that is considered energetically impossible <sup>[2]</sup>.

Under this view, ions and other biocompounds such as aminoacids are excluded from membrane bulk due to their low solubility in the hydrocarbon region <sup>[3]</sup>. However, experimental evidences have shown that water can be found as pockets in the membrane structure favoring the permeation of some polar aminoacids <sup>[4][5]</sup>. Thus, the classical concept of permeability in which the bilayer is considered as a hydrocarbon slab where the dielectric constant is 2 has strong limitations.

Based on the concept of the lipid assemble as a phase, the bilayer suffers structural changes induced by temperature and water content by which permeability, area per lipid, and thickness are drastically modified. The phase transition is mainly ascribed to the fusion process of the hydrocarbon region in fully hydrated membranes.

The current models focus on the presence of different lipid lateral arrangements in the membrane plane (domains) due to the heterogeneity in composition. Some lipids in their pure form can stabilize in water forming non-lamellar structures such as phosphatidylethanolamines (PE) and glyceryl monooleate (GMO) <sup>[6][7]</sup>. Therefore, it has been speculated that when those lipids are present in the membrane, non-bilayer structures may be formed and therefore explain changes in permeability to ions and polar solutes. In these conditions, some lipids may act as ionophores <sup>[8]</sup>. However, the phenomena seem to be an all or none process, in which selectivity, specificity for ions, and gradual modulation are not described. In all cases, little or no role of the water surface state of the membrane has been considered.

The proposal of membrane theory relies on rules mainly deduced for bulk phases large enough to neglect interfacial phenomena. Under this view, permeation occurs driven by a chemical potential difference of the permeant between the bulk phases on both sides of the membrane. Thus, permeability is interpreted in terms of the Henry law (partition of a single solute between bulk water and the hydrocarbon region without water). In addition, diffusion is considered to be governed by Fick's law, meaning that the diffusion coefficient is constant during the process.

The solubility-diffusion theory was questioned introducing the role of the polar head group arrangements in a three-layer theory that incorporates the area dependence as a primary modulating parameter <sup>[9]</sup>. This theory implicitly considers the presence of water in the bilayer structure.

For convenience, bilayers (liposomes, vesicles) and monolayers (extended on the air-water surface) have been extensively used as experimental model systems in a nearly independent way. Monolayers' behavior was mostly analyzed considering that lipids behave as a van der Waals gas spread on the water surface <sup>[10][11]</sup>. The water/lipid interaction is not taken into account and, consequently, the membrane is described as a closed system in thermodynamic equilibrium with the adjacencies. On the other hand, bilayers are modeled as fully hydrated lipids in which lateral pressure cannot be controlled <sup>[11][12]</sup>.

From the phenomenological point of view, an extensive discussion has led to some consensus on the conditions in which monolayers may be considered equivalent to a bilayer of the same lipid species. The bilayer equivalent pressure is accepted to be at around  $\Pi = 30$  mN/m at which the phospholipase  $A_2$  activity is similar in both systems <sup>[13][14][15]</sup>. Estimation of the bilayer equivalent pressure is purely theoretical because bilayer lateral pressure is not experimentally measurable. Another frequently cited point is the bilayer equivalent molecular area, which for DPPC bilayers is  $\sim 64$  Å<sup>2</sup>, which is coincident with that determined in monolayers at a saturation point <sup>[16][17]</sup>.

## 1.2. The Coacervate Theory

The coacervate theory was first proposed by the Russian biochemist A.I. Oparin in 1936 <sup>[18]</sup>. According to it, the origin of life was preceded by the formation of mixed colloidal units called 'coacervates'. These are particles composed of two or more colloids which might be proteins, lipids, or nucleic acids.

Under the view of this theory, the cell is described as a colloid with distribution coefficients and adsorption coefficients as prime physical-chemical parameters allowing a negative-entropy driven bioenergetics based on coherence <sup>[19]</sup>.

Ling developed a complete colloid model for the living cell, the so-called 'association-induction-hypothesis' (AIH), which is claimed to be able to explain the coherent behavior of cells without the need to invoke the presence of the membrane <sup>[20]</sup>.

In short, the membrane theory favors the idea that a cell is a solution of proteins while the coacervate view considers the cell as proteins dissolving water.

