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Review

The basic structure and dynamics of cell membranes: An update of the Singer–Nicolson model ☆

Q1 Félix M. Goñi *

Q2 *Unidad de Biofísica (CSIC, UPV/EHU), Universidad del País Vasco, P.O. Box 644, 48080 Bilbao, Spain*
Departamento de Bioquímica, Universidad del País Vasco, P.O. Box 644, 48080 Bilbao, Spain

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ABSTRACT

The fluid mosaic model of Singer and Nicolson (1972) is a commonly used representation of the cell membrane structure and dynamics. However a number of features, the result of four decades of research, must be incorporated to obtain a valid, contemporary version of the model. Among the novel aspects to be considered are: (i) the high density of proteins in the bilayer, that makes the bilayer a molecularly "crowded" space, with important physiological consequences; (ii) the proteins that bind the membranes on a temporary basis, thus establishing a continuum between the purely soluble proteins, never in contact with membranes, and those who cannot exist unless bilayer-bound; (iii) the progress in our knowledge of lipid phases, the putative presence of non-lamellar intermediates in membranes, and the role of membrane curvature and its relation to lipid geometry, (iv) the existence of lateral heterogeneity (domain formation) in cell membranes, including the transient microdomains known as rafts, and (v) the possibility of transient and localized transbilayer (flip-flop) lipid motion. This article is part of a Special Issue entitled: Membrane structure and function: Relevance in the cell's physiology, pathology and therapy.

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1. Introduction

Biomembranes constitute the cell boundaries, and the boundaries of organelles within the cell. They consist of a hydrophobic matrix, formed by an oriented double layer of phospholipids (glycolipids in plants) to which proteins are bound in different forms. Membranes exist in a condensed state, and belie the extended notion that all biochemical reactions occur in aqueous solutions. A very important part of the biochemical processes that are essential for the cell occur within the cell membranes, *i.e.* in a condensed state. This is shown by the fraction of cell enzymes that exist in membrane-bound form, higher in the more complex organisms, and as high as one-fourth in the human species.

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* Fax: +34 94 601 33 60.
E-mail address: felix.goni@ehu.es.

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Our current view of the structure and dynamics of biological membranes is framed within the 1972 "fluid mosaic" model of Singer and Nicolson [1]. In turn, this was influenced by the previous Danielli and Davson (1935) model [2], which had already proposed the double layer of phospholipids as the basic structural element of biomembranes (Fig. 1). Singer and Nicolson's model was an instant success, because it incorporated in a simple, rational form a large number of experimental observations and ideas amassed in the 50s and 60s, many of which appeared to be irreconcilable at the time. The success was not only very fast, it has also been long-lasting since, after four decades, the Singer–Nicolson "cartoon" appears unchanged in the Membranes chapter of every textbook in Biochemistry or Cell Biology.

In fact, the fluid mosaic model has resisted remarkably well the ravages of time, and this in a field where research has been very active, with important new hypotheses having appeared and disappeared in the mean time. As a consequence our view of biomembrane structure does not remain the same as forty years ago. A number of fundamental concepts have been established in this period, which complement and expand the original model, without destroying its foundations. The present review is aimed at summarizing some of these novel aspects of biomembrane structure and dynamics (novel with respect to 1972). Q4

2. Membranes according to Singer and Nicolson (1972)

It may be useful as a starting point to review briefly the main features of the Singer and Nicolson model. To begin with, the "fluid mosaic" owes its name on one hand to the obvious similitude of the lipid polar headgroups in Fig. 1B with the *tesellae* in a Roman mosaic, and on the other hand to the fact, emphasised by Singer and Nicolson, that unlike in the ancient mosaics, in cell membranes both lipids and proteins are in constant motion, *e.g.* diffusing along the plane of the membrane, or rotating around an axis perpendicular to the membrane plane. Among the specific features of the model, we should mention: Q5

(a) Lipids are organized in a double layer, or bilayer [3]. Membrane lipids are amphipathic, *i.e.* they possess both a hydrophobic and a hydrophilic moiety. This occurs in phospholipids, glycolipids, and sterols. Because of this amphiphatic character, in an aqueous medium they can organize themselves on both sides of an imaginary plane, with the hydrophobic portions facing each other, and the polar moieties oriented to the outer, aqueous space. In fact, when dry lipids are mixed with water, they spontaneously organize themselves in bilayers, *e.g.* during liposome formation. (Note however that certain lipids do not give rise spontaneously to bilayers, they are the so-called "non-lamellar lipids", see below.) The bilayer in aqueous medium provides a simple method for the thermodynamic stabilization of a population of molecules that are neither entirely hydrophobic nor entirely hydrophilic. As mentioned above, Singer and Nicolson recovered the bilayer concept from Danielli and Davson, after the idea had been severely criticized in the 60s.

