## REFERENCES

Atri, A., J. Amundson, D. Clapham, and J. Sneyd. 1993. A single-pool model for intracellular calcium oscillations and waves in the *Xenopus laevis* oocyte. *Biophys. J.* 65:1727–1739.

Györke, S., and M. Fill. 1993. Ryanodine receptor adaptation: control mechanism of $Ca^{2+}$-induced $Ca^{2+}$ release in heart. *Science (Wash. DC).* 260:807–809.

Keizer, J., and G. De Young. 1993. Effect of voltage-gated plasma membrane $Ca^{2+}$ fluxes on $IP_3$-linked $Ca^{2+}$ oscillations. *Cell Calcium.* 14:397–410.

Li, Y.-X., J. Rinzel, J. Keizer, and S. Stojilkovic. 1993. Calcium oscillations in pituitary gonadotrophs: Comparison of experiment, and theory. *Proc. Natl. Acad. Sci. USA.* Submitted for publication.

Miyazaki, S., M. Yuzaki, K. Nakada, H. Shirakawa, S. Nakanishi, S. Nakade, and K. Mikoshiba. 1992. Block of $Ca^{2+}$ wave and $Ca^{2+}$ oscillation by antibody to the inositol 1,4,5-trisphosphate receptor in fertilized hamster eggs. *Science (Wash. DC).* 257:251–255.

## Lipid Molecular Shape and High Curvature Structures

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It has been a long standing puzzle why cells go to such length to meticulously maintain distinct lipid composition profiles for each of their organelle membranes. This question is especially puzzling when there is still a prevailing group of membranologists regarding membrane lipids to be merely a passive matrix serving no more than a structural frame for functioning protein components. A closer look into the lipid profiles of biomembranes reveals an interesting correlation, that those membranes having higher protein-to-lipid ratios contain more lipids that do not self-assemble into a planar bilayer form, which is expected for membrane lipids (Hui and Sen, 1986). These membranes include the energetically active mitochondrial inner membranes, and membranes of thylakoid and of photoreceptor discs in the retina rod outer segment. On the other hand, inactive membranes such as myelin, which has a low protein to lipid ratio, contains mostly bilayer-forming lipids. It seems that lipids which do not remain in plane bilayer form by themselves at physiological conditions are necessary for certain membrane functions. The article by Lee et al. (1993) adds a simple but intriguing aspect to many recent studies of the molecular packing of these lipids.

What distinguishes lipids that self-assemble into planar bilayers from those that do not? In spite of a wealth of experimental data on the classification of membrane phospholipids according to their polymorphic phase preference (see review by Seddon, 1990), a quantitative criterion is still not available. Isrealachvili et al. (1977) first defined a packing factor $f = v/al$ for amphiphilic molecules, where $v$ and $l$ are the unconstrained volume and length of the hydrophobic moiety of the lipid, and $a$ is the optimal (unconstrained) hydrophilic surface area. Molecules with $f = 1$ tend to form planar bilayers, whereas those with $f < 1$ or $f > 1$ tend to form positive or negative curvature structures, respectively. In other words, if the cross sections of the hydrophobic and hydrophilic moieties of the lipid molecule are unequal, it is energetically unfavorable to pack these lipid molecules into a planar bilayer form.

The next problem is to measure the parameters $v$, $a$, and $l$ experimentally. Intuitively, one would expect these geometric parameters, especially $v$ and $l$, to vary with temperature. Increasing temperature presumably would increase $v$ and reduce $l$ due to increasing thermal motion of the hydrocarbon chains, and indeed increasing temperature favors the formation of negative curvature structures from lamellar structure (Seddon, 1990). Yet to obtain the absolute values of $v$, $l$, and $a$ is not trivial. Hui and Sen (1989) approximated the values of $l$ by equivalent chain lengths deduced from chromatographic retention times, and the values of $v$ by the equivalent specific volumes of corresponding hydrocarbons. Determining the values of $a$ required more assumptions and approximations. The conformation of many headgroups are still unknown. Furthermore, there is the question: should any water molecules be included in the headgroup volume estimation, according to the polarity of the headgroup? How to account for possible hydrogen bonding or electrostatic repulsion between headgroups? Even if all this information is in hand, reducing them to a representative value of $a$ still involves some modelling assumptions.

