Statistical Mechanics of Thermal Fluctuations of Nearly Spherical Membranes: the Influence of Bending and Stretching Elasticities

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Abstract—Theoretical studies of nearly spherical vesicles and microemulsion droplets, that present typical examples for thermally-excited systems that are subject to constraints, are reviewed. We consider the shape fluctuations of such systems constrained by fixed area $A$ and fixed volume $V$, whose geometry is presented in terms of scalar spherical harmonics. These constraints can be incorporated in the theory in different ways. After an introductory review of the two approaches: with an exactly fixed by delta-function membrane area $A$ [Seifert, Z. Phys. B, 97, 299 (1995)] or approximatively by means of a Lagrange multiplier $\sigma$ conjugated to $A$ [Milner and Safran, Phys. Rev. A, 36, 4371 (1987)], we discuss the determined role of the stretching effects, that has been announced in the framework of a model containing stretching energy term, expressed via the membrane vesicle tension [Bivas and Tonchev, Phys. Rev. E, 100, 022416 (2019)]. Since the fluctuation spectrum for the used Hamiltonian is not exactly solvable an approximating method based on the Bogoliubov inequalities for the free energy has been developed. The area constraint in the last approach appears as a self-consistent equation for the membrane tension. In the general case this equation is intractable analytically. However, much insight into the physics behind can be obtained either imposing some restrictions on the values of the model parameters, or studying limiting cases, in which the self-consistent equation is solved. Implications for the equivalence of ensembles have been discussed as well.

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INTRODUCTION

The biomembrane consists of a lipid bilayer, in which integral proteins float [1]. Within this model, their physical properties are tightly connected with those of the lipid bilayer. The complicated role of biological membranes helped forward the study of artificial lipid-based models with a primary view of reconstituting their inherent functions in vitro. Lipid membranes are important model systems for biological membranes (see [2] and refs. therein). Easily formed from lipid solutions this field involves the investigation of transport mechanisms, permeation properties, adhesion, and fusion kinetics (see [3] and refs. therein).

In this review we shall consider the role of thermal fluctuations on the behavior of closed free standing artificial membranes. To a large extent, the physics of closed membranes is the physics of microemulsions and vesicles (also known as liposomes).

The microemulsions are thermodynamically stable water-oil mixtures and one or few surface active agents (called also surfactants). Probably one of the simplest microemulsion systems are droplets of water in oil (or vice versa), covered with a monolayer of surfactant molecules.

The vesicles are analogous to droplet type microemulsions where the most important difference is that their interface is a bilayer instead of a monolayer. They are closed-surface membranes formed spontaneously from molecules in aqueous environment due to the hydrophobic effect. For example, Giant unilamellar vesicles (GUVs) have diameters in the interval 1–200 $\mu$m. Because of the extremely small thickness of the membrane as compared to the square root of their area, the vesicle for many purposes can be modeled as two-dimensional flexible surface embedded in three-dimensional space.

Thought both the vesicle and the microemulsion systems belong to quite different length scale, their
thermodynamic behavior can be understood from a unified point of view based on study of the free energy of the deformed membrane [4].

The shape of a monolayer membrane depends mainly on its stretching $g_s$ and curvature $g_c$ energy densities

$$ g = g_s + g_c. \quad (1) $$

The elastic energy of stretching per unit area (in a quadratic approximation) has the form

$$ g_s = \frac{1}{2} K_s (\Delta A/A_0)^2, \quad (2) $$

where $\Delta A/A_0$ is the relative area change of the membrane, $A_0$ is the area in its tension free state, and $K_s$ is the stretching elasticity modulus [5].

The curvature elasticity, as one of the most important quantities for determining the membrane shape, was introduced in the beginning of the seventies of the last century with the theory developed by Canhamm [6], Helfrich [5] and Evans [7]. The theory of spherical vesicles is based on the notion that their bending elastic energy is size independent, since the bending energy per unit area of a symmetric bilayer is a quadratic form in curvatures [8]. In the used quadratic approximation the curvature-elastic energy per unit area of a fluid layer may be written as [5]

$$ g_c = \frac{1}{2} K_c (c_1 + c_2 - c_s)^2 + K_g c_1 c_2. \quad (3) $$

Here $c_1, c_2$ are the principal curvatures and $c_s$ is the spontaneous curvature. The constant $K_c$ is the bending rigidity modulus. The last term in (3) contains the modulus of the Gaussian curvature $K_G$, which should be omitted, in general, as when integrated over a closed surface it is a topologically invariant constant.

The derivation of $K_s$ and $K_c$, from the first principles for the membrane energy functional $g$, is given in [9]; where it has been obtained for the typical phospholipids, $K_s \sim 200 \text{erg/cm}^2$ and $K_c \sim 2 \times 10^{-12} \text{erg}$. Actually, the quadratic form Eq. (3) seems to be the best possible approximation consistent with isotropy, fluidity and Euclidean invariance shape dependence of the membrane (for a comment, see Appendix A of [9]). For more complete and detailed comments the reader can see the review [10], where the tools of differential geometry are used to obtain the Helfrich Hamiltonian.

The effective Hamiltonian (the total bending energy stored in the infinitely thin interface $A$ of the vesicle in a second order expansion of curvatures) has the form:

$$ H_c = \int dS \left[ \frac{1}{2} K_c (c_1 + c_2 - c_s)^2 + K_g c_1 c_2 \right], \quad (4) $$

where the integration is carried out over the total area $A$ of the membrane.

At first in our consideration, the membranes will be assumed to be unstretchable (viz. with $K_s = \infty$) and their finite thickness will be disregarded. As we shall see below, the former is not a obligatory requirement, while the last approximation is assumed in order to avoid difficulties of integration over random surfaces [11] in the calculations of the free energy and corresponding thermodynamic mean values. The material quantities $K_s$ and $K_c$ depend on the intermolecular interactions and structural properties of the membrane. Elasticity of lipid monolayers in the framework of different molecular models are discussed in some details in Ch. 4.2 of the monograph [2]. Strictly speaking, $K_s$ and $K_c$ cannot be considered independently of the thermal fluctuations, because integrating out the microscopic degrees of freedom, in the Helfrich theory, the resulting coarse-grained Hamiltonian (4) will contain the temperature dependent phenomenological parameters $K_s$ and $K_c$. The convention in this review is that when we talk about thermal fluctuations we take into account only fluctuations of the geometry of the membrane [10]. The spectrum of thermally excited undulation modes of a quasi-spherical vesicle can be calculated analytically in the limit of large bending rigidities $K_c/k_B T \gg 1$, $T$ is the temperature and $k_B$ is the Boltzmann constant. (Helfrich, 1986 [8], Milner and Safran, 1987 [12], Seifert, 1995 [13]). It can be applied to determine experimentally the bending rigidity $K_c$ through the the contour fluctuations of quasi-spherical vesicles using phase contrast microscopy combined with fast image processing, nowadays also called as flicker spectroscopy analysis [15–25].

## 1. MEMBRANE GEOMETRY AND THE HELFRICH BENDING HAMILTONIAN IN TERMS OF SPHERICAL HARMONICS

We consider a vesicle with volume $V$ that has the form of slightly deformed sphere, i.e. a quasi-sphere. Let us denoted by $R_0$ the radius of an ideal spherical vesicle with the same volume $V = (4\pi/3)R_0^3$ as that the studied one. The statistical fluctuations of the shape of the vesicle membrane in time are around the reference sphere with area $4\pi R_0^2$. In this case the membrane configuration can be well represented using spherical harmonic functions. Let us take the quasi-sphere radius $R$ to be a function of the time $t$, the polar angle $\varphi$ and the azimuthal angle $\theta$, writing

$$ R(\theta, \varphi, t) = R_0 [1 + u(\theta, \varphi, t)], \quad (5) $$

thus $R_0 = [3/(4\pi V)]^{1/3}$ is the effective radius from which the displacements (the fluctuations) $u(\theta, \varphi, t)$
are supposed to start. It is assumed that \( |u(\theta, \phi, t)| \ll 1 \), so that all the further calculations are performed up to the second order in \( u(\theta, \phi, t) \) in order to simplified the theoretical expressions. The dimensionless function \( u(\theta, \phi, t) \) can be decomposed in a series of spherical harmonics as follows:

\[
  u(\theta, \phi, t) = \sum_{n=0}^{n_{\text{max}}} \sum_{m=-n}^{n} u_n^m(t)Y_n^m(\theta, \phi),
\]

where \( Y_n^m(\theta, \phi) \) is the orthonormal basis of the spherical harmonics functions and since the displacement is real the relation \( (u_n^m)^* = (-1)^m u_n^{-m} \) takes holds. For vesicles of slightly deformed spherical shapes, one can calculate the bending energy \( H_c \) by inserting the spherical harmonics expansion Eq. (6) into Eq. (4) and use, as a rule, the lowest approximation neglecting all terms of higher than quadratic order in coefficients \( u_n^m \). It can be proved that all using expressions containing complex amplitudes may be rewritten in such a way that the imaginary parts of \( u_n^m \) vanish and only real amplitudes appear. Thus without loss of generality \( u_n^m \) should be chosen real. For details see, e.g. [8, 17, 26–28].

For numerical computations it is also more convenient to use real amplitudes of spherical harmonics instead of the complex ones.

The lipid vesicle is subject to various geometric constraints. If it is viewed as impermeable and incompressible the number of lipid molecules in the membrane is fixed. In this case the vesicle has constrained area \( A \) and constrained volume \( V \). Expressing the geometrical quantities \( A \) and \( V \), and the effective Hamiltonian \( H_c(u) \) of the vesicle as a function of the expansion coefficients \( u_n^m \) one has [8, 12, 14, 18, 26, 27, 29–31]:

\[
  A(u) = 4\pi R_0^2 \left[ \frac{u_0}{\sqrt{\pi}} + \frac{(u_0^*)^2}{4\pi} \right] + \left( \frac{n}{2} \right) \left( \frac{n+1}{2} \right) u_n^{m^2} + O(u_n^{m^4}),
\]

for the area, and

\[
  V(u) = \frac{4\pi}{3} R_0^3 \left[ 1 + \frac{u_0^0}{\sqrt{4\pi}} + \frac{3}{4\pi} \sum_{n=2}^{n_{\text{max}}} \sum_{m=-n}^{n} u_n^{m^2} \right] + O(u_n^{m^4}),
\]

for the volume. Here and hereafter the symbol “\( u \)” is used as a shorthand for the real value functions \( u_0^0, u_1^0, \ldots, u_{n_{\text{max}}}^0 \), which are the spherical harmonics amplitudes, appearing in the expansion of the vesicle shape fluctuations from the equivalent volume sphere with radius \( R_0 \) (see Eq. (6)).

A cut-off \( n_{\text{max}} = 2\sqrt{n_{\text{max}}/\lambda} \) is introduced in the sum, where \( \lambda \) is of the order of the intermolecular distance. As the harmonics with indexes \( n = 1 \) and \( m = -1, 0, 1 \) correspond to pure translation of the vesicle, the origin \( O \) of the coordinate system can be chosen in away that \( u_0^m = 0 \). Thus, from now on all sums start at \( n = 2 \).

Finally, considering the special case of vanishing spontaneous curvature \( (c_s = 0) \), for the effective Hamiltonian \( H_c(u) \) in terms of \( u_n^m \), one finds:

\[
  H_c(u) = 8\pi K_c + \frac{K_s}{2} \sum_{n=2}^{n_{\text{max}}} \sum_{m=-n}^{n} (n-1)n(n+1) (u_n^m)^2 + O((u_n^m)^4).
\]

Further we shall discard in \( H_c(u) \) the constant energy term \( 8\pi K_c \).

2. THE AREA AND THE VOLUME CONSTRAINTS

The constant–area constraint or the constant-volume constraint can be easily incorporated in the theory, separately [13, 29, 32], by choosing \( u_0^0 \) to satisfy

\[
  A = 4\pi R_0^2 \text{ in Eq. (7), or } V = \frac{4}{3}\pi R_0^3 \text{ in Eq. (8)}.
\]

However, if it is technically easy to implement the second constraint, then it is difficult to handle the first one or vice-versa. Regardless of either volume or area is kept constant these conditions leads to the elimination of the \( u_0^0 \)-term. In what follows, we shall assumed the vesicle volume \( V \) to be invariant under shape fluctuations. Thus, the volume constraint

\[
  V(u) = \frac{4}{3} \pi R_0^3
\]

implies

\[
  u_0^0 = -\frac{1}{4\pi} \sum_{n=2}^{n_{\text{max}}} \sum_{m=-n}^{n} (u_n^m)^2 + O((u_n^m)^4).
\]

After that, inserting Eq. (11) in Eq. (7), for the area, keeping terms to \( O(u^2) \), one gets

\[
  A(u) = 4\pi R_0^2 \left[ 1 + \frac{1}{8\pi} \sum_{n=2}^{n_{\text{max}}} \sum_{m=-n}^{n} (n+2)(n-1)(u_n^m)^2 \right].
\]

Now, it is a more sophisticated problem to fix the area, Eq. (12), of the membrane:

\[
  A(u) = \text{A}.
\]

In order to include Eq. (13) in our consideration one needs to use the methods of statistical mechanics. First of all let us recall some basic definitions. We start from the Helmholtz free energy \( f[H(u)] \):

\[
  f[H(u)] = -k_B T \ln \{ Z[H(u)] \}.
\]
where $Z[H(u)]$ is the partition function of the considered quasi-spherical membrane (droplet microemulsion and vesicle) with an effective Hamiltonian $H(u)$ (see below):

$$Z[H(u)] = \int D[u] \{ \exp[-\beta H(u)] \},$$

where $\beta = (k_B T)^{-1}$.

Note that the correct definition of the measure $D[u]$ is a subtle task in statistical mechanics of two-dimensional surfaces (see [13, 14, 31, 33, 34] and refs. therein). However, for a quasi-spherical membrane we don’t need to go beyond the so-called normal gauge, which is known to be correct for small fluctuations, at least to the level of accuracy consistent with the used quadratic approximation in Eq. (9) [13, 14, 30]. At this level the proper measure is $D[u] = \text{const.} \{ d[u_2^{-2}], d[u_2^{-1}], \ldots, d[u_{\text{max}}^{n_{\text{max}}}] \}$ and the integration over $u_n^{n_{\text{max}}}$ in Eq. (15) is carried out from 0 to $\infty$.

