Membrane stretching elasticity and thermal shape fluctuations of nearly spherical lipid vesicles

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One of the most widely used methods for determination of the bending elasticity modulus of model lipid membranes is the analysis of the shape fluctuations of nearly spherical lipid vesicles. The theoretical basis of this analysis is given by Milner and Safran [Phys. Rev. A **36**, 4371 (1987)]. In their theory the stretching effects are not considered. In the present study we generalized their approach including the stretching effects deduced after application of the statistical mechanics to vesicles.

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I. INTRODUCTION

The mechanical properties of biomenbranes determine to a great extent their structure and functioning. According to the model of Singer and Nicolson [1], the biomembrane consists of a lipid bilayer, in which integral proteins float. Within this model, the mechanical properties of the biomembrane are tightly connected with those of the lipid bilayer. Because of its very small thickness compared to the square root of its area, the lipid bilayer may be appropriately modeled as a two-dimensional flexible sheet and effectively studied theoretically, experimentally, and by computer simulations [2–24].

The notion of membrane tension plays a key role in the consideration of the elastic deformation of the lipid bilayers, their bending and stretching. The importance of curvature energy to the elasticity of membrane has been highlighted by Helfrich in his pioneering paper from 1973 [2], while the stretching effects were mentioned only in passing. A few years later Brochard, De Gennes, and Pfeuty [3] considered the vesicle membrane as compressible and revealed the role of the changes of the local density on the elastic energy. Renormalization of the membrane tension and elastic area expansion modulus in the frame work of this theory has been treated in Ref. [9].

Due to some ambiguity around the definition of the surface tension, the study of this issue is continuously growing [4,5,7,8,10–14,16–19,21,22]. In these papers, a number of questions were raised. They concern the physical meaning of the various definitions of tensions, the consistency between reasonable approximations and theoretical predictions, equivalence of ensembles, which requires implicitly the existence of thermodynamic limits, regimes where equilibrium thermodynamics is far from being justified, etc. These phenomena are still a source of both theoretical and experimental challenges; see Refs. [19,21,25] and references therein.

The state of a closed incompressible bilayer (e.g., a vesicle), which does not contain membrane reservoirs, is determined by the influence of the bending elasticity and the constraints on the total surface area and on the enclosed volume. The vesicle has a constrained area and constrained volume, since the number of the lipid molecules in the membrane is fixed. While it is technically easy to implement the second constraint, it is difficult to handle the first one. Instead of working with a fixed area, an effective tension as Lagrange multiplier conjugated to the fixed membrane area has been used [4,7], expecting that the two ensembles are equivalent [24,25].

The aim of our study is to elucidate the theoretical basis of the analysis initiated by Milner and Safran [4] and made more precise by Seifert [7] in order to take into consideration the role of the membrane compression and tension in terms of stretching elasticity, which are introduced into the theory by nonlocal (anharmonic) terms.

II. MILNER AND SAFRAN APPROACH

The main purpose of this section is to review the approach of Milner and Safran [4] and Seifert [7] proposed for studding vesicles with an isolated and incompressible surface. In Refs. [4] and [7] a theory for membranes possessing bending elasticity, having no stretching elasticity and an area A, which does not depend on the shape fluctuations of the vesicle, has been developed.

Let us have a *nearly spherical* lipid vesicle with fixed (i.e., not fluctuating) volume V and fixed area A. Let R be the radius of a *sphere* with the same volume V. In the considered theory the shape of the membrane fluctuated around the sphere with area $4\pi R^2$.

Let $\mathcal{R}(\theta,\varphi,t)$ be the modulus of the radius vector of a point on the surface of the vesicle, with polar coordinates (θ,φ), at time t in a laboratory reference frame, with origin O placed inside the vesicle. Let us define the dimensionless quantity

$$\frac{\mathcal{R}(\theta,\varphi,t)-R}{R}=u(\theta,\varphi,t). \tag{1}$$

The function $u(\theta,\varphi,t)$ is decomposed in a series of spherical harmonics as follows:

$$u(\theta,\varphi,t)=\sum_{n=0}^{n_{\max}}\sum_{m=-n}^{n}u_n^m(t)Y_n^m(\theta,\varphi), \tag{2}$$

