Advances in Colloid and Interface Science 208 (2014) 189–196

Contents lists available at ScienceDirect

Advances in Colloid and Interface Science

journal homepage: www.elsevier.com/locate/cis

Nonlocal membrane bending: A reflection, the facts and its relevance

S. Svetina [a,b,*], B. Žekš [a,c]

[a] Institute of Biophysics, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[b] Jožef Stefan Institute, Ljubljana, Slovenia
[c] University of Nova Gorica, Nova Gorica, Slovenia

ARTICLE INFO

Available online 24 January 2014

Keywords:
Lamellar membranes
Area difference elasticity
Vesicle shape
Membrane tethers
Flip-flop
Vesicle fusion
Monocellular sheets

ABSTRACT

About forty years ago it was realized that phospholipid membranes, because they are composed of two layers, exhibit particular, and specific mechanical properties [1–3]. This led to the concept of nonlocal membrane bending, often called area difference elasticity. We present a short history of the development of the concept, followed by arguments for a proper definition of the corresponding elastic constant. The effects of the nonlocal bending energy on vesicle shape are explained. It is demonstrated that lipid vesicles, cells and cellular aggregates exhibit phenomena that can only be described in a complete manner by considering nonlocal bending.

Contents

1. Introduction

Envelopes of phospholipid vesicles, cellular organelles, cells and certain more complex biological entities with a closed surface are in general lamellar membranes or their analogous layered structures. In many cases the distances between the individual layers of these structures are fixed. For example, the hydrophobic interaction between the two layers of a phospholipid membrane dictates that they are in close contact. A salient feature of this bilayer is, however, that these two layers are unconnected, meaning that they can, if forced to, slide one over the other. Consequently, lateral stresses on them are relaxed independently. Such a response is essentially nonlocal because the

---

* Corresponding author at: Institute of Biophysics, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia. Tel.: +386 1 5437602; fax: +386 1 5437601.
E-mail address: sasa.svetina@mf.uni-lj.si (S. Svetina).

0001-8686/$ – see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.cis.2014.01.010

relaxation is spread over the whole closed surface. It has to be noted that, while the stretching deformation of a single-layered membrane in its liquid state is described by a single deformational mode, that of a membrane bilayer involves two independent deformational modes, one pertaining to the area expansivity and the other to the relative stretching of the two layers, which can be also viewed as nonlocal bending. Envelopes of cells can have, in addition to their phospholipid bilayer other accompanying layers, which implies their more complex behavior. However, if an additional layer is at a fixed distance from the already existing layers, its area is determined by their areas and it does not constitute a new degree of freedom. A single nonlocal bending energy term, of the same type as that derived for the bilayer, is thus applicable also to membranes with a number of layers larger than two.

Nonlocal bending energy has been comprehensively discussed in several reviews [4–8]. However, there remain some motives for further discussion. One is to provide a more focused discussion, since none of those reviews were devoted solely to the nonlocal bending aspects. Further, there are some technical issues which still need to be settled: the energy term is known under different names (relative stretching, nonlocal bending, area difference elasticity), and there are different definitions for the corresponding material constant. Use of the concept may be hampered by the absence of well established, unified views. The nonlocal aspect of bending energy is also often left in the shade. For example, in an influential review on biological applications of membrane bending, the nonlocal bending contribution is scarcely mentioned [9]. An even stronger reason for a critical review is that, despite the comprehensive work of Miao et al. [10], it is still possible to find in the literature some disparate views about the effect of nonlocal bending energy on vesicle shape. A possible reason for some ambiguities in the use of this energy term and its neglect could be that some earlier developments of the related concepts are in widely scattered and not so readily accessible literature. It thus seems appropriate to round up the subject by collecting all the essential concepts together. The particular reason for this review to be part of this volume is the pioneering contribution of Wolfgang Helfrich [1] in identifying the problems of the mechanics of bilayer membranes.

The review is divided into sections on the mathematical formulations of membrane nonlocal and local bending energies, on the history of the development of the concept of nonlocal bending, on the definition and measurement of the corresponding membrane material constant, and on the effects of the nonlocal bending energy on vesicle shape. We conclude with a selection of examples aimed at illustrating the role of nonlocal bending energy in vesicle and cell phenomena.

