Review of: "[Review] The Studies of Lipid Phase Polymorphism in Model Membranes"

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Potential competing interests: No potential competing interests to declare.

Lipid phase polymorphism in model membranes is an important topic and the current title suggests to provide an overview of what we know about this. In this review the authors do a brave attempt to collect and discuss a few, mostly qualitative, aspects of lipid polymorphism and put these in a biological context. The review falls short in providing insight into the why's (model) lipid bilayers undergo topological changes and it large ignores quantitative aspects. Therefore it is of use for only a sub-population of researches interested in this field.

As we know from all textbooks, (model) membranes ideally have a bilayer architecture, but we all know that there is more to it: not all lipid assemblies have the basic bilayer topology (see for example the lipid organization in chloroplasts-the most abundant ‘membrane’-like assemblies on earth). The bilayer topology is challenged in basically two ways. (i) On the one end of the spectrum, the bilayer configuration is lost via pore formation and eventually it gives way to disks, worms or micelles. (ii) On the other end of the spectrum the bilayers start to attract each other (see one of the figures in the review), form saddle shapes (not pointed at in the review) between them which leads to sponge (not mentioned), cubic of (inverted) hexagonal phases (mentioned in the review). Both transitions can be induced by additives (lipids, surfactants, peptides etcetera) but in fundamentally different ways of course. Indeed the list of all possible ways we already know to trigger either of these bilayer instabilities is very long indeed (much longer than discussed in this review). To forward this field therefore, it becomes increasingly important to address the fundamental underlying reasons. When it comes to the why's, we need to take a physics point of view (if we like it or not!): this physics point of view arguably started by Helfrich about 50 years ago. Edge active agents (peptides, copolymers) or strongly negatively charged lipids in combination with low ionic strength conditions may trigger pore formation. On the other side of the spectrum, the sign switch of the Gaussian bending modulus from negative (stable bilayers) to positive (inducing saddles) is the key trigger. In recent years our molecular level of understanding increased significantly. It is known how physical chemical parameters and molecular additives may induce a sign switch of the Gaussian bending modulus or -on the other side of the spectrum- stabilize pores.

When you are active in this field of research, you know that there is a key role of ‘amounts that you need' to trigger transitions. The quantitative aspects are truly important, also to understand the biological implications. Of course we understand (or feel implicitly) that the peptides and molecules mentioned in the review are very potent to induce these transitions for the specified cases, but more than some implicit feeling -some modes of interactions are discussed- for this is not provided by the reviewers. Of course adding quantitative information will make the review more technical and much longer, which is an unfortunate side effect.

I therefore suggest that the authors scale down their ambition level, both in the title as well as in the abstract, so that the review's audience is less likely to be disappointed. On top of this I also challenge the reviewers to come up with a few relevant statements about why ‘membranes’ may loose their bilayer topology. With such statements in mind the reader may try to rationalize membrane behavior in various scenarios.