If the Hamiltonian $H(u)$ is a positive definite diagonal quadratic form in the real value functions $(u_2^{-2}, u_2^{-1}, \ldots, u_{\text{max}}^{n_{\text{max}}})$ then the multiple integral in Eq. (15) over $u_n^{n_{\text{max}}}$ splits into a product of $N = \sum_{n=2}^{n_{\text{max}}} \sum_{m=-n}^{n_{\text{max}}} n_{\text{max}}^2 + 2n_{\text{max}} - 3$ one-dimensional Gaussian integrals and the integration can be performed easily.

Commonly there are two alternative possibilities how to incorporate the area constraint in the partition function Eq. (15): exact treatment of the area constraint with a delta function [13, 14, 35, 36] and with an effective tension through Lagrange multiplier [12, 13, 18, 37]. It is evident that the two approaches model two different statistical ensembles; $A$-ensemble and $\sigma$-ensemble. The equivalence of the ensembles is taken for granted too often in the membrane fluctuation theories. However, it is questionable whether this equivalence holds for all characteristics of the system. As we show below this problem needs to be carefully considered.

### 3. THE EXACT TREATMENT OF THE AREA CONSTRAINT

First, in our consideration we keep the global surface area constant, so we can assume that the area compressibility modulus $K_s = \infty$. The exact treatment of the area constraint by delta-function is based on the evaluation of the following partition function (see, e.g. [13, 36]):

$$Z[H_s(u); A] = \int D[u] \delta \left( \frac{A - A(u)}{4\pi R_0^2} \right) \exp[-\beta H_s(u)].$$

Hereafter for convenience the dependence on $A$ in the argument of the delta-function is explicitly shown in the arguments of the partition function and in the corresponding free energy

$$F[H_s(u); A] = -\beta^{-1} \ln \{ Z[H_s(u); A] \}. \quad (17)$$

In order to impose condition Eq. (13) we use the Laplace transform representation of the delta-function

$$\delta(x-y) = \frac{1}{2\pi i} \int_{a-i\infty}^{a+i\infty} e^{s(x-y)} \, ds, \quad (18)$$

where $s$ is a complex variable and its real part is $a > 0$. In our case we have (compare with Eq. (15) in [36])

$$\delta \left( \frac{1}{8\pi} \sum_{n=2}^{n_{\text{max}}} \sum_{m=-n}^{n_{\text{max}}} (n + 2)(n - 1)(u_n^{m_2})^2 - \Delta \right) = \frac{1}{2\pi i} \int_{a-i\infty}^{a+i\infty} ds \times \exp \left[ \frac{1}{8\pi} \sum_{n=2}^{n_{\text{max}}} \sum_{m=-n}^{n_{\text{max}}} (n + 2)(n - 1)(u_n^{m_2})^2 - \Delta \right],$$

where

$$\Delta \equiv \frac{A - 4\pi R_0^2}{4\pi R_0^2},$$

defines the dimensionless (positive) excess area used in the further consideration as a small parameter in the model. Note that our definition of the excess area differs from those used in [13] by $4\pi$. After interchanging the integrals in Eq. (16), one obtains

$$Z[H_s(u); A] = \frac{1}{2\pi i} \int_{a-i\infty}^{a+i\infty} dse^s Z[H(u;s)]. \quad (21)$$

Here, $Z[H(u;s)]$ is the partition function of the temperature dependent “Hamiltonian”

$$H(u; s) = H_s(u) + \frac{s}{\beta} \left[ \frac{1}{8\pi} \sum_{n=2}^{n_{\text{max}}} \sum_{m=-n}^{n_{\text{max}}} (n + 2)(n - 1)(u_n^{m_2})^2 - \Delta \right], \quad (22)$$

with the auxiliary complex parameter $s$. The real part $a > 0$ of $s$ is chosen so that the integral in Eq. (21) is finite. It will be convenient to introduce a new dimensionless quantity

$$\tilde{\sigma}_s = \frac{s}{4\pi \beta K_s}. \quad (23)$$

From Eqs. (22) and (9), we obtain:

$$H(u,s) = 4\pi K_s \Delta \tilde{\sigma}_s + \sum_{n=2}^{n_{\text{max}}} \sum_{m=-n}^{n_{\text{max}}} a_n(\tilde{\sigma}_s)(u_n^{m_2}), \quad (24)$$

where

$$a_n(\tilde{\sigma}_s) = \frac{1}{2} K_s (n-1)(n+2) [n(n+1) + \tilde{\sigma}_s]. \quad (25)$$

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Now, it is convenient to introduce the following quantities:

\[ w_n^m \equiv u_n^m \left( \frac{K \beta n}{2} (n + 2)(n - 1) \right)^{1/2}, \tag{26} \]

\[ p_n \equiv n(n + 1), \quad \frac{1}{\tau} \equiv 4\pi K_c \beta \Delta. \]

Then partition function \( Z[H(u; s)] \) is presented as:

\[
Z[H(u; s)] = Z_0 \int D[w] \times \exp \left( -\sum_{n=2}^{\infty} \sum_{m=-n}^{n} (p_n + \sigma_n)(w_n^m)^2 + \frac{\tau}{4} \right),
\]

where \( Z_0 \) is an independent of \( s \) factor. The partition function \( Z[H(u; s)] \) is known (the corresponding integrals over \( w_n^m \) are Gaussian). Thus one obtains

\[
Z[H_1(u); A] = \int_{\sigma - \tau} \int Ds \exp \left( -\sum_{n=2}^{\infty} \sum_{m=-n}^{n} (p_n + \sigma_n)(w_n^m)^2 + \frac{\tau}{4} \right).
\]

For \( \tau \ll 1 \), i.e. \( 1/(\beta K_c) \ll 1 \) and \( \tau \gg 1 \), i.e. \( 1/(\beta K_c) \gg 1 \), analytical calculations for the mean square amplitudes \( u_n^m \) were performed in [13, 14]. For completeness let us briefly sketch the results for each of the two cases. The integral in Eq. (28) can be treated by the method of steepest descent.

In the case, \( \tau \ll 1 \), the results are:

\[
\langle (u_n^m)^2 \rangle_{H(u; A)} = \frac{1}{5} \frac{1}{\beta K_c \tau} \times \left[ 1 - \frac{\tau}{2} \sum_{n=2}^{\infty} \frac{1}{(n + 2)(n - 1)(n^2 + n - 6)} + O(\tau^3) \right],
\]

for \( n = 2 \), and

\[
\langle (u_n^m)^2 \rangle_{H(u; A)} = \frac{1}{\beta K_c} \times \left[ \frac{1}{(n + 2)(n - 1)(n^2 + n - 6)} + O(\tau^2) \right],
\]

for \( n \geq 3 \). An expansion beyond the leading terms for small \( \tau \) is possible but in this case the truncated higher order terms in the expansions Eqs. (7)–(9) should be taken into account for the consistency of the used approximation.

In the opposite case, \( \tau \gg 1 \), the bending energy can be treated as small perturbation and in lowest order the result is:

\[
\langle (u_n^m)^2 \rangle_{H(u; A)} = \frac{1}{\beta K_c} \left[ \frac{2}{N(n + 2)(n - 1)} + O(\tau) \right],
\]

where \( N = \sum_{n=2}^{\infty} \sum_{m=-n}^{n} (n_{\text{max}} + 1)^2 - 4 \) is the available number of modes.

\[
4. \ \text{THE CONVENTIONAL APPROACH WITH EFFECTIVE TENSION}
\]

The approach to the problem, due to the Milner and Safran (1987), and Seifert (1995), is to treat \( Z[H(u; s)] \) in Eq. (21) as a “grand-canonical” partition function, where now \( s \) is a real variable (called effective tension and denoted with \( \sigma \) ) conjugate to \( A(u) \). Rather than a free parameter. The value of \( \sigma \) is chosen so that the area constraint Eq. (13) is satisfied on the average. Note that the situation here strongly resembles the relation between the Berlin and Kac spherical model and Lewis and Wannier mean spherical model in the theory of magnetism, which belong to different ensembles with “canonical” and “grand canonical” partition functions, see e.g. [38] and Ch. 3 in [39].

In other words, instead of working with fixed area \( A(u) \), an effective tension as Lagrange multiplier \( \sigma \) conjugated to \( A(u) \) has been used. In this case the Hamiltonian of the model takes the form:

\[
H(u; \sigma) = H_1(u) + \sigma A(u).
\]

This model is essentially a Gaussian model with a constraint on the area of the vesicle enforced by \( \sigma \). The partition function can be thought as corresponding to an ensemble which extends the \( A \)-ensemble by allowing fluctuations of the area in a system of fixed volume \( V \). The partition function is given by

\[
Z[H(u; \sigma)] = \int D(u) \exp \left[ -\beta H(u; \sigma) \right],
\]

and the corresponding free energy is given by

\[
F[H(u; \sigma)] = -\beta^{-1} \ln \{ Z[H(u; \sigma)] \}.
\]

We shall define the thermodynamic average of the quantity \( A(u) \) with \( H(u; \sigma) \) in the standard way:

\[
\langle A(u) \rangle_{H(u; \sigma)} = \int D(u) A(u) \exp \left[ -\beta H(u; \sigma) \right].
\]

Let us introduce

\[
\bar{\sigma}_{\text{MS}} = \frac{K_c^2}{\sigma}
\]

which is the Milner and Safran dimensionless effective tension. If for convenience we change the notation \( H(u; \sigma) \equiv H(u; \bar{\sigma}_{\text{MS}}) \), with the help of Eqs. (9) and (12) it is easy to obtain the explicit form of the Hamiltonian Eq. (32):

\[
H(u; \bar{\sigma}_{\text{MS}}) = 4\pi \bar{\sigma}_{\text{MS}} K_c + \sum_{n=2}^{n_{\text{max}}} \sum_{m=-n}^{n} a_n(\bar{\sigma}_{\text{MS}})(u_n^m)^2,
\]

where

\[
a_n(\bar{\sigma}_{\text{MS}}) = \frac{1}{2} K_c (n - 1)(n + 1)(n(n + 1) + \bar{\sigma}_{\text{MS}}).
\]
It is constructive to compare the Hamiltonians Eqs. (24) and (37). The only difference is the change of $\sigma_0$ in the former with $\sigma_{MS}$ in the last.

Here and further on, we accept the convention the bar over any quantity to mean “dimensionless due to the multiplier $R_0^2/K_c$.”

Now, the calculation of the Gaussian integrals in Eqs. (33) and (35) is straightforward. The area constraint is

$$\langle A(u)\rangle_{H(u;\sigma_{MS})} = A,$$

or equivalently (compare with Eqs. (12) and (13))

$$1 - \frac{4\pi R_0^2}{A} \frac{R_0^2 n_{max}}{A} \sum_{n=2}^{n_{max}} \sum_{m=-n}^{n} \left[ \frac{(n+2)(n-1)}{2} \right] \times \left\langle \left( u_n^m \right)^2 \right\rangle_{H(u;\sigma_{MS})} = 0.$$  \hspace{1cm} (40)

Thus, the value of $\sigma_{MS}$ is determined from the condition that the area constraint Eq. (13) is satisfied in average. A possible equivalence of this new introduced statistical ensemble with those considered in the previous Section 3 we shall discuss in the next Section 5.

Here, for the mean square amplitudes

$$\left\langle \left( u_n^m \right)^2 \right\rangle_{H(u;\sigma_{MS})} = \left\{ Z[H(u;\sigma_{MS})] \right\}^{-1} \times \int D(u) \left( u_n^m \right)^2 \exp[-\beta H(u;\sigma_{MS})],$$

one immediately obtains (as follows from Eq. (37) the integrals are Gaussian)

$$\left\langle \left( u_n^m \right)^2 \right\rangle_{H(u;\sigma_{MS})} = \frac{8\pi \gamma}{(n-1)(n+2)[n(n+1) + \sigma_{MS}]}.$$  \hspace{1cm} (42)

where

$$\gamma \equiv \frac{1}{8\pi \beta K_c}. \hspace{1cm} (43)$$

It is commonly accepted, as a more simple approach, the membrane area constraint to be guaranteed by the Lagrange multiplier $\sigma$ (see, Eq. (32)) conjugate to the real area $A(u)$ [14, 30, 37, 40, 41]. The Lagrange multiplier cannot be measured directly, and is experimentally determined thorough the temperature and the physically meaningful quantity named excess area $\Delta_{MS}$ [13, 37]. The formula Eq. (42) allows to infer the values of $K_c$ (as follows from Eq. (43)) and $\sigma_{MS}$, treating them as fit parameters, from flicker spectroscopy analysis.

By definition the (dimensionless) excess area $\Delta_{MS}$ is related to a vesicle with fixed volume $V = \frac{4\pi}{3} R_0^3$, and with fixed in mean area, which fluctuates (due to thermal fluctuations at temperature $T > 0$) around the shape $4\pi R_0^2$, through the relation:

$$\Delta_{MS} \equiv \langle A(u) \rangle_{H(u;\sigma_{MS})} - 4\pi R_0^2 > 0. \hspace{1cm} (44)$$

Combining Eq. (40) with Eq. (44), one gets:

$$\Delta_{MS} = \frac{1}{8\pi} \sum_{n=2}^{n_{max}} \sum_{m=-n}^{n} (n+2)(n-1) \left\langle \left( u_n^m \right)^2 \right\rangle_{H(u;\sigma_{MS})}. \hspace{1cm} (45)$$

Finally, from Eqs. (42) and (45) one may conclude that the excess area obeys the implicit equation [13, 35]

$$\Delta_{MS} = \sum_{n=2}^{n_{max}} \frac{2n+1}{n(n+1) + \sigma_{MS}}.$$  \hspace{1cm} (46)

Thus, after the elimination of the Lagrange multiplier $\sigma_{MS}$, the mean value of the square of the amplitudes $\left( u_n^m \right)^2$, as it follows from Eqs. (42) and (46), depends only on $\Delta_{MS}/\gamma$ and $n_{max}$.