Despite the considered complications in the determination of $a$, Lee et al. (1993) showed that the sum of covalent volumes of headgroup atoms of a series of homologous phospholipids inversely correlated with their potential to destabilize the bilayer. In other words, when $v$ and $l$ of these lipids are equal, the tendency to form negative curvature structures decrease linearly with $a^{3/2}$ (hence $1/f^{3/2}$) of equivalent covalent spheres of the headgroup. This simple correlation is very impressive, considering the years of qualitative argument of the shape hypothesis without reliable ways to measure the optimal shape of molecules. Although it is not a direct determination of the $f$ values, it gives some confidence in using covalent volume of headgroups to deduce $f$.

The monotonic relation of $a$ and $T_H$ reported by Lee et al. (1993) is not surprising even that the polarity and charge of the headgroups were deliberately overlooked. The electrostatic repulsion between headgroups of charged lipids is negligible in mixtures containing only dilute charged lipids. The dipole field that orders water molecules on the bilayer surface is not a simple sum of those of isolated headgroups, therefore accounting water molecules is imprecise. These factors may not be of sufficient significance to disrupt the reported monotonic relationship. However, an intriguing point of this paper is the linear relationship. The lowering of $T_H$ is not simply related to the free energy $\Delta G$ due to curvature frustration. The value of $\Delta G$, when a spontaneously curved surface is constrained to a flat bilayer, is proportional to the bending modulus $k$ and the square of the spontaneous curvature $c_0$ (Winterhalter and Helfrich, 1992):

$$\Delta G = (\tfrac{1}{2})kc_0^2.$$

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Even for a simple geometry, $c_0$ is not a simple function of $f$ (Hui and Sen, 1989). Therefore a linear relationship between $\Delta T_H$ and $1/f^{3/2}$ may be fortuitous. It could indicate that there may exist a simpler relationship between $\Delta T_H$ and $a^{3/2}$. Hopefully, future experimental data would be added to include more lipids, to check the linear relationship. Obvious candidates are dioleoyl glycolipids such as monogalactosyl- and monoglucosyl-glycerides; the headgroups of these lipids are very large, but these lipids still tend to have low $T_H$ (Gounaris et al., 1983).

## REFERENCES

Gounaris, K., A. Sen, A. P. R. Brain, P. J. Quinn, and W. P. Williams. 1983. Polyunsaturated fatty acyl residues of galactolipids are involved in the control of bilayer/non-bilayer transitions in higher plant chloroplast. *Biochim. Biophys. Acta.* 732:229–242.

Hui, S. W., and A. Sen. 1989. Effects of lipid packing on polymorphic phase behavior and membrane properties. *Proc. Natl. Acad. Sci. USA.* 86:5825–29.

Isrealachvili, J. N., D. J. Mitchell, and B. W. Ningham. 1977. Theory of self-assembly of lipid bilayers and vesicles. *Biochim. Biophys. Acta.* 470:185–201.

Lee, Y.-C., T. F. Teraschi, and N. Janes. 1993. Support for the shape concept of lipid structure based on a headgroup volume approach. *Biophys. J.* 65:1429–1432.

Seddon, J. M. 1990. Structure of the inverted hexagonal (HII) phase, and non-lamellar phase transitions of lipids. *Biochim. Biophys. Acta.* 1031:1–69.

Winterhelter, M., and W. Helfrich. 1992. Bending elasticity of electrically charged bilayers: coupled monolayers, neutral surfaces and balancing stresses. *J. Phys. Chem.* 96:327–330.