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where $Y_n^m(\theta,\varphi)$ is the orthonormal basis (for simplicity chosen real) of the spherical harmonics functions. A cutoff $n_{\max} \sim 2\sqrt{\pi}R/\lambda$ is introduced in the sum, where λ 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 can be chosen in a way that $u_1^m = 0$. Because of the requirement for volume V conservation, the amplitude $u_0^0(t)$ can be expressed as

$$u_0^0(t) = -\frac{1}{2\sqrt{\pi}} \sum_{n=2}^{n_{\max}} \sum_{m=n}^{n} \left[u_n^m(t)\right]^2. \tag{3}$$

Then, as has been shown in Ref. [4] (see also Ref. [7]), the deformation energy G of the vesicle is

$$G = \frac{1}{2} K_c \sum_{n=2}^{n_{\max}} \sum_{m=-n}^{n} \left\{(n-1)(n+2) \times [n(n+1) + \overline{\Sigma}_{\mathrm{MS}}]\left[u_n^m(t)\right]^2\right\}. \tag{4}$$

In Eq. (4) K_c is the bending elasticity modulus, and the dimensionless expression

$$\overline{\Sigma}_{\mathrm{MS}} = \frac{R^2}{K_c}\sigma \tag{5}$$

has been introduced. The quantity σ is a Lagrange multiplier, not fluctuating with time, which ensures the mean area of the vesicle membrane to be equal to some prescribed value. The energy G from Eq. (4) can be considered as sum of the energies of not interacting "oscillators." As a result, for $n \geqslant 2$ the time mean squares $\langle[u_n^m(t)]^2\rangle$ of the amplitudes $u_n^m(t)$ of the different fluctuation modes were calculated by Milner and Safran:

$$\left\langle\left[u_n^m(t)\right]^2\right\rangle = \frac{kT}{K_c} \frac{1}{(n-1)(n+2)[n(n+1) + \overline{\Sigma}_{\mathrm{MS}}]}, \tag{6}$$

where kT is the Boltzmann constant times temperature. This result is used for the analysis of the shape fluctuation of nearly spherical vesicles.

It is worth noting that deformation energy G of the membrane does not depend on the stretching elasticity modulus K_s and is a function only of K_c and $\overline{\Sigma}_{\mathrm{MS}}$.

In our further consideration it is convenient (following Ref. [7]) to introduce the excess area α, which is related to a vesicle with fixed volume $V = \frac{4\pi}{3}R^3$, which defined R, and with fixed area A, which fluctuates around the shape $4\pi R^2$:

$$\alpha \equiv \frac{A - 4\pi R^2}{4\pi R^2} > 0. \tag{7}$$

The excess area obeys the implicit equation

$$\alpha = \gamma \sum_{n=2}^{n_{\max}} \frac{2n+1}{n(n+1) + \overline{\Sigma}_{\mathrm{MS}}(\alpha)}, \tag{8}$$

where

$$\gamma \equiv \frac{1}{8\pi}\frac{kT}{K_c}. \tag{9}$$

Equation (8), has been analyzed by many authors [4,6,7,14,24]. In such a type of theory (for a conventional approach with effective tension, see Ref. [7]) the dimensionless excess area is used traditionally as a small parameter $\alpha \ll 1$. Consequently the term in the rhs of Eq. (8) is also small and respectively $\overline{\Sigma}_{\mathrm{MS}}(\alpha)$ should be large. Our inspection of Eq. (8) [see Eq. (A15) in the Appendix] shows that the following functional dependences take place:

$$\overline{\Sigma}_{\mathrm{MS}}(\alpha) = Ne^{-\frac{\alpha}{\gamma}}, \quad e^{-\frac{\alpha}{\gamma}} \ll 1, \tag{10}$$

and its inverse

$$\alpha(\overline{\Sigma}_{\mathrm{MS}}) = \gamma \ln\left(\frac{N}{\overline{\Sigma}_{\mathrm{MS}}}\right), \quad \frac{\overline{\Sigma}_{\mathrm{MS}}}{N} \ll 1, \tag{11}$$

where $N \approx (n_{\max})^2$ is the number of lipid molecules in the vesicle membrane. Hereafter, when it does not cause confusion, we shall omit the argument in the functional dependence in $\overline{\Sigma}_{\mathrm{MS}}$ and α. A similar relation was first derived in Ref. [7] (see also the comment in Ref. [8]) simply by replacing the sum defining α in the right-hand side of Eq. (8) with an integral. In our consideration to calculate this sum we use the Euler-McLaurin summation formula. This reflects in a different range of validity of the result defined by the inequality in Eq. (10).