## 2. The Membrane as an Open System: Thermodynamic Consequences

The introduction of water as a membrane component changes the definition of a membrane system from a closed to an open one. In consequence, the time-invariant state is not an equilibrium in a closed system in which the maximum entropy or minimum energy is reached when all forces are zero. In contrast, in an open system, the entropy is maintained constant in a time-invariant state (steady-state) in which non null forces are canceled out. In this state, the membrane exchanges water with the adjacent milieu at given surface pressure. An unbalance either of surface pressure or water exchange produces a transient state that the system tries to compensate for.

The approach of Defay-Prigogine in which the interphase is an ionic solution is particularly adequate to describe this process and illustrative to extend the role of water in the membrane in accordance with the coupled processes between solute and water named above. According to these researchers, when a solute is injected in the subphase of a monolayer, it can diffuse from the bulk aqueous solution to the interphase driven by a concentration gradient. In this process, the water activity at the interphase decreases which produces a coupled flux of water into the interphase. This can explain the increase in surface pressure produced by the insertion of bioeffector in the monolayers at a constant area, and extended to bilayers also when the decrease in membrane density is considered <sup>[21][22]</sup>. It must be taken into account that this increase in surface pressure is indeed a decrease in the surface tension of the interphase, a point that will be analyzed in detail later.

Consequently, several of the above paradigms concerning permeability and dielectric properties must be revised. Permeability is described by the interrelation of a partition process of the permeant between water and membrane bulk, which is taken as a pure hydrocarbon phase without water, and its diffusion in a homogeneous phase. This is supposed to be valid for single water permeation driven by a permeant solute gradient of concentration across the membrane. A more realistic picture was offered when Thermodynamics of Irreversible Processes (TIP) was applied to explain the permeation of nonelectrolytes. It was concluded that solute diffusion promotes a water flux and that osmosis induces also solute permeation. These conclusions were sustained for the process across the membrane, but no consideration of the changes in water content in the membrane itself was made [23].

### **3. Critical Water Activity and the Cut off Surface Pressure**

#### **3.1. Critical States: Packing and Cut off Pressure**

Recalling that the surface tension of water varies according to the dimension and quality of its environment, it is not difficult to comprehend that the physical chemistry of water confined between lipids with its hydration hardcore (dark blue) can determine the membrane thermodynamic response.

The typical curves denote the response of a monolayer at a given initial surface pressure to a bioeffector added to the subphase. The plot of the magnitude of the response ( $\pi_f - \pi_i$ ) as a function of the initial surface pressure ( $\pi_i$ ) indicates that there is a cut off surface pressure above which no membrane response is observed. This behavior is usually related to the packing of the lipids at the interphase. In a simplistic interpretation, there is no area available to the bioeffector to penetrate the monolayer.

However, the insertion process is not driven by the area but by free energy changes. Therefore, other properties concerning the interphase must be relevant.

Packing is frequently taken as the equivalent of the ordered state. However, packing is referred to lipid molecules i.e., the special arrangement in terms of distance. Such ordering is ascribed to lipids immersed in water since properties are assumed to be measured in fully hydrated membranes. The packing increased by compression enhances the hydrophobic interactions of the monolayer or bilayer promoting a decrease in water order. Therefore, the two concepts must be compatibilized with each other.

Packing is a geometric criterium and order-disorder is a thermodynamic one. However, the geometrical criterium to some extent can be translated into thermodynamic terms if the energy contribution is considered in terms of the excluded volume as described above.

#### **3.2. Cut off and Critical Water Activity**

The surface pressure can be expressed in terms of water activity ( $a_w^i$ ) according to equation  $\pi = -C \Gamma_w RT \ln(a_w^i)$ , where  $\Gamma_w$  is the water concentration at the interface and C is function of the frictional coefficient lipid-lipid, lipid water and water lipid [24]. Thus, the cut-off pressure reflects a critical water activity.

At the cut-off pressure, water activity beyond the hardcore is zero and no water domains are formed. Thus, no effect of bioeffectors is found. This is produced at the critical water activity above which water domains are formed and the excess free energy triggers the bioeffector perturbation [21]. The water domains are characterized by a surface tension fixed by the water activity according to Equation (6).

For a given water activity at the membrane, the perturbation ( $\Delta\pi$ ) depends on the type of bioeffector, and of lipids and it may have different consequences. Among them, drastic changes in the dielectric permittivity of the membrane maintaining the bilayer conformation allow permeation of polar and ionic solutes, a process that cannot be explained by the classical non-polar slab of the bilayer in classical models [25][26]. Another consequence is the induction of non bilayered structure abandoning the bilayer conformation [27].

