From the Physics of Confined Fluids to a Mechanism for Gating in Ion Channels

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In recent studies it was suggested that the physical mechanism responsible for controlling the ion flux through biological ion channels with hydrophobic gating region could be the forming and breaking of vapor bubbles. In this model the gate is treated as a two state system: if the gate is filled with water it is in the open state and allows for ion flux, if the gate is blocked by a bubble it is in the closed state and stops any ion flux.

1 The model

Any van der Waals like fluid, with a pair interaction that shows a strong repulsion at short distance and an attraction at intermediate separation can phase separate into a gas and a liquid phase, if the attraction is sufficiently strong [1]. In the gas phase, the number density of fluid particles is low, which leads to a relatively large mean interparticle distance. This in turn causes the internal energy of the gas phase to be rather small, because at the mean particle distance the attraction of the pair interaction potential practically vanishes. However, the low number density also causes the entropy of the gas phase to be large. In the liquid phase the argument is reversed. Cause by the high number density in the liquid phase, the entropy is small, however, the internal energy is large, because the particles strongly interact at the small mean inter particle distance. At the liquid-gas phase coexistence the loss of entropy of the gas phase is balanced by the gain of internal energy of the liquid phase.

Here we consider a van der Waals fluid in the grand canonical ensemble [1], that resembles water at ambient conditions. In the unconfined bulk ($V \to \infty$) the fluid is in the liquid phase with (high) number density ρ_l. This means that at the state point considered, which is specified by the temperature T and the chemical potential μ, the liquid with density ρ_l has the lowest grand potential, $\Omega^l_{bulk} = -p_l V$, with the pressure in the liquid phase p_l. Just like water at ambient condition, the fluid considered here is very close to a liquid-gas phase coexistence. This implies that in the bulk there exists a metastable gas phase with lower density ρ_g and a slightly

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higher pressure, $p_g > p_l$, which directly follows from

$$\Omega^g_{bulk} = -p_g V > \Omega^l_{bulk} = -p_l V. \tag{1}$$

Since the considered liquid is close to liquid-gas coexistence the system under confinement can undergo a further phase transitions, namely capillary evaporation in a hydrophobic confinement [2, 3]. In the hydrophobic confinement, the interaction between fluid particles and the confining walls are less attractive than among fluid particles. Therefore, the liquid phase, which due to high number density is more disfavored by the confinement than the low density gas phase, could be destabilized if the confinement is strong enough, i.e. if the volume is confined by enough surface area.

2 Morphological Thermodynamics

Capillary evaporation is well studied for various length scales. Here we focus on very narrow, slightly hydrophobic, channels, which represent the gating region of biological ion channels. To this end we require a generalization of the grand potential, Eq. (1), for confined fluids. Morphological thermodynamics provides this generalization and separates the grand potential into four morphological, or geometrical, terms [4]:

$$\Omega^i = -p_i V + \sigma_i A + \kappa_i C + \bar{\kappa} X, \quad i = l, g \tag{2}$$

where V, A, C and X are the volume, the surface area and the integrated (over the surface area) mean and Gaussian curvature, respectively, of the confinement. The corresponding thermodynamic coefficients of phase i, which are independent of the confining geometry, are the pressure p_i, the surface tension σ_i and two bending energies κ_i and $\bar{\kappa}_i$.

Biological ion channels are very important membrane proteins that allow for passive transport of ions through the membrane along their electro-chemical gradient [5]. Typically ion channels have two important properties: they can allow specific ion types to pass through the channel and reject others, a process called selectivity, and they can switch the ion flux on or off, a process called gating. Ion channels are responsible for many important physiological processes in a living organism. While gating is well studied experimentally, it still remains unclear which underlying *physical* mechanism is responsible for gating.

Using the morphological thermodynamics, Eq. (2), we show that capillary evaporation can occur at a channel diameter, which is only a few times the particle diameter [6]. From this observation we suggest a mechanism for gating in biological ion channels [6, 7]. The suggested gating mechanism is based on the idea that the hydrophobic gate of the channel can form or break a small vapor bubble by changing its geometrical conformation. If a bubble forms in the gate, the ionic current through the channel is stopped.

It is important to notice that due to the finite number of fluid particles involved in the transition, we observe a pseudo phase transition and instead of a sharp transition we can only predict a probability of finding either the one or the other phase in the gate, which is the probability of finding the gate either open of closed.

In order to test this gating mechanism experiments are required. Based on the model it is possible to *predict* the gating behavior of a single ion channel, if the suggested mechanism is employed. Thereby it should be possible to suggest precise experiments that can pick up signatures of bubbles.

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