Equation (46) has been obtained and analyzed by many authors [12, 13, 30, 31, 35]. Excess area $\Delta_{MS}$ as a function of the ratio $\sigma_{MS}/N$ for various values of $N$ has been analyzed numerically in [31]. In such a type of theory (conventional approach with effective tension) the dimensionless excess area is used as a small parameter $\Delta_{MS} \ll 1$. Consequently the term in the r.h.s. of Eq. (46) is also small and respectively $\sigma_{MS}(\Delta_{MS})$ should be large. Our inspection of the Eq. (46) (see the details in [42]) shows that the following functional dependences take place:

$$\sigma_{MS}(\Delta_{MS}) = N \exp\left( -\frac{\Delta_{MS}}{\gamma} \right), \exp\left( -\frac{\Delta_{MS}}{\gamma} \right) \ll 1, \hspace{1cm} (47)$$

and its inverse

$$\Delta_{MS}(\sigma_{MS}) = \gamma \ln \left( \frac{N}{\sigma_{MS}} \right), \frac{N}{\sigma_{MS}} \gg 1, \hspace{1cm} (48)$$

where $N = (n_{max})^2$ is the number of lipid molecules in the vesicle membrane. Further on, when it does not cause confusion, we shall omit the arguments in $\sigma_{MS}$ and $\Delta_{MS}$. A similar relation was obtained in [13] (see also the comment in [37]) simply by replacing the sum in the r.h.s. of Eq. (46) with an integral. In our consideration [42] this sum is estimated by the Euler–McLaurin summation formula. This defines a different range of validity of our result given by the inequality in Eq. (47).

As $K_c \rightarrow 0$, the bending energy becomes irrelevant for the fluctuation amplitudes, and one may assume that
Each mode contributes equally to the excess area [12]. Thus, from Eqs. (40), and (44) immediately follows
\[
\Delta_{\text{MS}} = \frac{1}{4\pi N} \left[ \frac{(n+2)(n-1)}{2} \right] \langle (u_n^m)^2 \rangle_{H(u_0;\sigma_{\text{MS}})} \tag{49}
\]
in full consistence with Eq. (31) obtained above in the exact delta-function approach. In this limit, from Eq. (42) one gets
\[
\langle (u_n^m)^2 \rangle_{H(u_0;\sigma_{\text{MS}})} = \frac{8\pi \gamma}{(n-1)(n+2)\sigma_{\text{MS}}} \tag{50}
\]
Eliminating \( \langle (u_n^m)^2 \rangle_{H(u_0;\sigma_{\text{MS}})} \) from both equations, one obtains
\[
\sigma_{\text{MS}} = \frac{\gamma}{\Delta_{\text{MS}}} N. \tag{51}
\]
Thus, for a vesicle close to a spherical shape, i.e. \( \Delta_{\text{MS}} \to 0 \), the effective tension is expected to be proportional to \( N \) [12, 28]. Analogous to Eqs. (47) and (51) results were derived for almost planar membrane in [36]. A similar equation to Eq. (47) was analyzed for almost planar membrane in the low-tension regime in [43] attributed to entropic-tense and stretched-tense regimes, respectively. The analysis of the simulation data in the experimentally accessible tension range shows that the stretching effects of the membrane area must be taken into account.

5. EQUIVALENCE OF ENSEMBLES

In our case, on physical grounds, one is interested in the situation where the total area \( A \) of the vesicle is kept fixed. Let us mention at once that, instead of working with exactly fixed membrane area \( A \) via delta-function, an effective tension as Lagrange multiplier \( \sigma \) conjugated to \( A \) has been commonly used. In this different \((\sigma,V)\)—statistical ensemble, the free energy \( F \) depends on \((\sigma,V)\), while in the former free energy \( f \) depends on \((A,V)\). From statistical point of view the model with delta-function is defined by the joint probability distribution of the \( u_n^m \)—variables given by a measure which is different from the corresponding probability distribution for the model with Lagrange multiplier \( \sigma \). Thus the two models are in general, statistically inequivalent. Although the two approaches model two different statistical ensembles, it is widely assumed that they give equivalent results. First of all, it is worth to note that the equivalence of the ensembles is closely related with the notion of thermodynamic limit which must be well defined. Thus it will be useful to make a short comment on the subject.

The proof of the equivalence of two statistical ensembles goes back to Gibbs [44] and is a key problem of the equilibrium statistical mechanics. On the contemporary understanding the term equivalence has three different meanings, each on a different level of information (see, [45, 46]). Since the parameter \( \sigma \) cannot be measured directly one may think that the most appropriate way should be the use of the \((A,V)\)—ensemble, but as shown in the previous sections calculations within the \((\sigma,V)\)—ensemble are simpler than the calculations in the \((A,V)\)—ensemble. Thus in constrained by calculating difficulties one prefers to use the \((A,\sigma)\) and after that goes to the physically relevant parameters \((A,V)\). The change from \((A,V)\) to \((\sigma,V)\)—variables is to be performed via the Legendre—Fenchel transform, which expresses the thermodynamic potential \( f(A,V) \), in terms of \( F(\sigma,V) \) as:
\[
f(A,V) = \max_\sigma [F(\sigma,V) + \sigma A]. \tag{52}
\]
It reduces to the Legendre transform in the case of convex, differentiable functions. The first level of ensemble equivalence (i.e. at the level of thermodynamic potentials) takes place if all thermodynamic potentials in the thermodynamic limit are related to each other by a Legendre—transform for the corresponding values of parameters entering in the Hamiltonian of the system. Roughly speaking this kind of equivalence is usually given in the absence of phase transitions, i.e., only for those thermodynamic parameters where there are no singularities.

The transform Eq. (52) is well behaved only if \( F(\sigma,V) \) is a convex function:
\[
\frac{\partial^2 F(\sigma,V)}{\partial \sigma^2} < 0. \tag{53}
\]
Since in our case \( F(\sigma,V) = F[H(u;\sigma)] \) is a differentiable function of the parameter \( \sigma \) Eq. (53) holds. It attains its maximum with respect to the later at the unique solution of the equation
\[
\frac{dF(\sigma,V)}{d\sigma} = A, \tag{54}
\]
or equivalently in more detail
\[
\frac{\partial}{\partial \sigma} F[H(u;\sigma)] = -\frac{K_0}{\beta K_c} \frac{\partial}{\partial \sigma_{\text{MS}}} \ln Z[H(u;\sigma_{\text{MS}})] = A, \tag{55}
\]
which relates implicitly \( \sigma \) to \( A \). Eq. (55) coincides exactly with Eq. (39). The thermodynamic of the vesicle in the \((A,V)\)—variable is fully specified by Eqs. (34) and (52).

More precisely, in the thermodynamic limit, the corresponding canonical free energy density
\[
f_c(A,V) = \lim_{N \to \infty} \frac{f(A,V)}{N} \tag{56}
\]
is related to the grand canonical free energy
\[
f_p(\sigma,V) = \lim_{N \to \infty} \frac{F(\sigma,V)}{N} \tag{57}
\]
by means of the Legendre transform,
\[
f_c(A,V) = f_c(\sigma(A),V) + \sigma(A)A, \tag{58}
\]
where $\sigma(A)$ is the solution of
\[ \frac{dF_v(\sigma,V)}{d\sigma} = A. \] \hspace{1cm} (59)

This is the way to derive the $(A,V)$—result from the $(\sigma,V)$-one. Equivalence of both ensembles holds only if $F_v(\sigma,V)$ also can be recovered from $f_v(A,V)$ by means of a Legendre transform. The requirement both type of Legendre transformations to take place makes the check of equivalence a complicated task solved only in the thermodynamic limit, i.e. the ensembles are equivalent in the limit of infinitely large membranes.

This is a crucial point which must to be scrutinized in each considered case. As it was pointed out in [47] there is a situation in Monge model presentation where the ensembles are not equivalent. The amplitude of fluctuations depend on the statistical ensemble under consideration as a result of the ambiguity of the very definition of the thermodynamic limit which compromise the used assumption that the membrane is planar.

On the pure physical ground, there is one more sophisticated obstacle, namely, infinitely large membrane at finite tension is an object not at thermodynamic equilibrium [48]. This contradicts the basic assumption that the system we considered is assumed to be in thermodynamic equilibrium.

6. THE STRETCHING ELASTICITY AND THE SOFT AREA CONSTRAINT

It is well recognized that the bending modulus $K_s$ is preferably studied in the literature of the flexibility of membranes (see e.g. the comments in [51]). Physical situation in which the membrane may fluctuate through stretching or compressing are of significant interest as well [41–43, 49–55].

The presented in this section approach is a reminiscence of an earlier work of Shapiro and Rudnick [57] concerning the quite other field of magnetism. In this work, the spherical constraint (an analog of the area constraint in our case) is replaced with a Gaussian damping term into the partition function. Here, our present consideration is twofold. First, to trace out an useful further resemblance with the spherical model, and second, to introduce in a different way a mean softened area constrained instead of those enforced with Lagrange multiplier.

An instructive question is whether it is possible to reveal the microscopic origin of $\sigma_{MS}$ in the formulas of Milner and Safran for the mean square amplitudes Eq. (42) and excess area Eq. (46), or more precisely, of the quantities which appear instead. In particular, this should allow to include the experimental determination of the stretching elasticity modulus $K_s$ in the scenario of the flicker spectroscopy analysis.

First, let us recall that there is yet another form of the delta-function as the limit of a normalized Gaussian:
\[ \delta(x) = \lim_{\epsilon \to 0} \frac{1}{\sqrt{2\pi\epsilon}} \exp\left(-\frac{x^2}{2\epsilon}\right). \] \hspace{1cm} (60)

For our aim, the crucial issue is to define $\epsilon$, which physically must correspond to $K_s$ and $A$, and in addition, if we want to mimic a part of a Hamiltonian in the Gibbs exponential, with the inverse temperature $\beta$. The only dimensionless combination between $K_s$, $A$ and $\beta$ is $\beta A K_s$. As we are interested to study the limit $K_s \to \infty$ ($\beta$ and $A$ fixed), or $A \to \infty$ ($K_s$ and $\beta$ fixed) we choose in the definition Eq. (60):
\[ \epsilon \equiv \frac{1}{\beta A K_s} \equiv \frac{1}{N} \to +0. \] \hspace{1cm} (61)

Having this in mind, we start with the Gaussian
\[ \left(\frac{\beta A K_s}{2\pi}\right)^{1/2} \exp\left\{\frac{\beta A K_s}{2} \left[\frac{A(u) - 1}{A}\right]^2\right\} \] \hspace{1cm} (62)

as a factor in the integrand of the partition function $Z[H_s(u)]$. In the limit $\epsilon = 0$ this factor becomes a delta function and the exact area constraint (19) is recovered
\[ Z[H_s(u); K_s] \xrightarrow{x \to \infty} Z[H_s(u); A] \] \hspace{1cm} (63)

where, the new (with the relaxed area constraint) partition function $Z[H_s(u); K_s]$ is defined as:
\[ Z[H_s(u; K_s)] = \left(\frac{\beta A K_s}{2\pi}\right)^{1/2} \int \mathcal{D}[u] \times \exp\left\{\frac{\beta A K_s}{2} \left[\frac{A(u) - 1}{A}\right]^2\right\} \exp\left[-\beta H_s(u)\right]. \] \hspace{1cm} (64)

Also, as follows from Eq. (64), the quantity in the exponentials of $Z[H_s(u); K_s]$, formally may be considered as a Hamiltonian. In this way we come to the effective Hamiltonian:
\[ H(u; K_s) = H_s(u) + \frac{K_s}{2A} [A(u) - A]^2, \] \hspace{1cm} (65)

where the last term in the above expression has the form of the stretching energy functional,
\[ \frac{1}{2} \left[\frac{\sigma(u)}{K_s}\right]^2 A = H_s(u) \] \hspace{1cm} (66)

if we express the membrane vesicle tension $\sigma(u)$ as,
\[ \sigma(u) = K_s \frac{A(u) - A}{A}. \] \hspace{1cm} (67)

The interesting point here is that we obtain the expression Eq. (66), based on the requirement of the relaxation of the exact delta-function constraint through normalized Gaussian, Eq. (60). Indeed, Eq. (67) is a definition of $K_s$ which depends on $A$. Since the stretching modulus $K_s$ can be measured
experimentally, in addition, one needs to refine the meaning of \( A \) in order to make track with the experiment [36, 43]. We shall postpone the consideration of this issue to the next section.

Now, we shall consider the model Hamiltonian \( H(u; K) \) which can be rewritten (up to an irrelevant constant) in the following alternative form:

\[
H(u; K) = \mathcal{T}(u) + |\mathcal{A}(u)|^2, \tag{68}
\]

where

\[
\mathcal{T}(u) = \frac{1}{2} K \sum_{n=1}^{\infty} \sum_{m=-n}^{n} \frac{(n+1)(n+2)}{2} (n(n+1) + \sigma_0) |u_n^m|^2, \tag{69}
\]

and

\[
\mathcal{A}(u) = \left( \frac{K}{2A} \right)^{\frac{1}{2}} \sum_{n=1}^{\infty} \sum_{m=-n}^{n} \frac{(n+2)(n-1)}{2} (u_n^m)^2. \tag{70}
\]

In Eq. (69)

\[
\sigma_0 = \frac{R_0^2}{K} \sigma_0^*, \tag{71}
\]

where the notation

\[
\sigma_0 = K_s \frac{4\pi R_0^2 - A}{A}, \tag{72}
\]

has been used.

The considered partition function reads:

\[
Z[H(u; K)] = \left( \frac{\beta A K_s}{2\pi} \right)^{1/2} \int d\lambda e^{-\beta H(u; \lambda)} \exp \left\{ -\beta \mathcal{T}(u) + |\mathcal{A}(u)|^2 \right\}. \tag{73}
\]

However, then the corresponding Hamiltonian \( H(u; K) \) in the exponential of Eq. (73) is nonlinear with respect to the squares \((u_n^m)^2\) of the amplitudes \(u_n^m\), due to the nonlinearity of \( H_s(u) \). To solve this problem one can follow two different approaches, named: steepest descent method and variational method (see below).