Compression produces the collapse of the lipid monolayer at high pressures. In this stage, lipids are packed to a limit in which the hard core first hydration layers are in contact. This is the minimum excluded volume (blue spheres) which implies a volume non available for solutes. In a  $\Delta\pi/\pi$  curve, this value is reflected by the critical cut-off, i.e., the pressure at which no response is observed. The response is observed when the initial surface pressure is below the cut off, which is somewhat below the collapse pressure. In consequence, the water activity at the cut-off is higher than that at the collapse.

This means that the excluded volume sensitive for membrane response is larger than the hardcore water inferred from the collapse pressure. This implies that the geometrical space created is much lower than the molecule volume of the bioeffector. Therefore, the insertion of the biocompounds can be more suitably explained in terms of energetic considerations.

## **4. Unifying Membrane Approach with Water Colloid Systems**

If the membrane is taken, thermodynamically speaking, as an open system, it is thought that exchanges of matter with the surroundings are allowed. The classical idea of close systems is that membrane material is constant. The exchange of water through the membrane barrier (transient or non-stationary water) is explained without altering its composition and even maintaining constant its density (packing) along the process. However, density can change maintaining the lipid constant, at surface pressures well below the collapse, because the water content is modified. This is more noticeable when water is dragged by a permeant. Water dissolves in kinks affecting the density of the lipid matrix <sup>[28][29][30]</sup> and its dielectric properties due to solute penetration <sup>[26][31]</sup>. In this sense, both, open and non-autonomous systems are interrelated concepts.

In a non-autonomous system, the limit of the aqueous layer is not determined by the membrane itself but by the media which is in contact with. Thus, if the membrane faces a colloid aqueous one, such as cytoplasm, it will have different states than if the media is pure bulk water.

In terms of compartmentalization, continuous semipermeable membranes are not required as the FMM model does. Compartmentalization can be taken as a kinetic process and not necessarily as a physical barrier. Different kinetics of solute penetration were found at different cholesterol ratios in lipid monolayers and constant areas and at different surface pressures, all of them related to changes in water activity in the interphase <sup>[16][28][32]</sup>.

It is possible that the presence of lipids with the propensity to stabilize in non-bilayer ensembles strongly affects the kinetics of permeation. The proposal that the dependence of the conformation of the lipids with the state of the internal cytosol is an extension of the concept of an open (non-autonomous) system, since it considers a structural change in the lipid arrangement much more drastic than the lipid density changes in bilayers. This would deserve further analysis within the frame of Thermodynamics of Irreversible Processes (TIP) <sup>[24]</sup>.

## **5. The Thermodynamic Response: Membrane State/Hydration State/State-Function Relationship**

As said, the concept of the open/non autonomous phase can be framed in terms of Gibbs free energy. J.W. Gibbs was a visionary. It is not known if he was conscious of that, but the extension of the physical thermodynamics to chemical systems is one of the most relevant theoretically based experimental formalisms on which science is based today <sup>[33][34]</sup>.

The free energy decrease can be enthalpically or entropically driven. If water is the messenger in order to make coherent the biochemical processes in cells including lipids, the two aspects are fundamental. First, the energy exchange is driven by the energy of hydrogen bond networks (water-water, water-lipid interactions) and by the entropy change due to the unique properties of the structure of water itself. An example of this is the water exchange between monomers and tetramers.

The important observation that the periodicity of glycolytic oscillations and that the attendant coupled oscillations in water relaxation are slowed down by deuterium oxide (heavy water) makes it reasonable that this is a consequence of the stronger energy of the D-bonds in comparison to the H-bonds <sup>[27]</sup>. Thus, this increase in stability enhances hydrophobic interactions and dampens oscillations.

Therefore, unstable or metastable systems have the root in the H bond strength of water with itself and with the walls in a restricted environment <sup>[34][35][36][37]</sup>. Therefore, more details in relation to hydrogen bonding energy in different spatial configurations are needed.

