A unifying membrane model

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Abstract
I explain the history and significance of a new theoretical framework for membrane biology that challenges previous ways of thinking.

Main
To honour the centenary of the Gorter and Grendel model, which proposed that membranes are lipid bilayers[1], I offer this personal account to fill a crevice in the history of science.

Until last year, membrane biology remained entangled in its greatest inquiry: creating a unifying model. It was anticipated that such a model would be a landmark concept; membranes are the frontiers of cells, they media through which they interact, the barriers that viruses and other pathogens must overcome, the residences of most drug targets, and the catena of legions of processes. The central mystery arising from the 1970s was how membrane proteins and lipids are spatially organized. Most theories on this topic involved modifications to the eminent lipid raft theory, which in 1997 proposed that certain lipids self-assemble into ordered membrane subregions that recruit proteins[2]. Akihiro Kusumi, for example, believed that the actin cytoskeleton creates a barrier that regulates the growth of lipid rafts[3]. Sarah Veatch and Sarah Shelby, among others, believed lipid rafts were akin to thermodynamic phases and that such structures appear due to the closeness of the membrane to a miscibility critical point[4,5].

It became apparent to me that these modifications are what philosophers of science call *ad hoc*. An *ad hoc* modification is added on top of a theory to prevent it from being falsified. The lipids that supposedly form rafts did not appear to cluster through interactions among themselves at physiological temperatures. However, when the temperature of a simplified system was lowered, it decomposed into two phases, one of which was enriched in the featured lipids[6,7]. Consequently, a myth took hold that membranes contain two phases, and proteins and lipids sort to one or the other. It was ignored that this two-phase decomposition is an expected outcome of a sufficient decrease in temperature. This confirmation bias shaped much of the thinking in the field, particularly within research groups centered around lipid rafts, such as the Levental lab and its collaborators like Veatch and Shelby.

Amid the confusion, an illuminating idea was offered in 2017/18 by Peter Tieleman, Siewert Marrink *et al.*, who proposed that proteins had lipid fingerprints; unique lipid distributions[8]. I considered this to be a long-overdue concept. Lipid fingerprints need not resemble phases; they are just distributions that include both tightly and loosely associated lipids. They are also an easy way of representing extraordinary complexity; of the hundreds or thousands of lipid types in a membrane, each protein has a unique selection and pattern. Fingerprints can be generalized. For example, each protein also has a solvent fingerprint, or more broadly, each

component has a fingerprint of other components. I believed that any reasonable membrane model had to acknowledge that all components have preferential interactions with each other.

As theories became more numerous and complex, some suggested that a unifying membrane model was impossible[9,10]. I thought this mindset was unproductive and suggested to my mentor Michael Overduin that we publish a model that contradicts the lipid raft theory, which I considered inconsistent with thermodynamics for several reasons that I will explain in an upcoming paper. Michael was an expert on phosphoinositide lipids, which feature prominently in our model, and had for a long time wanted to unite membranes with the genetic code. We converged on a formulation in 2023, which we called the proteolipid code[11]. The central concept was that membranes are composed of structural and functional units called zones, and it suffices as a unifying model to explain how all the zones assemble.

In our paper published last year[11], we described membranes as networks of interacting zones, as might be represented with a graph or topological space (Figure 1). One type of zone is a protein with its lipid fingerprint. When proteins cluster, they create zones called protein islands that have collective fingerprints. There are zones that are devoid of protein called voids, which grow when proteins cluster. These zones have emergent properties and are thermodynamically coupled, which we described by generalizing the idea of the primary, secondary, tertiary, quaternary structure hierarchy used in biochemistry. There are numerous lipid classes that distinguish and regulate zones. Lipid glue is part of lipid fingerprints and stabilizes protein islands[12]. Lipid antagonists compete with lipid glue to occupy fingerprint sites[13]. Lipid codons allow proteins from outside the membrane to find their designated zones and thus encode spatial location[14]. The model can be formalized with a branch of mathematics called sheaf theory.

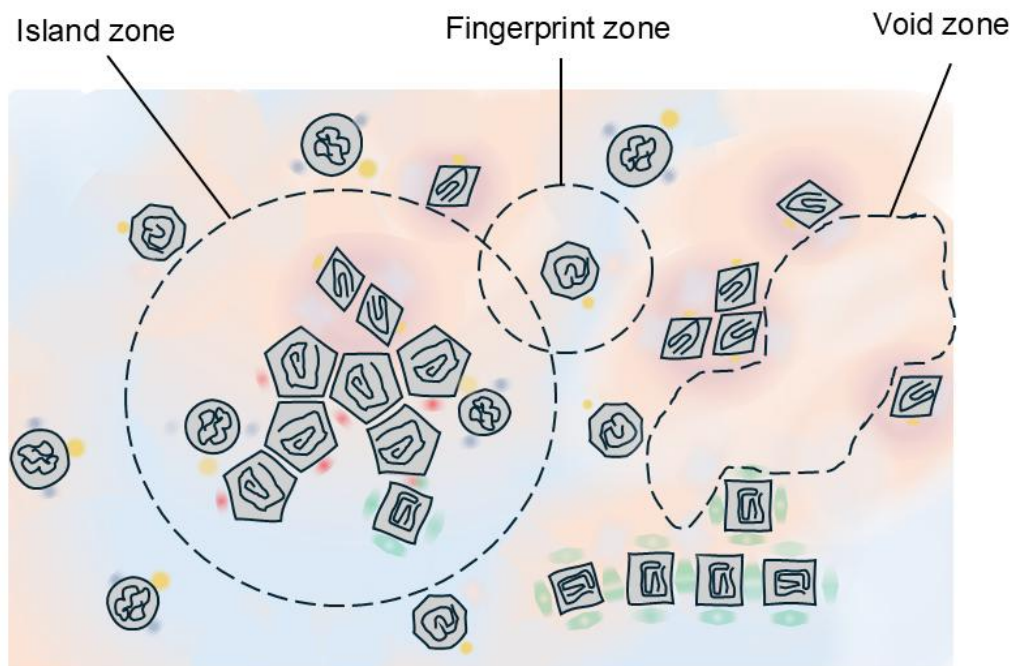

Figure 1. Depiction of the proteolipid code, with proteins as grey shapes and averaged lipid distributions as coloured gradients. Three zones are labeled, which can be imagined as open sets on a topological space. Each protein has a unique lipid fingerprint that interacts with other fingerprints. Any departures from the true proteolipid code are entirely a result of the illustrator's carelessness and not his misapprehension.

The proteolipid code has been generally well-received, though it has encountered resistance from proponents of the lipid raft theory. This has limited the model's visibility so far. Nonetheless, I think the proteolipid code's ability to challenge prevailing assumptions underscores its value. Looking ahead, a database of zones should be built and used with artificial intelligence to predict the structures and dynamics of membranes with high accuracy. Despite having climbed the cryo-EM sample preparation learning curve, I am transitioning away from experiments to continue developing and applying the proteolipid code.

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