2. Mathematical formulation of nonlocal and local bending energies

The nonlocal bending energy (W_r) is introduced by showing how the material parameters involved depend on those of the constituent layers. For a thin, closed membrane composed of any number of layers, it can be expressed as

$$W_r = \frac{1}{2}\,\frac{k_r}{A_0}\left(\overline{C} - \overline{C}_0\right)^2 \tag{1}$$

where k_r is the nonlocal bending constant, A_0 is the membrane area, $\overline{C}$ is the integral of the sum of the principal membrane curvatures C_1 and C_2 over the membrane area (which, from here on, we call the integrated curvature)

$$\overline{C} = \int (C_1 + C_2)\, dA_0, \tag{2}$$

and $\overline{C}_0$ the preferred (equilibrium) value of this integral (the preferred integrated curvature).

Phospholipid membranes in their liquid state at curvatures smaller than the reciprocal of few membrane thicknesses exhibit no shear. The material properties that appear in Eq. (1) can be for such membranes expressed [11] in terms of the preferred areas ($A_{0,\mathrm{i}}$) and the area expansivity moduli (K_i) of the constituent n layers ($\mathrm{i} = 1,2,\ldots n$) and the distances between their neutral surfaces and the membrane neutral surface (h_i) as

$$A_0 = \frac{\sum_{\mathrm{i}=1}^{n} K_\mathrm{i}}{\sum_{\mathrm{i}=1}^{n} \frac{K_\mathrm{i}}{A_{0,\mathrm{i}}}}, \tag{3}$$

$$k_r = A_0 \sum_{\mathrm{i}=1}^{n} \frac{K_\mathrm{i} h_\mathrm{i}^2}{A_{0,\mathrm{i}}}, \tag{4}$$

and

$$\overline{C}_0 = \frac{A_0}{k_r} \sum_{\mathrm{i}=1}^{n} K_\mathrm{i} h_\mathrm{i}. \tag{5}$$

The membrane neutral surface is defined as the surface that determines the extension of the whole membrane relative to its preferred area A_0. Its distance from a chosen layer is defined by the condition

$$\sum_{\mathrm{i}=1}^{n} \frac{K_\mathrm{i} h_\mathrm{i}}{A_{0,\mathrm{i}}} = 0 \tag{6}$$

from which its position can be obtained from the $n - 1$ distances between neighboring layers. In general, Eq. (1) is not limited to the description of closed surfaces; it also contributes to the mechanical behavior of any membrane whose layers are all laterally constrained at the membrane border. Why Eq. (1) is a convenient definition of the nonlocal bending energy term will be discussed in Section 4.

The nonlocal bending energy is distinct from the ordinary membrane bending energy that represents local membrane properties and is given by the integral over the area densities of the local (W_b) and Gaussian (W_G) bending energies

$$W_b + W_G = \frac{1}{2} k_c \int (C_1 + C_2 - C_0)^2 dA_0 + k_G \int C_1 C_2 dA_0, \tag{7}$$

where k_c is the local bending constant, k_G is the Gaussian bending constant, and C_0 is the spontaneous curvature [12]. The nonzero spontaneous curvature C_0 reflects transmembrane asymmetry — an unsupported piece of an asymmetrical membrane would assume mechanical equilibrium in a curved conformation with radius $2/C_0$. The local and Gaussian bending constants are sums over the corresponding constants of the constituent layers, whereas the spontaneous curvature is given in terms of these constants as

$$C_0 = \frac{\sum_{\mathrm{i}=1}^{n} k_{c,\mathrm{i}} C_{0,\mathrm{i}}}{k_c}, \tag{8}$$

where $k_{c,\mathrm{i}}$ is the bending constant and $C_{0,\mathrm{i}}$ is the spontaneous curvature of the i-th layer [11].

3. History of the nonlocal bending concept

The nonlocal bending concept was established in three independent works published in 1974 to describe the elastic behavior of lipid bilayers. Helfrich [1] considered blocked lipid exchange between the monolayers of the bilayer and concluded that the effect of the consequent non-equilibrium lipid distribution goes hand in hand with membrane spontaneous curvature. Sheetz and Singer [2], by analogous reasoning, explained the shape transformations of a red blood cell arising from