The common approach is based on the Habbard–Stratonovich transformation (which in our case is nothing but an identity on Gaussian integrals), with the subsequent use of the steepest descent method [36, 43, 52]. It turns out that the problem is exactly solvable (only) in the thermodynamic limit [36, 40, 43, 52]. Let us recall that this aspect of the membrane fluctuation theory was first discussed for almost planar membranes in the context of the spherical model of phase transitions in 1976 [49].

Quite recently, a different approach to linearize the Hamiltonian in Eq. (73) based on the Bogoliubov variational inequalities has been proposed [42]. In our opinion this yields a more clear picture of the proposed approximation. Moreover, the used approximation avoids the analysis on the complex plane and is not always related to the notion of the thermodynamic limit.

In the next sections we shall compare both approaches.

### 7. STEEPEST DESCENT METHOD AND THE CALCULATION OF THE PARTITION FUNCTION

By means of the well known identity on Gaussian integrals

\[
e^{-\beta \mathcal{A}(u)^2} = \frac{1}{\sqrt{4\pi}} \int_{-\infty}^{+\infty} d\lambda e^{-\beta^{1/2} \mathcal{A}(u) + \lambda^2/4}. \tag{74}
\]

Eq. (73) may be presented in the form (the order of \( \lambda \) and \( u \) integrations can be interchanged)

\[
Z[H(u; K)] = \frac{1}{2\pi i} \int_{-\infty}^{+\infty} d\lambda \exp \left\{ -\beta \mathcal{T}(u) + \frac{\lambda}{\beta^{1/2}} \mathcal{A}(u) - \frac{\lambda^2}{4\beta} \right\}. \tag{75}
\]

In Eq. (75) the shape fluctuation modes \((u_n^m)^2\) are decoupled due to Eq. (74) so that the corresponding integrals become Gaussian. Note that a similar procedure based on the integral representation Eq. (74) in the membrane theory has been used in [36, 43, 49, 50]. However, working with complex functions is just one of the prices one has to pay to work with Gaussian integrals over fluctuation modes.

The partition function Eq. (75) may be rewritten in the form:

\[
Z[H(u; K)] = \frac{1}{2\pi i} \left( \frac{\beta A K_s}{2} \right)^{1/2} \int_{-\infty}^{+\infty} d\lambda \left\{ \int D[u] \exp \left[ -\beta H(u; \lambda) \right] \right\}. \tag{76}
\]

The effective Hamiltonian in the exponential is given by:

\[
H(u; \lambda) = \frac{K_s}{2} \sum_{n=1}^{\infty} \sum_{m=-n}^{n} \frac{(n-1)(n+2)}{2} \left[ n(n+1) + \Sigma(\lambda) \right] (u_n^m)^2 \tag{77}
\]

where

\[
\Sigma(\lambda) := \sigma_0 + \sigma_s(\beta) \lambda; \quad \sigma_s(\beta) = \frac{K_s R_0^2}{2 \beta A K_s}. \tag{78}
\]
If we now look at the the partition function \( Z[H(u; K)] \), we have
\[
Z[H(u; K)] = \frac{1}{2\pi i} \left( \frac{\beta AK}{2} \right)^{1/2} \int \frac{d\lambda}{\lambda} \exp \left\{ \frac{\lambda^2}{4} - \psi(\beta, \lambda) \right\},
\]
where
\[
-\psi(\beta, \lambda) = -F[H(u; \lambda)] + \frac{\lambda^2}{4} = \ln \int \mathcal{D}[u] \exp \left\{ -\beta \left[ \sum_{n=1}^{\infty} \frac{1}{4} K(n-1)(n+1)(n(n+1) + \Sigma(\lambda)) \right] (u_n^m)^2 \right\}.
\]

The exponential in Eq. (80) is a diagonal quadratic form in the real value functions \( (u_1^2, u_1^3, \ldots, u_{\text{max}}^m) \). As a result the multiple integral over \( u_m^m \) splits into a product of one-dimensional Gaussian integrals. These integrals over \( u_m^m \) in Eq. (80) can be performed easily. This statement is correct as long as
\[
\Re \mathcal{E}(n(n+1) + \Sigma(\lambda)) > 0,
\]
which implies \( \Re \mathcal{E}(\Sigma(\lambda)) > -6 \). Thus, we obtain the following expression for \( \psi(\beta, \lambda) \):
\[
\psi(\beta, \lambda) = \sum_{n=1}^{\infty} \frac{2n+1}{2} \ln \left\{ (n-1)(n+2)[n(n+1) + \Sigma(\lambda)] \right\} + \frac{N}{2} \ln \left( \frac{\beta K}{2\pi} \right).
\]

Changing the variable
\[
\frac{\lambda}{2\sqrt{N}} = \xi, \quad N \equiv e^{-1},
\]
from Eqs. (79), (82) and (83) we obtain:
\[
Z[H(u; K)] = \frac{1}{2\pi i} \left( \frac{\beta AK}{2} \right)^{1/2} 2^{N^{1/2}} \times \int_{-i\infty}^{i\infty} d\xi \exp \left\{ N[\xi^2 - N^{-1}\psi(\beta; 2\xi^{1/2})] \right\}.
\]

Let us briefly sketch the idea how one could compute the asymptotic expansion of the above integral, where \( N \gg 1 \). If the term in the rectangular brackets in the exponential of Eq. (84) has a finite limit \( \Psi(\beta, \xi) \) provide \( N \to \infty \), the integral over \( \xi \) in Eq. (84) can be carried out by the method of steepest descents. For this aim one needs to find the saddle point \( \xi_0 \) of the (holomorphic) function \( \Psi(\beta, \xi) \) and to deform the path of integration in a way that does not affects its end points (as one may by Caushy’s theorem) so that it passes through the saddle point. Thus for the problem at hand one needs to deform the path of integration until the maximum of \( \Re \Psi(\beta, \xi) \) along path of integration is also a stationary point of the \( \mathcal{F} \) for \( \Psi(\beta, \xi) \). One expects the integral to be dominated by the saddle point \( \xi_0 \). Here, the following comments are in order.

First, one needs to compute \( \Psi(\beta, \xi) \), i.e. the density free energy in the thermodynamic limit, which means \( N \to \infty \) and \( R_0 \to \infty \) while keeping \( 4\pi R_0^2 / N \) constant. In this limit, the modes \( (l,m) \) are mapped onto wavevectors \( q \) contained in the plane \( z = 0 \), with the relation \( q^2 = [n(n+1) - 2(\lambda_0)] \), and we shall recover the planar model in the Fourier space (for details, see [31]). The entire consideration of the difference between the free energy as given by the discrete sum of Eq. (82) and as given by the continuum expression \( \Psi(\beta, \xi) \) indicates that for a spherical membrane the finite-size effects are also important when are compared to the curvature ones [58].

Second, precise justification of the method of steepest descent in our case needs some mathematical efforts. It goes without saying that the integral in Eq. (84) can be replaced by the integrand:
\[
Z[H(u; K)] = \left\lbrace \exp N\left[ \xi^2 - N^{-1}\psi(\beta; 2\xi^{1/2}) \right] \right\rbrace + O(N^{-1}),
\]
with \( \xi \) obtained from the saddle point equation determining the extremum of the expression in the square brackets:
\[
d\frac{d}{d\xi} \left[ \xi^2 - N^{-1}\psi(\beta; 2\xi^{1/2}) \right] = 0,
\]
or equivalently
\[
\xi = \frac{1}{2N} d\frac{d}{d\xi} \Psi(\beta; 2\xi^{1/2}),
\]
or equivalently in the explicit form
\[
\lambda = \sigma_1 \sum_{n=1}^{\infty} \frac{2n+1}{n(n+1) + \Sigma(\lambda)}.
\]

The free energy is now (up to an irrelevant constant)
\[
F[H(u; K)] = \frac{\lambda^2}{4} - \psi(\beta; \hat{\lambda}),
\]
where \( \hat{\lambda} \) is the solution of Eq. (88).

The study of the spectrum of thermally-excited shape fluctuations of bending and stretching deformations in vesicle membranes together, is one of main topics of this review. This could be performed in two alternative methods. First, as it is done so far, the...
membrane is considered to be compressible in the framework of a relaxed version of the conventional delta-function constraint. Then, one comes to a model effective Hamiltonian Eq. (65) which is a result from Gaussian constrained membrane area (see, Eq. (62)). Second, in the next section, we shall consider a model where the area compressibility is taken into account by additively added stretching energy term to the bending one. As a result, the self-consistent equation (see below) used to ensure a certain membrane area constraint is found to be identical with the saddle point Eq. (88). Furthermore we shall present an alternative method for calculating the partition function of the model Hamiltonian Eq. (65) that avoids the consideration in the complex plane [42].

8. THE MODEL HAMILTONIAN WITH AN ELASTIC CONTRIBUTION TERM

In this section we consider a vesicle whose membrane is made of a fixed number of constituent molecules $N$. Let us assume its deformed/actual surface area $S$ is governed by an elastic contribution to the model Hamiltonian. Following [49], (see also [43, 55]) the elastic contribution is proportional (with the coefficient of proportionality the compressibility modulus $K_s$) to the square of the difference between the actual surface $S = N/\bar{p}$ and optimal surface of the membrane $S_0 = N/p_0$, where $\bar{p}$ is the average value of the surface density of the constituent molecules in the deformed state, and $p_0$ is the average value of the surface density of the constituent molecules in the flat tension free (equilibrium) state. Optimal surface $S_0$ (called also saturated or Schulman area [55]) is determined by the intermolecular forces. Note that the effects of thermal fluctuations in the case of a nearly flat membrane using the Monge gauge have been studied in [55].

One can present the area functional of the actual (stretched) membrane $S(v)$ in the form:

$$S(v) = 4\pi R_2^2 + \Delta_S(v),$$

where the quantity

$$\Delta_S(v) = \frac{R_2^3}{2},$$

$$\times \sum_{n=2}^{n_{max}} \sum_{m=-n}^{n} (n-1)(n+2)(v_n^m)^2 + O((v_n^m)^3),$$

(91)

is the difference between the area of the vesicle’s membrane and the area $4\pi R_2^2$ of a sphere with a reference volume equal to that of the vesicle, i.e. it is the dimensional excess area of the vesicle. The symbol $v$ is used as a shorthand for the real spherical harmonics amplitudes $(v_2^2, v_2^{-1}, ..., v_1^{n_{max}})$, appearing in the expansion of the vesicle shape fluctuations from the equivalent volume sphere with radius $R_0$ (see Eq. (6)). To point out the lack of the area constraint, we use the new notations for the dynamical variables $v_n^m$ instead $u_n^m$ previously used in Eq. (6) and $S(u)$ for the actual area of the vesicle instead of $A(u)$.

When the area functional $S(v)$ deviates (after stretching or compression) from the optimal area $S_0$, the membrane experiences a surface tension $[5, 59]$

$$\sigma(v) = K_s \frac{S(v) - S_0}{S_0},$$

(92)

where $K_s$ is the area compressibility modulus.

The effective Hamiltonian we consider is presented as a sum of two terms:

$$H(v) = H_c(v) + H_s(v),$$

(93)

where

$$H_c(v) = \frac{1}{2} K_s \sum_{m=2}^{n_{max}} \sum_{n=2}^{n} (n-1)(n+1) \times (n+2)(v_n^m)^2 + O((v_n^m)^3)$$

(94)

for the bending energy term, and

$$H_s(v) = S_0 \left| \sigma(v) \right|^2,$$

(95)

for the stretching energy term expressed via the membrane vesicle tension $\sigma(v)$, see $[5, 43, 49, 54, 55]$. It will be instructive to clarify the relation of the considered here approach with the approach of Milner and Safran (see, Section 4). The term in the rectangular brackets in Eq. (95) may be presented identically in the form

$$\left| \sigma(v) \right|^2 = 2 \left< \sigma(v) \right>_{H(v)}, \sigma(v) - \left< \sigma(v) \right>_{H(v)}^2 \left< \sigma(v) \right>_{H(v)},$$

(96)

where the mean value is over the Hamiltonian Eq. (93). The last term

$$\left| \sigma(v) - \left< \sigma(v) \right>_{H(v)} \right|^2,$$

(97)

is the mean square fluctuations of the surface tension, which could be disregarded assuming that the fluctuations of the surface tension are small.

Then, using Eqs. (90) and (92)), one finds for the stretching energy functional:

$$H_s(v) = H_{MF}(v) = \left< \sigma(v) \right>_{H(v)} S(v) + \text{const.}$$

(98)

In fact, skipping the term Eq. (97) and keeping only the term linear with $(v_n^m)^2$ we come to a mean-field Hamiltonian $H_{MF}(v)$, similar to the one used in the Milner and Safran approach, see Eq. (32), in which the Lagrange multiplier $\sigma$ is replaced by $\left< \sigma(v) \right>_{H(v)}$.
If so, for the mean square amplitudes calculated with $H_{\text{MF}}(\nu)$ we get
\[
\left\langle \left| a \right|^{2} \right\rangle_{H_{\text{MF}}(\nu)} = \frac{8\pi \gamma}{(n-1)(n+2)[n(n+1) + (\gamma(v))_{H_{\text{MF}}(\nu)}]}, \quad (99)
\]

Here, the following comments are in order. Indeed, using parameter $\gamma$ (respectively $K_{c}$) and dimensionless $\gamma(v)$ as fitting parameters, one can infer information about them from the flickering analysis, but the information about $K_{c}$ (i.e. the role of the stretching effects) on the thermal fluctuation of the membrane remains hidden. The main problem is that we do not calculate the mean of $\sigma(v)$ with the Hamiltonian $H(v)$ in the denominator of the r.h.s. of Eq. (99) (it is possible self-consistently only in the mean-field approximation) and we can’t estimate the error made where skipping the last term in Eq. (96). In what follows we shall try to shed light on these problems.