(b) Membrane proteins can be associated either to the lipid bilayer polar headgroups (peripheral proteins) or to the hydrophobic matrix (integral proteins). Protein binding to the bilayer outer region had been proposed by Danielli and Davson, but the idea of proteins embedded in a hydrophobic milieu, while supported by experimentation in the late 60s and early 70s, had never been proposed in a clear and explicit way before. In fact peripheral (or extrinsic) and integral (or intrinsic) proteins [4] were independently defined in a purely operational way: peripheral proteins would be those that could be released from membranes using relatively gentle methods, such as changes in buffer pH, or ionic strength, while integral proteins would be amphipathic molecules requiring the use of more drastic agents, *e.g.* detergents, or organic solvents. In practice, the correspondence between these two groups of proteins classified after their solubilization properties, and the two ways of protein association to bilayers in the Singer–Nicolson model have led to the almost always accurate identification of the two kinds of proteins in the model with the corresponding two groups of differently solubilized membrane proteins in the test tube.

(c) Both lipids and proteins are in constant motion (hence the *fluid* mosaic name mentioned above). In principle three main modes of motion could be considered, rotational, translational and transbilayer, but the latter one is forbidden by the model. *Rotational* motion occurs essentially around an axis perpendicular to the plane of the membrane. Both lipids and proteins rotate around their long axis, under physiological conditions, at frequencies in the order of 10^8–10^9 s^{-1} (lipids) and 10^3–10^5 s^{-1} (proteins). Protein rotation had been considered in the original model, but not given much attention. It was experimentally demonstrated by Chapman and co-workers [5]. It was later found that all proteins, even those anchored to the cytoskeleton, rotate, and that when rotation was prevented by any means, the proteins lost their functionality. *Translational diffusion* of lipids and proteins occurs along the plane of the membrane, unhindered (in the original model) by diffusion barriers. Translational (or lateral) diffusion occurs as in conventional molecular diffusion (*e.g.* solutes in water) only in two dimensions. The diffusion coefficients are in the 10^{-8}–10^{-9} cm^2 s^{-1} range for lipids and 10^{-9}–10^{-11} cm^2 s^{-1} for integral membrane proteins [6]. Finally *transbilayer* (or flip-flop) diffusion, though in theory possible, would not occur because of the energy barrier presented by the bilayer hydrophobic core to the polar groups of lipids and proteins.

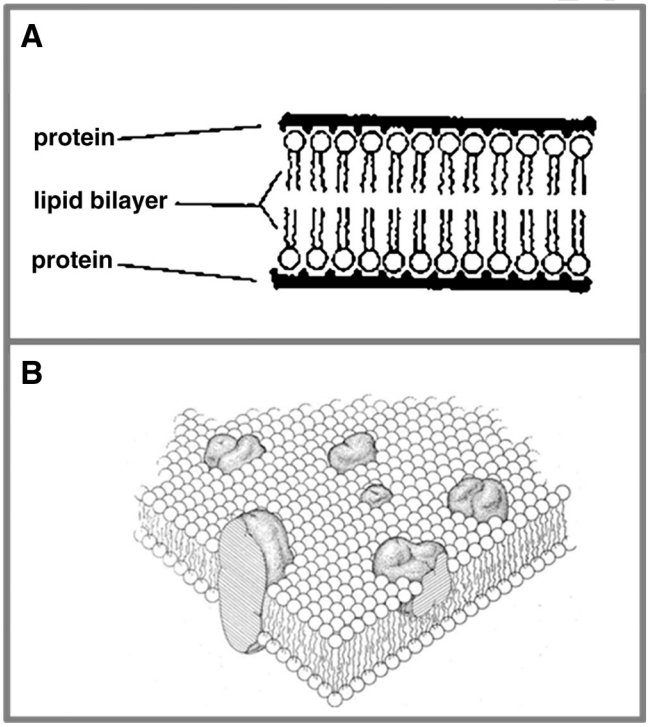

Fig. 1. Models of biomembrane structure. (A) Danielli–Daawson model (M35). (B) Singer–Nicolson model (1972).

It may be useful at this point to clarify the difference between "fluidity" and "order". They are both concepts that are widely used in the membrane field but, because they are not true physical parameters, with defined dimensions, they can be confused. *Fluidity* refers to the ensemble of molecular motions in the membrane. It is often estimated through the polarisation of fluorescence emission of hydrophobic

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