Self-sustained potential oscillations and the main phase transition of lipid bilayers

M. J. Zuckermann
Dept. of Physics, McGill University, Montréal, Québec, Canada H3A 2T8

In a recent paper Yagisawa et al. (1) proposed a model for self-sustained oscillations of the electric potential between two ionic solutions divided by a lipid bilayer membrane. The driving mechanism proposed by the authors is the main phase transition between the gel phase of lipid bilayers, which is essentially a quasi-2d crystal phase, and the fluid or liquid crystalline phase of the bilayers. The authors suggest that the oscillations are driven by repetitive phase transitions which themselves are triggered by the repetitive absorption and desorption of protons at the interface between the ionic solutions and the polar head region of the lipid bilayer.

This is to my mind an extremely exciting theoretical paper which proposes a relationship between dynamic effects caused by lipid bilayers and their phase behavior. Lipid bilayers are models for the plasma membranes of biological cells. They are structures which self-organize when a mixture of amphiphilic lipid molecules with an aqueous medium is vortexed and they are composed of two opposing lipid monolayers in such a way that the polar heads of the lipid molecules form hydrated interfaces with the aqueous media. Lipid bilayer systems can be produced in several forms (2), for example, multi-bilayer liposomes in which the bilayer-water system forms a one-dimensional stack of bilayers and large unilamellar vesicles composed of a single closed bilayer with dimensions in the micron range. Lipid molecules can also be prepared as surfactant monolayer films in a Langmuir-Blodgett trough.

Lipid systems exhibit complex phase behavior as functions of temperature and hydrostatic pressure (3). The standard example is provided by one-component bilayer systems composed of saturated lecithins, i.e., diacyl phosphatidylcholine molecules with two saturated methyline chains linked to a charged or zwitterionic polar head by a glycerol backbone. The chain length ranges from 12 to 22 carbons. Multi-bilayers containing saturated lecithins exhibit several crystalline phases, but the most dramatic phase transition known as the main phase transition takes the system from a quasi two-dimensional crystal (gel) phase in which the acyl chains are rigid and mostly in their ground or all-*trans* conformation to a quasi-2d-fluid (liquid crystalline) phase in which the molecules can diffuse laterally and are in flexible conformations with several gauche bonds. Both the transition temperature and the enthalpy of transition increase with chain length. The transition temperature changes considerably when the degree of unsaturation of the acyl chains is increased and when the nature of the polar heads is altered by size, hydrogen bonding capability, charge, etc.

Theoretical models for the phase behavior of lipid bilayers take several forms (3) and they are studied by both analytic and numerical simulation techniques. The authors (1) use the simplest possible theoretical model in which the main phase transition is modeled by a two-state model, one state representing acyl chains in the all-*trans* conformation and the second describing flexible acyl chain conformations typical of the fluid phase. The chains interact via dispersion forces which depend on the chain states and each chain state is characterized by an internal energy, entropy and cross-sectional area. The authors include a term describing the Coulomb interaction between polar heads which depends on the occupational probability of the chain states. This is reasonable since the lateral density of the polar heads increases as the bilayer passes from the gel to the liquid crystalline phase.

The problem is to understand what happens when a lipid bilayer which separates two ionic solutions is subject to an applied voltage at the main phase transition. Several experimental workers have found that self-sustained potential oscillations occur accompanied by pulse-like behavior of the ionic current under a salt gradient. Other workers report the occurrence of spontaneous potential oscillations in lipid bilayers produced from Langmuir-Blodgett films interspersed between different ionic solutions. All these experimental results are attributed to repetitive phase transitions between lipid bilayer phases of high and low resistance, respectively. The suggestion is that this phenomenon is the basis of cellular functions such as the transduction of stimuli and changes in ion channels and receptors due to external potentials. My one reservation about the biological significance of the work of Yagisawa et al. (1) is that it is not clear at all that the main phase transition occurs in biological systems. However, this work should lead to a better understanding of self-sustained oscillations in biology.

The analysis of the self-sustained oscillations requires a representation of the electrostatics of a charged lipid bilayer. The system is therefore modeled by a lipid bilayer composed of two monolayers, each with its own ionic double layer of associated charge with accumulation and/or absorption of some of these charges at the interfaces of the bilayer with the aqueous solution. The double layers are described by standard Gouy-Chapman

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theory plus Stern theory for absorption isotherms (4) and the transmembrane current is then obtained from Maxwell's equation for the ionic and displacement currents which basically leads to a version of the Goldman equation. The theory is extremely involved and a considerable number of approximations are required to obtain the desired solution. Clearly, since both Gouy-Chapman-Stern theory and the phase transition theory used are equilibrium theories, this requires the assumption that the relaxation time required for the ions and the lipid molecules to relax to their equilibrium values as dictated by the phase of the bilayer is much shorter than the characteristic periodic time of the oscillations. The phase transition theory described above provides surface (polar head) charge densities for the theoretical expression for the bilayer permeablity of the ionic species and for double layer theory.

Yagisawa et al. (1) produce the required self-sustained oscillations from their theory with an internal consistency that justifies their assumptions. The interesting part of their analysis is that they explain how the self-sustained oscillations are related to repetitive phase transitions of the lipid bilayer. The two important ionic species are taken to be protons (H^+) and alkaline ions denoted by M^+, each species being on opposite sides of the membrane. When H^+ ions pemeate the membrane, the related monolayer can switch phases from fluid to gel since H^+ binding to the polar heads favors the gel phase. When M^+ ions then permeate in the reverse direction the H^+ ions desorb and the monolayer changes back to the fluid state. The self-sustained oscillations proceed by repitition of this cycle. The authors also show that, when an alternating electric current is imposed on the system, the oscilations can under certain circumstances become chaotic.

I will leave interested readers the opportunity of finding out more details (Materials and Methods) for themselves from reference 1. If the excellent work of Yagisawa et al is to bear fruit in the realm of biophysics, it will be necessary to go beyond the case of repeated bilayer phase transitions. One possibility is to move to phase coexistence in lipid mixtures or to examine the effect of protein-lipid interactions on the self-sustained oscillations or both. Other interesting possibilities are to find out if self-sustained oscillations occur in the presence of lateral concentration and density fluctuations in a fluid lipid bilayer close to a "hidden" critical point (5) or to see how drug or anesthetic molecules disturb these oscillations by removing phase transitions or phase coexistence (6). After these problems have been dealt with, the situation of an ionic channel in the membrane could be studied. These comments are meant to illustrate that Yagisawa et al. have indeed iniciated a new and exciting line of theoretical research.

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REFERENCES

1. Yagisawa, K., M. Naito, K-I. Gondaira, and T. Kambara. 1993. *Biophys. J.* 64.
2. Gennis, R. B. 1989. Biomembranes. Springer Verlag, Heidelberg and New York.
3. Mouritsen, O. G. 1991. *Chem. Phys. Lipids.* 57:179–194.
4. Borkis, J., and A. K. Reddy. 1970. Modern Electrochemistry. Plenum Press, New York.
5. Jørgensen, K., M. M. Sperotto, O. G. Mouritsen, J. H. Ipsen, and M. J. Zuckermann. 1993. *Biochem. Biophys. Acta.* In press.
6. Jørgensen, K., J. H. Ipsen, O. G. Mouritsen, D. Bennett, and M. J. Zuckermann. 1991. *Biochem. Biophys. Acta.* 1067:241–253.