Since the Hamiltonian, Eq. (93) (with Eqs. (90) and (95)) is exactly the same as Eq. (65) with $A$ replaced by $S_{0}$ we may use for convenience the equivalent (up to an irrelevant constant) presentation
\[
H(v) = \mathcal{T}(v) + [\mathcal{A}(v)]^{2}, \quad (100)
\]
where $\mathcal{T}(v)$ and $\mathcal{A}(v)$ are defined by Eqs. (69) and (71), respectively. The last term due to its nonlinearity with respect to the squares of the amplitudes $\nu^{m}_{n}$ causes computational problems which as it was shown in the previous section can be solved using the steepest descent method. Below, to overcome this obstacle we shall follow a different way. We shall linearize the Hamiltonian (100) using “approximating Hamiltonian method” (about this method, see, e.g. Ch. 2 in [39] and [61–63]) based on the Bogoliubov variational inequalities. This approach might be an advantage over the former, because it avoids computations in the direct implementation of the thermodynamic limit procedure.

9. THE APPROXIMATING HAMILTONIAN AND THE CALCULATION OF THE PARTITION FUNCTION

The idea of the proposed approximation is to replace the non-solvable initial Hamiltonian $H(v)$ with a more simple linearized Hamiltonian $H_{\text{app}}(v, X)$ depending on a variational parameter $X$. The resulting Hamiltonian is called “approximating Hamiltonian” if under a proper choice of its free parameter $X$ it can be proved asymptotically closer to the initial one, in the sense that both Hamiltonians generate the same thermodynamic behaviour. Thus the problem of interest is reduced to a simpler one, which allows to obtain its thermodynamic functions in an analytical form. Below we shall realize this program following our studies in [42].

The second term in Eq. (68) may be presented in the form:
\[
[\mathcal{A}(v)]^{2} = 2X \mathcal{A}(v) - X^{2} + [\mathcal{A}(v) - X]^{2}, \quad (101)
\]
where $X$ is an arbitrary real parameter. We define the linearized Hamiltonian $H_{\text{app}}(v, X)$ as:
\[
H_{\text{app}}(v, X) = \mathcal{T}(v) + 2X \mathcal{A}(v) - X^{2}. \quad (102)
\]

The last equation is obtained from Eq. (68) by removing the term $[\mathcal{A}(v) - X]^{2}$ from the right-hand-side of (101). The problem is to prove that the skipped term is in some sense small. Then the defined in this way Hamiltonian $H_{\text{app}}(v, X)$ is linear with respect to $(\nu^{m}_{n})^{2}$ and the corresponding partition function
\[
Z[H_{\text{app}}(v, X)] = \exp\{-\beta F[H_{\text{app}}(v, X)]\}
\]
\[
= \int D[\nu] \exp\{-\beta \mathcal{T}(v) + 2X \mathcal{A}(v) - X^{2}\}, \quad (103)
\]
is a trivial Gaussian integral.

A simple comparison of the terms in the curly brackets in Eqs. (75) and (103) shows that they define the same (up to an irrelevant factor) partition function provided $\lambda = 2^{1/2}X$. In this sense, the use of the soft-area constraint Eq. (62) is equivalent to the inclusion of the stretching energy term Eq. (95) in the Hamiltonian. However, the crucial difference is that the arbitrary complex parameter $\lambda$ and the real parameter $X$ should be fixed under different rules.

Anyway, we may perform the integrations in Eq. (103) directly by using the result Eq. (80), which for the free energy gives
\[
F[H_{\text{app}}(v, X)] = k_{B}T \sum_{n=1}^{n_{\text{max}}} \frac{2n + 1}{2} \times \ln \left\{ \left( n - 1 \right) \left( n + 2 \right) \left[ n(n + 1) + \Sigma_{\text{app}}(X) \right] \right\}
\]
\[
- X^{2} + \frac{N}{2} \ln \left( \frac{\beta K_{c}}{2\pi} \right), \quad (104)
\]
where
\[
\Sigma_{\text{app}}(X) := \sigma_{0} + \sigma_{1}X, \quad (105)
\]
with
\[
\sigma_{0} = K_{c} \frac{R_{s}^{2}}{K_{c}} - S_{0}, \quad \sigma_{1} = \frac{2K_{c}}{\sqrt{S_{0}K_{c}}}, \quad (106)
\]

Our goal is to develop an approach which allows to control the approximation (104) via the parameters of the considered model. In what follows we shall prove that it is possible to work with $F[H_{\text{app}}(v, X)]$ provided the parameter $X$ is fixed in an appropriate way.
10. THE APPROXIMATING HAMILTONIAN AND BOGOLIUBOV VARIATIONAL INEQUALITIES

In their most convenient form the Bogoliubov variational inequalities are given by

\[
\langle H - H_{\text{app}}(X) \rangle_H \leq F[H] - F[H_{\text{app}}(X)] \leq \langle H - H_{\text{app}}(X) \rangle_{H_{\text{app}}(X)},
\]

(107)

where \( F[H] \) is the free energy of a valid Hamiltonian \( H \) and \( F[H_{\text{app}}(X)] \) is the free energy of a presumably simpler Hamiltonian \( H_{\text{app}}(X) \), depending on a variational parameter \( X \). The variational parameter \( X \) must be determined from the condition of the best approximation of \( F[H] \). As we said earlier in the case of the best approximation \( H_{\text{app}}(X) \) is called Approximating Hamiltonian.

It is worth noting that, although the two-side estimate (107) is almost an evident consequence of the convexity of the free energy, its proof on a rigorous level needs significant mathematical efforts, for details see Section 3.4, and for historical remarks Section 3.5 in [60].

The recipe for the determination of the Approximating Hamiltonian in combination with the Bogoliubov variational inequalities is the essence of the so-called approximating Hamiltonian method (AHM). The advantage of the method is that in many cases it is possible to estimate the correlator in the left and right sides of the inequalities (107). This gives a further insight into the common approximation, usually based on physical intuition, and leads to new results as well. There exists an extensive literature about the AHM, see, e.g. Ch. 2 in [39, 53–60] for a list of different applications in the theory of critical phenomena and condensed matter physics.

The following comment is in order here. The second of the inequalities Eq. (107) is known as Bogoliubov variational upper bound of the exact free energy [64], (see also Ch. 2 in [4]). Using only this part of the inequalities (107) the best approximation from above is obtained, if the variational parameter \( X \) minimizes the variational free energy \( F_{\text{var}}(X) \), defined as follows:

\[
F_{\text{var}}(X) := F[H_{\text{app}}(X)] + \langle H - H_{\text{app}}(X) \rangle_{H_{\text{app}}(X)}.
\]

(108)

This allows to obtain approximation from above

\[
F[H] \leq \min_X F_{\text{var}}(X)
\]

(109)

(although some times quite crudely) for the exact free energy of the studied physical system. The approach based on (108) is effectively used in order to obtain closed-form expression for the spectra of the thermal fluctuation of spherical vesicles incorporating nonlinear curvature elasticity terms [65].

We shall use another quite different approach which allows to estimate the used approximation. If the lhs of (107) is positive definite, the best approximation of \( f[H] \) from below is obtained maximizing \( f[H_{\text{app}}(X)] \) with respect to \( X \). In this case one can estimate the approximation through the estimation of the thermodynamic mean value in the r.h.s. of (107). The use of inequalities (107) in the statistical mechanics of a lipid vesicle has been announced in [66].

In the inequalities (107) we choose

\[
H := H(v; K_s) = \mathcal{T}(v) + \langle \mathcal{A}(v) \rangle^2,
\]

(110)

and its linearized version as:

\[
H_{\text{app}} := \mathcal{H}_{\text{app}}(v, X) = \mathcal{T}(v) + 2X\mathcal{A}(v) - X^2.
\]

(111)

Since the thermal average of a nonnegative quantity is nonnegative, it follows that:

\[
\langle H(v; K_s) - \mathcal{H}_{\text{app}}(v, X) \rangle_{H_{\text{app}}(v)} = \langle \mathcal{A}(v) - X^2 \rangle_{H_{\text{app}}(v)} \geq 0.
\]

(112)

Then Eqs. (107) and (112) imply that for each \( X \):

\[
0 \leq F[H(v; K_s)] - F[H_{\text{app}}(v, X)] \leq \langle \mathcal{A}(v) - X^2 \rangle_{H_{\text{app}}(v)}.
\]

(113)

Now, we can determine \( X \) from the condition of the best approximation

\[
F[H_{\text{app}}(v, \bar{X})] = \max_{\bar{X}} F[H_{\text{app}}(v, X)].
\]

(114)

Hereafter, in order to be unambiguous we shall use notations linearized and approximating Hamiltonian for \( H_{\text{app}}(v, X) \) and \( H_{\text{app}}(v, \bar{X}) \), respectively.

Since \( F[H_{\text{app}}(v, X)] \) is a differentiable function of \( X \), thus \( \bar{X} \) is defined as solution of the equation:

\[
\frac{\partial F[H_{\text{app}}(v, X)]}{\partial X} = 0.
\]

(115)

Differentiating

\[
F[H_{\text{app}}(v, X)] = -\beta^{-1} \ln \left( \int D[v] \exp(-\beta [\mathcal{T}(v) + 2X\mathcal{A}(v)]) \right) - X^2,
\]

(116)

we obtain:

\[
\frac{\partial F[H_{\text{app}}(v, X)]}{\partial X} = 2\langle \mathcal{A}(v) \rangle_{H_{\text{app}}(v)} - X = 0.
\]

(117)

This is a typical self-consistent equation for the variational parameter \( X \).

Differentiating the lhs of Eq. (117) ones more, we obtain

\[
\frac{\partial^2 F[H_{\text{app}}(v, X)]}{\partial X^2} = -2\beta \left( \langle \mathcal{A}(v) \rangle_{H_{\text{app}}(v)} - A(v) \right)^2 + l < 0.
\]

(118)
Consequently, $F[H_{app}(v, \tilde{X})]$ is a convex function of $X$ and thus Eq. (117) has only one solution, namely $\tilde{X}$. From Eq. (113) it follows that:

$$F[H_{app}(v, \tilde{X})] \leq F[H(v)].$$  \hspace{1cm} (119)

Thus we show that the free energy $F[H_{app}(v, \tilde{X})]$ of the ensemble of not “interacting amplitudes $u_n^a$” described by the Hamiltonian (120) is the best approximation of below of the free energy, corresponding to the model Hamiltonian $H(v; K_r)$. It is important to note that the correlator in the r.h.s. of the inequalities (113) can be calculated and thus to estimate the approximation of $F[H(v; K_r)]$ through $F[H_{app}(v, \tilde{X})]$.

11. ANALYSIS OF THE SELF-CONSISTENT EQUATION

The mean squares amplitudes $\langle (u_n^m)^2 \rangle_{H_{app}(v,X)}$, calculated by the linearized Hamiltonian $H_{app}(v,X)$ (compare with Eq. (77)),

$$H_{app}(v;X) = -X^2 + \frac{1}{2} \sum_{n=2}^{n_{\text{max}}} \sum_{m=0}^{n} K_r(n-1)(n+2)$$

$$\times \left[ n(n+1) + \overline{\sigma}_0 + X \sqrt{\frac{2K_r R_0^4}{\beta A K_c}} \right] \langle (v_n^m)^2 \rangle,$$

are

$$\langle (v_n^m)^2 \rangle_{H_{app}(v,X)} = \frac{8\pi \gamma}{(n-1)(n+2)[n(n+1) + \overline{\Sigma}_{app}(X)].}$$  \hspace{1cm} (121)

As it can be seen after comparison with Eq. (42), the result for $\langle (v_n^m)^2 \rangle_{H_{app}(v,X)}$ formally reproduces the result of Milner and Safran. However, a significant difference takes place. In their theory $\sigma_{\text{MS}}$ is introduced as a Lagrange multiplier, while here $\overline{\Sigma}_{app}(X)$ with $X = \tilde{X}$ is obtained self-consistently from $F[H_{app}(v, \tilde{X})]$.

After differentiating Eq. (104) with respect to $X$ we obtain Eq. (115) in an explicit form (compare with Eq. (88))

$$X = \frac{kT \overline{\sigma}_0}{4} \sum_{n=2}^{n_{\text{max}}} \frac{2n+1}{n(n+1) + \overline{\sigma}_0 + \overline{\sigma}X}. $$  \hspace{1cm} (122)

This equation is the analogue in our case of the equation, obtained in [49, 50], for the renormalized surface tension of almost planar membranes. Using the definition Eq. (105) we shall rewrite Eq. (122) in a more convenient form:

$$\overline{\Sigma}_{app} = \overline{\sigma}_0 + \frac{C}{2} \sum_{n=2}^{n_{\text{max}}} \frac{2n+1}{n(n+1) + \overline{\Sigma}_{app}},$$  \hspace{1cm} (123)

where the short hands

$$\overline{\Sigma}_{app} = \overline{\Sigma}_{app}(\tilde{X}),$$  \hspace{1cm} (124)

and

$$\overline{C} = \frac{1}{2\beta S_0 (K_r)^2} = \gamma K_c \frac{R_0^2}{K_c}.$$  \hspace{1cm} (125)

are used. In the numerical computations sometimes it is reasonable to use the last term in Eq. (125) obtained after the approximation $R_0^2/S_0 = 1/4\pi$.

In the general case Eq. (123) can be solved only numerically. Note that it is possible first to obtain $\overline{\Sigma}_{app}(K_r, K_c)$ from Eq. (123), indeed numerically, and after that to calculate from Eq. (121) the dependence of $\langle (v_n^m)^2 \rangle_{H_{app}(v,X)}$ on $K_r$, $K_c$.

Further on for the sake of simplicity for the solution of Eq. (123) we shall use the notation $\overline{\Sigma}_{app}(\overline{C}, \overline{\sigma}_0, N = n_{\text{max}}^\gamma) = \overline{\Sigma}_{app}$. Equation (123) shows that $\overline{\Sigma}_{app}$ depends on $K_r$ and $K_c$ and geometrical parameters $R_0$ and $S_0$ only in the combinations $\overline{C}$ and $\overline{\sigma}_0$. Under the condition

$$-\frac{\overline{\overline{\sigma}_0}}{\overline{C}} = \frac{1}{4\pi R_0^2} \leq \sum_{n=2}^{n_{\text{max}}} \frac{2n+1}{n(n+1)}.$$  \hspace{1cm} (126)

Eq. (123) has only one solution which belongs to the interval $[0, \infty)$. If the opposite inequality takes place, $\overline{\Sigma}_{app}$ belongs to the interval $(-6,0]$. Let us present some numerical results for $\overline{\Sigma}_{app}$. For example, if $n_{\text{max}}^\gamma = 3 \times 10^4$, the quantity in the r.h.s. of the inequality (126) is $19.27$. In this case, under the condition $\overline{C} = 10^3$, if $-\frac{\overline{\overline{\sigma}_0}}{\overline{C}} = 19.27$, the solution is $\overline{\Sigma}_{app} = 0$. If $-\frac{\overline{\overline{\sigma}_0}}{\overline{C}} = 16.50$, the solution is $\overline{\Sigma}_{app} = 57.72$, and if $-\frac{\overline{\overline{\sigma}_0}}{\overline{C}} = 19.50$, the solution $\overline{\Sigma}_{app} = 57.72 = -0.82$.