### **Responsive Structures and H Bond Networks**

The presence of a cellular component governs the emergent properties that would affect the cellular interior dynamically. This implies that water organization mainly by hydrogen bonding should be higher, in terms of extension and stability, than bulk water. If this is so it should be reflected in dielectric relaxation and NMR results <sup>[26][36]</sup>. However, no more than 10% of cell water is supposed to be highly structured. The possibility of highly organized water was thought to be confirmed when

the polywater was apparently discovered but was promptly demonstrated as a failure [38][39]. In addition, if the highly structured water exists the strength of H bonds would damp oscillations as occurs in D<sub>2</sub>O as denoted above [27].

However, the new perspective of introducing water as a structural/functional component in cytoplasm and membranes can be reasonably accepted if interphase phenomena are considered to play a key role [40]. This is more logical when the cell interior is thought of as a crowded system, in comparison to a broth of protein ionic solution. In this regard, volume chemistry should be replaced by surface chemistry [41][42][43].

Lipids are part of the complex and crowded system and may determine kinetic and relaxation phenomena that are not restricted to permeation across the membrane. The relaxation implies the reorganization of water arrangements and therefore, changes in polarization, density, and compressibility. These are noticeable properties of water derived from hydrogen bonding network with noticeable plasticity [44].

The relaxation of water in the vicinity of lipid head polar groups measured with fluorescence probes in cellular aggregates of lipids is a strong indication that responsive behavior is due to water at the *interphase* which may be coupled to the cytosol [45][46][47]. The physical coupling can be a combination of properties emerging from water arrangements by H-bonds. As observed by FTIR, water bands are modified by the presence of lipids in different states (gel or liquid crystalline). These bands change at the phase transition mirroring the phase transition in the lipid phase [29]. The changes in bands are a consequence of the evolution of water populations from tetrahedral array (4H bonds) along 3, 2, 1, and 0H-bonded species [35]. The transition in the water populations “resonates” with the lipid state, and probably with the interior cell structure and central metabolism as well [48][49].

The strong cohesion in the cytoplasm can be extended not only between proteins and water but also between lipids and water. This statement fits with the association claimed in the association-induction hypothesis.

The living state is defined as a *cooperative* state indicating that each state is well defined and discrete and that there are neighbor-to-neighbor interactions among the individual elements. These features have been found in lipid molecules in the processes of adsorption of aminoacids and proteins to lipid membranes [50].

The cooperativity gives place to propagation. Polarized multilayers of water are not only in proteins but also in lipids and its propagation from and to the interphase is a property of the H bonds. According to AIH theory, fixed charges and associated counter-ions are separated by up to three dielectrically saturated water layers. This is comparable to the thickness of water layers in the membrane interphase polarized by charges such as phosphate and carbonyl groups, constituting the excluded volume which contributes to the repulsion forces and the responsiveness of the membrane [21][25][51][52]. The complete restriction of reorientation applies to the first hydration layer of these groups. However, the shells beyond it and in between the acyl chains can be modulated by surface pressure, mechanical constriction imposed by the water activity [53][54]. Membrane expansion-contraction may be induced by intrinsic processes of the cell driven by metabolic activity or by mechanical stress imposed by the external environmental conditions (osmotic swelling and shrinkage) [55].

The dynamic behavior of water at a constant temperature can be of electrical nature, more precisely derived from the dielectric properties implied in the polarization measured with fluorescent probes.

The dielectric permittivity is, in turn, much higher in ice than in liquid water explained by the higher degree of association of water molecules in a periodic array of tetrahedral coordination (4H-bond population predominates).

The dielectric permittivity is due to the orientation in an electric field of the dipoles. The common picture is that the reorientation implies the breaking of hydrogen bonds. However, a complete rotation of the dipole can be achieved by displacement of the H along with the H bond that remains unbroken. The water dipolar relaxation (rotational dynamics) is represented schematically below.

The inversion in the direction of the water molecular dipole (arrows) can be conducted without rotation of the molecule (i.e., without breaking H bonds), but with a displacement of the protons along with the linear H bond. The extent of the propagation will be limited by the density of states of 4, 3, 2, and 1-coordinated molecules by H-bonds giving a multiplicity of polarization states. Thus, polarization at the interphase and the propagation to the cell interior can be due to H displacement as in the Grothuss mechanism.

Moreover, if water populations change as a consequence of changes in lipid phase states or internal cell processes, a complex (and fast) response of polarization can result. The lack of water would alter this propagation essential for the

Thus, “dynamic interphase hydration” can be controlling the probability of lyotropic mesomorphic transitions, allowing lipid self-assemblies and metabolically reactive structures in the cell to be coupled.

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