Note that the ratio $\overline{\overline{\sigma}_0}/\overline{C}$ does not depend on $K_r$ and as follows from inequality (126) the sign of the solution $\overline{\Sigma}_{app}$ does not depend on $K_c$.

For $\overline{\Sigma}_{app} > 1$, Eq. (123) can be solved analytically in terms of the Lambert function (see Eq. (A.20) in the Appendix A). In this case two different regimes have to be distinguished (see the Appendix A):
The former case has to be attributed to finite $K_s$, while the latter to the limit case $K_s \to \infty$.

Now it is convenient to include an auxiliary effective tension related to a reference vesicle with fixed area and volume $A = S_0$, $V = \frac{4\pi}{3} R_0^3$ and with an excess area $\Delta = \bar{\Sigma}_{MS}$ defined in Eq. (46) (i.e. with the same values as those of the vesicle considered in Section 4 which is the reason to use the same notation $\bar{\Sigma}_{MS}$). Thus, the definitions Eqs. (43), (44), (71) and (125) employ the identity

$$-\frac{\Delta_{MS}}{\gamma} = \bar{\sigma}_0, \quad \bar{\sigma}_0 < 0. \quad (129)$$

Now it is possible to insert the value of $\bar{\Sigma}_{MS}$ from Eq. (47) in Eqs. (127) and (128). One gets:

(a')

$$\bar{\Sigma}_{app} = \bar{C} \ln \left( \frac{\bar{\Sigma}_{MS}}{\bar{C}} \right), \frac{N \exp(\bar{\sigma}_0/\bar{C})}{\bar{C}} \gg 1, \quad (130)$$

or

(b')

$$\bar{\Sigma}_{app} = \bar{\Sigma}_{MS}, \quad \frac{N \exp(\bar{\sigma}_0/\bar{C})}{\bar{C}} \ll 1. \quad (131)$$

Thus, one obtains $1 \ll \bar{\Sigma}_{app} \leq \bar{\Sigma}_{MS}$. Eqs. (130) and (131) allow to keep track of the two effective tensions, $\bar{\Sigma}_{app}$ and $\bar{\Sigma}_{MS}$, under the condition $\exp(-\Delta_{MS}/\gamma) \ll 1$, which validates the result Eq. (47).

12. THE SURFACE TENSION

It is worth noting that in the presented approach $\bar{\Sigma}_{app}$ has a natural physical interpretation: Eq. (123) (recall the relations Eqs. (90), (91) and (121)) implies:

$$\bar{\Sigma}_{app} = \frac{R_0^2}{K_s} \frac{\langle S(v) \rangle_{H_{app}(v, \bar{x})} - S_0}{S_0}$$

$$= \frac{R_0^2}{K_s} \frac{\langle \sigma(v) \rangle_{H_{app}(v, \bar{x})}}{S_0} \quad (132)$$

where $\sigma(v)$ is the (not normalized) tension of the membrane (see Eq. (67)). In the Appendix B it is shown that if the free energy of the initial and the approximating Hamiltonian are thermodynamically equivalent, then we have for the true (calculated with $H(v)$) tension (see the definition Eq. (92)):

$$\bar{\Sigma}_{app} \to \left( \frac{R_0^2}{K_s} \right) \langle \sigma(v) \rangle_{H(v)} \quad . \quad (133)$$

Let us replace $\bar{\Sigma}_{app}$ in favor of the other meaningful quantity-dimensionless excess area $\Delta(\bar{\Sigma}_{app})$:

$$\Delta(\bar{\Sigma}_{app}) \equiv \frac{\langle S(v) \rangle_{H_{app}(v, \bar{x})} - 4\pi R_0^2}{4\pi R_0^2}. \quad (134)$$

From Eqs. (90), (91) and (121) (with $X = \bar{X}$) it follows that:

$$\Delta(\bar{\Sigma}_{app}) = \gamma \sum_{n=2}^{\infty} \frac{2n + 1}{n(n + 1) + \bar{\Sigma}_{app}}. \quad (135)$$

Using the Eq. (A.16) obtained in the Appendix A the r.h.s. of the Eq. (135) may be transformed in a more simple form. Thus one gets:

$$\Delta(\bar{\Sigma}_{app}) = \gamma \ln \left( \frac{\bar{\Sigma}_{MS}}{\bar{\Sigma}_{app}} \right), \quad \frac{\bar{\Sigma}_{MS}}{N} \gg 1. \quad (136)$$

Now, it is possible to compare in an explicit form $\Delta(\bar{\Sigma}_{app})$ with the excess area obtained within the approach of Milner and Safran $\Delta(\bar{\Sigma}_{MS})$ (see Eq. (48)). One gets

$$\Delta(\bar{\Sigma}_{app}) - \Delta(\bar{\Sigma}_{MS}) = \gamma \ln \left( \frac{\bar{\Sigma}_{MS}}{\bar{\Sigma}_{app}} \right) \gtrless 0 \quad (137)$$

indeed, under the conditions:

$$\frac{\bar{\Sigma}_{app}}{N} \ll \frac{\bar{\Sigma}_{MS}}{N} \ll 1, \quad 1 \ll \bar{\Sigma}_{app} \leq \bar{\Sigma}_{MS} \quad (138)$$

Moreover, provided the inequality $\bar{\Sigma}_{app} \leq \bar{\Sigma}_{MS}$ takes place, by comparing the Eqs. (46) and (135) one may conclude that always $\Delta(\bar{\Sigma}_{app}) \geq \Delta(\bar{\Sigma}_{MS})$. Thus, as follows from Eqs. (46) and (135), a larger $K_s$ value will result in a smaller excess area $\Delta(\bar{\Sigma}_{app})$.

13. THE RELATION BETWEEN $\bar{\Sigma}_{app}$ AND $K_s$

From Eq. (46) with $A = S_0$ one can see that the effective tension $\bar{\Sigma}_{MS}$ obeys the equation:

$$0 = \bar{\sigma}_0 + \bar{C} \sum_{n=2}^{\infty} \frac{2n + 1}{n(n + 1) + \bar{\Sigma}_{MS}}. \quad (139)$$
Now, with the help of Eq. (139) the Eq. (123) may be presented in the form:

$$\Sigma_{app} = C (\Sigma_{app} - \Sigma_{MS})$$

$$\times \left(\sum_{n=1}^{n_{max}}\left[\frac{2(n+1)}{n(n+1) + \Sigma_{app}}\right]\right)^{-1} \times \left(\sum_{n=1}^{n_{max}}\left[\frac{2(n+1)}{n(n+1) + \Sigma_{MS}}\right]\right)^{-1}$$

Equation (140) shows the dependence of $\Sigma_{app}$ as a function of $K_s$, $K_s$ and $\Sigma_{MS}$ (respectively $S_0$) at fixed $R_0$ and $T$. For $\Sigma_{app} > 1$, this dependence may be obtained in terms of the Lambert function (see Eq. (A.22) in the Appendix A).

The simple relation between $\Sigma_{app}$ and $K_s$ prompts Eq. (140) to be inverted to yield $K_s$ as a function of $\Sigma_{app}$:

$$\frac{R}{K_s} = \mathcal{F}_s(\Sigma_{MS}, \Sigma_{app})$$

where

$$\mathcal{F}_s(\Sigma_{MS}, \Sigma_{app}) = \gamma \frac{\Sigma_{app}}{\Sigma_{MS} - \Sigma_{app}}$$

$$\times \left(\sum_{n=1}^{n_{max}}\left[\frac{2(n+1)}{n(n+1) + \Sigma_{app}}\right]\right)^{-1} \times \left(\sum_{n=1}^{n_{max}}\left[\frac{2(n+1)}{n(n+1) + \Sigma_{MS}}\right]\right)^{-1}$$

Note that by definition the stretching modulus $K_s$ is positive. Since negative values of $\Sigma_{MS}$ are allowed [13] the following two possibilities depending on the sign of $\Sigma_{MS}$ in Eq. (142) are relevant: (a) $\Sigma_{MS} < \Sigma_{app} < 0$, when $-6 < \Sigma_{MS} < 0$, (b) $\Sigma_{MS} > \Sigma_{app} > 0$, when $\Sigma_{MS} > 0$.

The obtained result determines the values of $\Sigma_{app}(K_s)$ when $K_s \to 0$ and $K_s \to \infty$ (when all the other model parameters are fixed).

For the first limit the result is:

$$\lim_{K_s \to 0} \Sigma_{app}(K_s) = 0.$$  \hspace{1cm} (143)

Trivially, the analogous case in the Milner and Safran approach is the case when the Lagrange multiplier $\sigma = 0$.

Since $\Sigma_{MS}$ does not depend on $K_s$, from the r.h.s. of Eq. (142) it follows that when $\Sigma_{app} \to \Sigma_{MS}$, one gets $K_s \to \infty$. The second limit is exactly the tension of the reference incompressible membrane $\Sigma_{MS}$ (see, also Eq. (A.22)):

$$\lim_{K_s \to \infty} \Sigma_{app}(K_s) = \Sigma_{MS}.$$  \hspace{1cm} (144)

The theory of Milner and Safran is adequate within regimes in which $K_s$ is not relevant. Eqs. (143) and (144) suggest that it is a limiting case of the presented theory. We showed that the self-consistent equation allows to obtain the stretching elasticity modulus $K_s$ via experimentally accessible quantities.

### 14. The Fitting Function

In this section we shall discuss the connection of the above theory with experimental studies of vesicle fluctuations in the context of flicker-noise measurements. As first, it is instructive to estimate the constants in $\gamma$, $\sigma_0$, and $C$. We shall use the following typical numerical values of the quantities [19] entering in our model Hamiltonian:

$$K_s \sim 10 \text{ erg/cm}^2; K_c \sim 10^{-12} \text{ erg}; R_0 \sim 10^{-3} \text{ cm};$$

$$S_0 \sim 4\pi R_0^2 \sim 1.256 \times 10^{-5} \text{ cm}^2; \sigma_t \equiv (R_0^2 / K_s) / \sigma_1 = 4 \times 10^9 \text{ erg}^{-0.5}; k_B T \sim 4 \times 10^{-14} \text{ erg}.$$

We accept for the estimation of membrane stretching the typical value $\sigma_0 \sim 1 \text{ erg/cm}^2$ and obtain the following values:

$$\Delta_\Sigma \sim 10^{-2}; \gamma \sim 10^{-3}; |\sigma_0| \sim 10^6; C \sim 10^5.$$

Evidently, the above constants obey the relation

$$\frac{\Delta_\Sigma}{\gamma} = \frac{|\sigma_0|}{C} \sim 10.$$  \hspace{1cm} (145)

Thus, the inequality Eq. (126) holds and Eq. (123) has a positive solution for $\Sigma_{app}$. Let us recall that two regimes resulting from the inequality between $\overline{C}$ and $\mathcal{N}$ are possible: (i) given by Eq. (127) (or alternatively Eq. (130)), or (ii) given by Eq. (128) (or alternatively Eq. (131)). In the above statement we accept also that the intermolecular distance $\lambda$ is of the order of 1 Å and then $n_{max} \sim 3 \times 10^4$ and $\mathcal{N} \sim 10^3$.

In the general case $\Sigma_{app}$ depends on $K_s$, $K_s$, $R_0$, $S_0$ and $\mathcal{N}$. If $R_0$ and $S_0$ can be calculated or measured by independent methods and are not correlated with $K_s$ and $K_s$, then, by fitting $\langle (v_n^m)^2 \rangle_{app(n,v,x)}$ with $K_s$ and $K_s$, we can determine them from the analysis of the thermal fluctuations of the vesicle shape. However, to perform the needed fitting procedure is a highly non-trivial task, since the fitting parameters are contained in an implicit form in $\Sigma_{app}$.

A straightforward way to obtain the fitting function in an explicit form is to replace the solution $\Sigma_{app}$ given by Eq. (A.22) in the Appendix A in the r.h.s. of Eq. (121). A visible simplification takes place if one use the approximating expression given in Eq. (A.30) instead. This gives

$$\langle (v_n^m)^2 \rangle_{app(n,v,x)} = \frac{8 \pi \gamma}{(n-1)(n+2) \left[\frac{n(n+1)}{\ln \Sigma_{MS} - \ln(\gamma K_s)}\right]}$$

\hspace{1cm} (146)
where \( \bar{K}_s = \frac{R_s^2}{K_c} \) is the dimensionless area compressibility modulus. Recall that (see Eq. (130)), the above equation becomes valid provided that the condition
\[
\frac{\bar{S}_{\text{MS}}}{\gamma K_s} \gg 1
\]  
(147)
takes place. As follows from Eq. (131), the opposite strong inequality provides the case considered by Miller and Safran:
\[
\langle (v_n^2) \rangle_{\text{app}(v, \bar{X})} = \frac{8\pi \gamma}{(n-1)(n+2)\{n(n+1) + \bar{S}_{\text{MS}}\}}.
\]  
(148)

Eqs. (146), (147) and (148) for the mean-square amplitudes could be used to determine experimentally \( K_s, \gamma \) (respectively \( K_c, \) ) and parameter \( \bar{S}_{\text{MS}} \) (instead of \( S_0 \) ) in the fitting procedure in the flicker spectroscopy method.

In the general case the solution of the self-consistent equation depends only on \( \bar{S}_{0}, \) and \( \bar{C}. \) Then as fitting parameters it is convenient to use \( \gamma, \bar{S}_{0}, \) and \( \bar{C}. \) Then for \( K_s \) and \( K_c \) it is easy to obtain:
\[
K_s = \frac{1}{8\pi \beta R_0} \frac{\bar{C}}{\gamma} \left( 1 - \frac{\bar{S}_{0} \gamma}{\bar{C}} \right)
\]  
(149)
and
\[
K_c = \frac{1}{\beta R_0} \left( \frac{\bar{C}}{\gamma} - \frac{\bar{S}_{0}}{\bar{C}} \right).
\]  
(150)

15. THE CLOSENESS OF THE MODEL HAMILTONIAN TO THE APPROXIMATING HAMILTONIAN

The validity of our method can be controlled by calculating the mean square fluctuations of \( \mathcal{A}(v) \) in the upper bound of the Bogoliubov inequalities Eq. (113), taking into account Eq. (114), defined as
\[
C(\bar{X}) \equiv \langle (\mathcal{A}(v) - \bar{X})^2 \rangle_{\text{app}}(v, \bar{X}).
\]  
(151)

From Eqs. (115) and (117) it follows that:
\[
\bar{X} \equiv \langle \mathcal{A}(v) \rangle_{\text{app}(v, \bar{X})}.
\]  
(152)

Obviously, the correlator \( C(\bar{X}) \) may be presented as:
\[
\left\langle (\mathcal{A}(v) - \langle \mathcal{A}(v) \rangle_{\text{app}(v, \bar{X})})^2 \right\rangle_{\text{app}(v, \bar{X})} = \left\langle (\mathcal{A}(v)^2) \right\rangle_{\text{app}(v, \bar{X})} - \langle \mathcal{A}(v)^2 \rangle_{\text{app}(v, \bar{X})}.
\]  
(153)

From Eqs. (70), (106), and (121) we obtain:
\[
\langle \mathcal{A}(v)^2 \rangle_{\text{app}(v, \bar{X})} = \frac{\sigma^2}{4\beta} \sum_{n=0}^{n_{\text{max}}} \frac{2n+1}{(n(n+1) + \bar{S}_{\text{app}})}.
\]  
(154)

From the other side Eqs. (91) and (70) imply:
\[
\left\langle (\mathcal{A}(v^2) \right\rangle_{\text{app}(v, \bar{X})} = \frac{K_s}{2S_0} \frac{R_0^4}{4}
\times \sum_{n=2m-\text{odd}}^{n_{\text{max}}} \sum_{n=2m-\text{even}}^{n_{\text{max}}} \sum_{n'=2m-\text{odd}}^{n'_{\text{max}}} (n-1)(n+2)
\times (n'-1)(n'+2) \left\langle (v_n^2 v_n'^2) \right\rangle_{\text{app}(v, \bar{X})}.
\]  
(155)

Taking into account that the amplitudes \( v_n^m \) are not correlated (the approximating Hamiltonian presents a system of not interacting oscillators) and have a Gaussian distribution, we obtain that:
\[
\left\langle (v_n^m)^4 \right\rangle_{\text{app}(v, \bar{X})} = 3 \left\langle (v_n^m)^2 \right\rangle_{\text{app}(v, \bar{X})}^2.
\]  
(156)

After some tedious but simple calculations we get:
\[
C(\bar{X}) \equiv \left\langle (\mathcal{A}(v) - \bar{X})^2 \right\rangle_{\text{app}(v, \bar{X})} = \frac{K_s}{S_0} \frac{R_0^4}{4} \left[ \frac{1}{\beta K_s} \right]^2 \sum_{n=2m-\text{odd}}^{n_{\text{max}}} \sum_{n=2m-\text{even}}^{n_{\text{max}}} 2n+1 \frac{2n+1}{(n(n+1) + \bar{S}_{\text{app}})}.
\]  
(157)

In the above expression \( \bar{S}_{\text{app}} \) is the solution of the self-consistent equation Eq. (123) at fixed \( kT, K_s, K_c, R_0, \) and \( S_0. \) When \( \bar{S}_{\text{app}} \rightarrow -\infty \) the correlator \( C(\bar{X}) \) diverges and the estimation becomes useless. However, one should always keep in mind that in this limit the contribution of the neglected higher order terms in the expansions Eqs. (7)–(9) increases and one would require an expansion in Eqs. (7)–(9) beyond the quadratic terms [13].

If the correlator is a small quantity in some sense (or equals zero), then due to the inequalities (Eq. (113)) the thermodynamics of the model system (Eq. (110)) is well approximated (some times called thermodynamically equivalent) by the approximating Hamiltonian \( H_{\text{app}}(v, \bar{X}). \)

It is instructive to consider the behavior of the correlator Eq. (157) as a function of \( K_s \) at the extreme values 0 and \( \infty. \) When \( K_s \rightarrow 0, \) from Eq. (143) it follows that at fixed \( kT, K_c, R_0, \) and \( S_0, \) the correlator in Eq. (157) also tends to zero. When \( K_s \rightarrow \infty, \) \( \bar{S}_{\text{app}} \) tends to \( \bar{S}_{\text{MS}} \) (see Eq. (144)), and the correlator tends to \( \infty. \)

The sum in the r.h.s. of the Eq. (157) has an asymptotic behavior in \( N \) given by Eq. (A.7) (see the Appendix A) in which \( \bar{S}_{\text{app}} \) must be replaced with its value from Eq. (127) or Eq. (128). As a result, it is easily seen that if \( N \rightarrow \infty \) then \( C(\bar{X}) \rightarrow 0 \) and our calculations are asymptotically exact in the thermodynamic limit \( \frac{N}{V} = \text{const}. \)

Since we discuss the role of the membrane stretching elasticity, we need to know the validity of our
approach as function of $K$. Here it is the place to note that the attempt to calculate even numerically the free energy in conjunction with the self-consistent equation may turn out a rather cumbersome task. A more efficient way of solving the problem, which avoids the numerical solution of the self-consistent equation, is to take into account the inverted form of the relation between $\Sigma_{\text{app}}$ and $K$, as given by Eq. (141). In other words due to the specific form of this relation it is more convenient instead of $\Sigma$ to use as an open parameter $\Sigma_{\text{app}}$. To this end we substitute the variable $\tilde{X}$ by $\Sigma_{\text{app}}$ in the Bogoliubov inequalities (107) using the relation (105). Thus, the Bogoliubov inequalities may be rewritten in the form:

$$0 \leq \frac{f[H] - f[H_{\text{app}}(\Sigma_{\text{app}})]}{f[H_{\text{app}}(\Sigma_{\text{app}})]} \leq R(\Sigma_{\text{app}}),$$

(158)

where

$$R(\Sigma_{\text{app}}) \equiv \frac{C(\Sigma_{\text{app}})}{f[H_{\text{app}}(\Sigma_{\text{app}})]}$$

(159)

is the relative error. The behavior of the function $R(\Sigma_{\text{app}})$ for some fixed $\Sigma_{\text{app}}$ is studied in [42]. Our numerical analysis shows that $R(\Sigma_{\text{app}}) \ll 1$, and therefore the used approximation provides a very good relative accuracy for any solution $\Sigma_{\text{app}}$ of the self-consistent equation which belongs to the open interval $(-1, \infty)$.

16. OUTLOOK OF THE METHOD CONSIDERED IN SECTION 10

So far, we restrict ourselves to the case when the vesicle membrane is a compressible 2D monolayer immersed in fluids having the same viscosity on the either side of the membrane. However actually the effects of interlayer coupling in fluctuating bilayer membrane is of strong interest. A review of some experimental and theoretical results, that have played seminal roles in the field, the reader can found in [67, 68]. Especially, theoretical descriptions in terms of the discrete spherical harmonics have been investigated intensively in [54, 69–72]. Further, investigations of bilayer structures involving inter interconnected effects of non-linear area-elasticity and relative displacement of the membrane monolayers would be of undoubted interest, therefore, some ideas and problems will be discussed below.

An important consequence of the membrane bilayer structure is that bending deformation is always accompanied with stretching of one monolayer (the outer) and compression of the other (the inner).

It is thus desirable to utilize the AHM considered in Sec. 10 to the study of the thermal fluctuations of a such more complex bilayer systems. As experience from other fields of condensed matter physics shows it is generally clear that any non-local term added in the Hamiltonian can be treated in this way [39, 61–63]. The result would be the appearance of an additional variation parameter satisfying the corresponding self-consistent equation.

A straightforward generalization of the model Hamiltonian Eq. (95) is to add the term due to the relative elastically expansion of the two individual membrane monolayers. In this model, each monolayer has a preferred (or relaxed) area $S_0^\text{in}$ and $S_0^\text{out}$, based on the number of lipid molecules it contains and can have the corresponding actual area $S_0^\text{in}$ and $S_0^\text{out}$, respectively. As a result an area difference elasticity (ADE) Hamiltonian [9, 73] between the two monolayers may be conveniently expressed in the form:

$$H_r = \frac{1}{2} \frac{K_\Lambda}{S_0} (\Delta S(v) - \Delta S_0)^2,$$

(160)

where $K_\Lambda$ is the appropriate elastic constant (non-local bending modulus) and for the term in the denominator the assumption $S_0^\text{out} \approx S_0^\text{in} = S_0$ is used. The term in the brackets, in spherical harmonics presentation up to the second-order approximation in the amplitudes $v_n^m$, takes the form [28]

$$\Delta S(v) \equiv S_0^\text{out}(v) - S_0^\text{in}(v) = 8\pi R_0 h \left[ 1 + \frac{1}{8\pi} \sum_{m=1}^{n_{\text{max}}} \sum_{n=0}^{m} (n-1)(n+2)(v_n^m)^2 \right],$$

(161)

where $2h$ is the separation between the two monolayers and $\Delta S_0 \equiv S_0^\text{out} - S_0^\text{in}$. If one introduces the tension due to relative area difference

$$\sigma_\Lambda = \frac{K_\Lambda}{S_0} (\Delta S_0),$$

(162)

Eq. (160) may be rewritten in the well known form

$$H_r(v) = \frac{S_0}{2K_\Lambda} (\sigma_\Lambda(v))\sigma_\Lambda(v),$$

(163)

and has to be added in Eq. (93):

$$H(v) = H_r(v) + H_r(v) + H_r(v).$$

(164)

Due to their uniform structure, the last two terms can be treated using the approximating Hamiltonian method developed in the Sections 9 and 10.

If one takes into account the bilayer structure of the membrane the role of the local lipid densities on each monolayer have to be scrutinized in the theory. It is well recognized that when the bilayer fluctuates the significant impact have physical processes that are result of the change in the local monolayer densities. The latter one can be brought about by the lateral flows of the lipid molecules. Thus, new dynamical degrees of freedom related with the lipid density dif-
ference between the two monolayers taking into account the quasi-spherical geometry of the membranes have been incorporated in the theory more or less on a phenomenological level [54, 69, 71, 74], or on the base of some fundamental principles [71, 72]. The problem is how to consider the transverse deformations with respect to an equilibrium reference configuration followed by a lateral redistribution of the molecules within the bilayer, namely flip-flop motions, and the effects of the intermonolayer friction. Here, it is not our aim to extend our theory on the case of bilayers. Rather, we give hint that it is possible pointing out the problematic items that should be solved in a such theory.

A quantitative theory describing the out-of-plane fluctuations of a flat membrane, taking into account the intermonolayer friction and two-dimensional viscosity has been developed in [74]. Explicit relations for the fluctuations of the form of a quasi-spherical vesicle, influenced by the mutual displacements of the monolayers, comprising its bilayer, for arbitrary values of the fluctuation wave vector, have been obtained in [69]. Later it was proved [70] that in the case of a bilayer membrane, the bending elasticity, participated in the theoretical results is that of a free flip-flop. The above result was obtained by taking into account the lateral displacement of the monolayers. Both theories [69, 70] reproduce in form the result of Milner and Safran (see Eq. (42) in the present study) for the mean square values of the amplitude \( u(\theta, \varphi, t) \), indeed, with more rich physical meaning of the corresponding effective bending elasticity modulus and effective surface tension. In order to be more concrete the comparison of Eq. (42) with the result obtained in [70] shows that \( K_c \) and \( \sigma + \varepsilon \) must be replaced by the free flip-flop bending elasticity \( K_{c}^{\text{fr}} \), blocked flip-flop bending elasticity \( K_{c}^{\text{bl}} \), and a function which is defined through an equation contained the difference between the molecular surface densities of the outer and inner monolayers and the flip-flop coefficient \( \xi \) (see Eq. (29) in [70]). Since the calculations in the above theories are essentially based on a Gaussian theory of fluctuation this is a hint that one may consider an extension to include the variation of the local density variations in the part given by Eq. (69) of our model Hamiltonian, Eq. (68), simply using the above formulated displacement as a mnemonic rule. A couple of remarks concerning the contributions of the above replacements on the excess area are due here. If we would like to speculate, using Eq. (137), whether values of \( \Delta(\Sigma_{\text{app}}) \) might legitimately be larger or smaller from \( \Delta(\Sigma_{\text{MS}}) \), the first we need is to have an estimation of the difference between the values of \( K_{c}^{\text{fr}} \) and \( K_{c}^{\text{bl}} \). The second remark concerns the solution \( \Sigma_{\text{app}} \). It must be obtained in a self-consistent way. The solutions of the former and the last problems are a difficult task.

A step in this direction, however beyond a self-consistent theory, has been done in [54, 70], where the effects related with the stretching elasticity of the bilayer in conjunction with lateral monolayer displacement in fluctuating nearly spherical vesicle have been considered. In these works, however a Milner and Safran type of mean-field approximation that the fluctuations of the effective tension are not correlated with the fluctuations of the amplitude \( u(\theta, \varphi, t) \) has been used. As a result the correlation between \( u(\theta, \varphi, t) \) and the surface tension has been lost resulting in an inability to determine the stretching elasticity modulus \( K_s \) from the flicker—noise analysis experiments.

Actually, a consistent approach based on some fundamental principles, have to be done in the framework of the theory proposed in [71] involving however the non-linear elasticity energy of the bilayer, i.e. term of the type Eq. (95).

Though our method based on the Bogoliubov inequalities is more generally applicable, in this case various less than trivial problems need to be solved. First, an inevitable issue is the justification of the appropriate choice of the effective Hamiltonian governing the elastic properties of the bilayer. Here, the obstacle is the appropriate choice of the physical parameters and the corresponding reference states entering in the definition of the Hamiltonian in order to make relations with the experiment (see e.g. the “second remark” in [71] about the involving a nonlinear area elasticity).

To include the local density variations in the two monolayer halves and the corresponding functional measure over an appropriate set of independent degree of freedom two more fields are needed in addition to \( u(\theta, \varphi, t) \) (in our notations to \( \varphi(\theta, \varphi, t) \)) and \( \varphi(\theta, \varphi, t) \), representing the local surface (number) densities of the outer and inner monolayer, respectively, and defined with respect to the surface described by \( R(\theta, \varphi, t) \). As it was pointed out in [71] the choice of the set of independent degrees of freedom in the corresponding expression of the Hamiltonian is a sophisticated problem, if the lateral flows of lipid molecules must to be taken into account. This might be a part of the general and complicated problem of the correct construction of statistical ensembles of surfaces [33]. These are the necessary points to be clarified in order to give correct self-consistent formulas for the free energies and correlation functions in the Bogoliubov variational inequalities (Eq. (107)). Moreover, the very solution of the variational problem will be more complicated. It is obvious that the case of fluctuating quasi-spherical bilayer involving a nonlinear area elasticity is still waiting for an exact theoretical development.

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17. SUMMARY

Depending on the geometry, there are two different ways to describe the behavior of a thermally fluctuating surface of a vesicle:

—out-of-plane fluctuations of a flat membrane, with periodic boundary conditions using the Monge representation, and

—shape fluctuations of a closed nearly spherical membrane, using a series expansion with respect to the spherical harmonics.

Only the latter case, with its specific features, has been analyzed in this review.

In most theoretical papers a key problem is how to introduce the volume and surface conservation of the vesicle from some basic principles. In the previous sections the area constraint has been considered within three different scenarios:

(i) in an exact manner through a delta-function in the partition function, see also [37, 36],

(ii) involving Lagrange multipliers in the Hamiltonian to accomplish constraints for the mean area, see also [12, 18, 37, 41].

(iii) involving an elastic contribution term in the Hamiltonian as considered in [42], see also [53, 54].

Though the importance of the results obtained in the first two scenarios are well evaluated, we like better the last one, as physically most natural and consistent with the statistical mechanics requirements. Let us briefly summarize the motivations for this statement.

In Sections 1 and 2 we consider the membrane as incompressible and impermeable. Then the volume and the area of the vesicle can be considered as constrained in the framework of scenarios (i) and (ii). In these cases the computational problem is the implementation of the fixed constant area if the volume has been already fixed.

Scenario (i) is considered in Section 3. It is the exact realization of the area constraint by adding a delta-function in the partition function. In this case calculations are based on the method of the steepest descent which requires skills in complex analysis in order to prove the existence of the solutions. Last but least this approach becomes exactly valid in the thermodynamic limit. The problem is reduced to solving the partition function, see also [37, 36],

approximation and have not need to use the complex plane analysis. Moreover, the approximation is not applicable. In order to solve this problem one can choose between two different paths:

(1) In the commonly used approach the linearization of the computational problem is based on the Hubbard–Stratonovich transformation with the subsequent use of the saddle-point approximation [36, 43, 52]. It turns out that the problem is exactly solvable (only) in the thermodynamic limit [36, 40, 43, 52]. Let us recall that firstly this aspect of the theory of flat membranes with periodic boundary conditions has been discussed in the context of the spherical model of phase transitions in 1976 [49].

(2) In the approach developed in [42] the linearization of the Hamiltonian in Eq. (100) is based on the Bogoliubov variational inequalities. In our opinion this approach allows easier analytical calculations (the corresponding integrals in the partition function and thermodynamic mean values are Gaussian) in comparison to scenario (i).

Scenario (iii) is considered in Sections 6 and 7, in which the membrane of the vesicle is treated as a stretchable/compressible thin surface whose elastic response depends on its intermolecular forces. An instructive question is whether it is possible to reveal the microscopic origin of the mean square amplitudes and excess area. This should allow to include the experimental determination of the stretching elasticity modulus in the flicker spectroscopy method. Having this in mind, the area dilation energy in the Hamiltonian of the fluctuating system should be taken into account as well. However, then the corresponding Hamiltonian becomes nonlinear with respect to the squares of spherical harmonics amplitudes, appearing in the expansion of the vesicle shape fluctuations. As a consequence the standard used tool—the equipartition theorem becomes inapplicable. In order to solve this problem one can choose between two different paths:

\[ \langle S(v) \rangle_{H(v, \sigma)} = A(\vec{X}), \quad (165) \]
Comparing with the argument of the delta-function, Eq. (19), where the microscopic area of the vesicle is fixed in an exact manner in the partition function, we see that the Eq. (165) (valid for membrane parameters: $S_0, K_c, K_c, R,$ and temperature $T$) imposes a “soft” constraint on the amplitudes of the shape fluctuations of the vesicle. It assures that the mean area of the membrane (l.h.s of Eq. (165)) is equal to the area $A(\tilde{X})$ (r.h.s. of Eq. (165)). As a first step, since $X$ has been introduced to linearize the Hamiltonian (Eq. (68)), the quantity $\Sigma_{app}(\tilde{X})$ no need to be considered as a direct experimentally measurable quantity. Further on, if $\Sigma_{app}(\tilde{X})$ is considered as a fitting parameter, then Eq. (121) for $\langle \nu_n^2 \rangle_{H_{app}(Y, X)}$ can be used to determine the bending elasticity modulus $K_c$. Of course, we may stop here in the interpretation of the obtained result. In other words, a $\sigma$-a Milner and Safran approach may be utilized also for vesicles with a compressible thin film membrane. If in this case the flickering analysis works well enough following the preexisting conventional approach only means that an experimental situation is realize where the importance of $K_c$ is not that important.

The problem with approach based on the Lagrange multiplier $\sigma$ is that its physical significance is somewhat ambiguous in the context of thermal fluctuations. There is no clear reason to believe that the membrane tension is independent of shape fluctuations, more so if one ignores the role of stretching elasticity of the membrane. There are no such problems with $\Sigma_{app}$ which is the membrane tension as follows from Eq. (132). Tough to extract from the functional expression Eq. (146) a quantitative information about $K_c$ is not so trivial, this is generally possible. To do this three quantities: $K_c, K_c$ and $\Sigma_{MS}$ have to be inferred as fitting parameters from the flickering analysis of the measurable shape fluctuations of the vesicle.

This consideration reveals a possibility to extract the value of the stretching elasticity modulus $K_c$ in conjunction with the estimation of the exactness of the used approximation. The degree of the exactness of the results can be obtained by estimating the correlator in the r.h.s. of the Bogoliubov inequalities (see Eq. (157)). This estimation can be applied for finite membranes as well.
in the case of Eqs. (46) and (123), and
\[ n_{\text{max}} \left( n + \frac{1}{2} \right) = \frac{1}{\Sigma_{\text{app}}} - \frac{1}{\Sigma_{\text{app}}} + N + O \left( \frac{1}{\Sigma_{\text{app}}} \right), \quad (A.7) \]
in the case of Eq. (157). In the above expressions it is used that \( n_{\text{max}} = \sqrt{N} \).

Solution of Eq. (46)

Let us introduce the notation
\[ x_0 = -\frac{\Sigma_{\text{MS}}}{N}. \quad (A.8) \]

With the help of Eq. (A.6) and the definition of \( \sigma_0 \) (see Eq. (71)), Eq. (46) may be presented (up to the used approximations) in the form:
\[ x_0 e^{x_0} = -e^{-\frac{A}{\gamma}}. \quad (A.9) \]

Eq. (A.9) can be solved in terms of the Lambert function \( W(x) \). A review of its mathematical properties and physical applications can be found in [76–80] and refs. therein. Recall that by definition
\[ W(xe^x) = x. \quad (A.10) \]

The Lambert function can take two possible real values for \(-\frac{1}{e} \leq x \leq 0\). Values satisfying \( W(x) \geq -1 \) belong to the principal branch denoted as \( W_0(x) \), while values satisfying \( W(x) \leq -1 \) belong to the \( W_1(x) \) branch. The two branches meet at the branch point for \( x = -\frac{1}{e} \), where \( W_0 \left( -\frac{1}{e} \right) = W_1 \left( -\frac{1}{e} \right) \). All values of \( W \) for \( x \geq 0 \) belong to the principal branch \( W_0(x) \).

The solution of Eq. (A.9) now reads
\[ x_0 = W \left( -e^{-\frac{A}{\gamma}} \right), \quad (A.11) \]
or finally
\[ \Sigma_{\text{MS}} = -NW \left( -e^{-\frac{A}{\gamma}} \right). \quad (A.12) \]

In the interval \(-e^{-1} \leq -e^{-\frac{A}{\gamma}} < 0\) the equation has two solutions given by \( W_0 \) and \( W_{-1} \), respectively.

For large \( x \), the function \( W(x) \) is approximated by
\[ W(x) = \ln x - \ln \ln x + o(1). \quad (A.13) \]

For small \( x \), the Taylor series around \( x = 0 \) is given by
\[ W(x) = x - x^2 + ... \quad (A.14) \]

The first few terms of the series expansion of \( W(x) \) near the branching point are
\[ W(x) = -1 + p - \frac{1}{3} p^2 + ..., \quad (A.15) \]
where \( p = \pm \sqrt{2(e \cdot x + 1)} \) for \( W(x)_{01} \).

Thus, using Eq. (A.14) for \( x = e^{-\frac{A}{\gamma}} \ll 1 \), one gets Eq. (47):
\[ W = N \left[ 1 - \sqrt{2(1 - e^{-\frac{A}{\gamma}})} \right]. \quad (A.16) \]

Solution of Eq. (123)

For \( \Sigma_{\text{app}} \gg 1 \), Eq. (123) can be treated in the same way. Let us introduce the notation
\[ x = \left( \frac{1}{C} - \frac{1}{N} \right) \Sigma_{\text{app}}. \quad (A.18) \]

Using Eq. (A.6) the self-consistent Eq. (123) may be presented (up to the used approximations) in the form:
\[ xe^x = \left( \frac{1}{C} - \frac{1}{N} \right) Ne^{\sigma_0 / C}. \quad (A.19) \]

In terms of the Lambert \( W(x) \) function the solution reads:
\[ \Sigma_{\text{app}} = \left( \frac{1}{C} - \frac{1}{N} \right)^{-1} W \left( \frac{1}{C} - \frac{1}{N} \right) N \exp \left( \frac{\sigma_0}{C} \right). \quad (A.20) \]

Thus, if \( \frac{1}{C} - \frac{1}{N} < 0 \) there will be two solutions or none (or only one solution if the argument of \( W \) is exactly \(-1\)). If \( \frac{1}{C} - \frac{1}{N} > 0 \) there will be one solution.

With the help of both expansions the Lambert \( W(x) \) function (A.13) and (A.14) one easily obtains Eqs. (127) and (128).

Not that if
\[ -\frac{\Delta}{\gamma} = \frac{\sigma_0}{C}, \quad (A.21) \]
combining Eqs. (A.20) and (A.9), the more general relation takes place
\[ \Sigma_{\text{app}} = \left( \frac{1}{C} - \frac{1}{N} \right)^{-1} \times W \left[ \left( \frac{1}{C} - \frac{1}{N} \right) \Sigma_{\text{MS}} \exp \left( -\frac{\Sigma_{\text{MS}}}{N} \right) \right]. \quad (A.22) \]
From the above result, if \( K_1 \to \infty \), immediately follows Eq. (144) where use has been made of definitions (125) and (A.10).

**APPENDIX B**

**THE GRIFFITS–FISHER LEMMA**

There is a mathematical statement known as Grif- 
fits–Fisher lemma [81, 82], which asserts that if a 
sequence of convex function converges pointwise 
to a limit function, then the sequence of its derivat 
ives converges to the derivative of the limit function 
at the points of its continuous differentiability. More 
precisely, if all functions \( f_n(x) \) and the limit function 
\( f_\infty(x) \) are differentiable at a point \( x_0 \in I \subset \mathbb{R} \), then

\[
\lim_{n \to \infty} f_n'(x_0) = f_\infty'(x_0). \tag{B.1}
\]

More general result due to Fisher consider the case 
of non-differentiable functions with left and right 
derivatives at any point \( x \in I \). The latter is relevant if 
the systems undergo thermodynamic phase transitions 
with spontaneously symmetry breaking. These state-
ments are useful in proving the asymptotic closeness 
of certain average values in the model and approximating 
system, see e.g. [39]. In our case, we consider both 
Hamiltonian \( H \), Eq. (110), and \( H_{\text{app}} \) (Eq. (111)), and 
introduce the following auxiliary Hamiltonians

\[
\mathcal{H}(h) = H + h\sigma(v) \tag{B.2}
\]

and

\[
\mathcal{H}_{\text{app}}(h) = H_{\text{app}} + h\sigma(v), \tag{B.3}
\]

where \( h \) is an auxiliary real parameter which at the end 
of the calculations will sent to zero. Further, we obtain 
that

\[
\langle \sigma(v) \rangle_H = \frac{\partial}{\partial h} F[\mathcal{H}(h)] \bigg|_{h=0} \tag{B.4}
\]

and

\[
\langle \sigma(v) \rangle_{H_{\text{app}}} = \frac{\partial}{\partial h} F[\mathcal{H}_{\text{app}}(h)] \bigg|_{h=0}. \tag{B.5}
\]

In the limit when the analog of the correlator 
Eq. (157) in the r.h.s. of the Bogoliubov inequalities 
with Hamiltonians (B.2) and (B.3) tends to zero as a 
function of its parameters:

\[
F[\mathcal{H}_{\text{app}}(h)] \to F[\mathcal{H}(h)]. \tag{B.6}
\]

Since \( F[\mathcal{H}_{\text{app}}(h)] \) and \( F[H(h)] \) are convex differentiable functions of \( h \) from the lemma follows that,

\[
\langle \sigma(v) \rangle_{H_{\text{app}}} \to \langle \sigma(v) \rangle_H. \tag{B.7}
\]

For the above proof to be correct the definition of 
the thermodynamic (or other) limit should be scruti-
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