An equation analogous to Eq. (10) was analyzed for almost planar membrane in the low-tension regime in Ref. [13]. 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.

III. MODEL-DEPENDENT DERIVATIONS

In the theoretical developments, the effective tensions of the vesicle may be analyzed within different scenarios: as in Sec. II, involving Lagrange multipliers (see also Refs. [4,5,8,25]) or self-consistently when the vesicle membrane is not an incompressible, but stretchable or compressible surface, taking into account its stretching elasticity modulus K_s [3,9,13,17,25]. We shall discuss below the latter scenario to keep track with the former one.

A. The surface tension

Let us consider a vesicle whose membrane is made of a fixed number of constituent molecules N and let its preferred surface area S be governed by an elastic contribution to the Hamiltonian of the model. Following Brochard *et al.* [3] (see also Refs. [12,13]) the elastic contribution is proportional (with the coefficient of proportionality the compressibility modulus K_s) to the square of the difference between the *preferred* surface $S = N/\overline{\rho}$ and *optimal* surface of the membrane $S_0 = N/\rho_0$, where $\overline{\rho}$ is the average value of the surface density of the constituent molecules in the deformed state, and ρ_0 is the average value of the surface density of the constituent molecules in the equilibrium (flat tension-free) state. Sometimes S_0 is called saturated or Schulman area and is determined by the intermolecular forces. The effects of thermal fluctuations on the saturated area elasticity in the case of a nearly flat membrane using the Monge gauge have been studied in Ref. [12].

In the theoretical modeling of the experiment concerning closed membranes two constraints are accepted: fixed volume $V = \frac{4}{3}\pi R^3$ and fixed area S_0. This allows us to exclude the

osmotic pressure effects in our further consideration; see the review [8], Sec. 2.4.4, and Ref. [13].

One can present the area functional of the membrane $S(\mathcal{V})$ in the form

$$S(\mathcal{V}) = 4\pi R^2 + \Delta S(\mathcal{V}), \tag{12}$$

where the quantity $\Delta S(\mathcal{V})$ is the excess area of the vesicle (the difference between the area of the vesicle's membrane and the area $4\pi R^2$ of a sphere with a volume equal to that of the vesicle). The symbol $\mathcal{V}$ is used as a shorthand for the real value functions $(v_2^{-2}, v_2^{-1}, \ldots, v_{n_{\max}}^{n_{\max}})$, which are the spherical harmonics amplitudes, appearing in the expansion of the vesicle shape fluctuations from the equivalent volume sphere with radius R [see Eq. (2)]. By reason of the lack of the area constraint in our consideration, we shall use for the dynamical variables the notations v_n^m instead of u_n^m used in Eq. (2).

In terms of v_n^m the excess area of the vesicle $\Delta S(\mathcal{V})$ is presented in the form (see Refs. [4,5,7,13])

$$\Delta S(\mathcal{V}) = \frac{R^2}{2}\left[\sum_{n=2}^{n_{\max}}\sum_{m=-n}^{n}(n-1)(n+2)\left(v_n^m\right)^2\right]. \tag{13}$$

Evidently, $\Delta S(\mathcal{V}) \geqslant 0$. This property of $\Delta S(\mathcal{V})$ does not depend on the form of the Hamiltonian.

When the area functional $S(\mathcal{V})$ deviates (after stretching or compression) from the optimal area S_0 the membrane experiences a surface tension [2,21]

$$\sigma(\mathcal{V}) = K_s\frac{S(\mathcal{V}) - S_0}{S_0}, \tag{14}$$

where K_s is the area compressibility modulus.

B. Model Hamiltonian and Bogoliubov variational inequalities

The effective Hamiltonian we consider is presented as a sum of two terms: a curvature-dependent term and an area-dependent term, in the following form:

$$H(\mathcal{V}) = H_c(\mathcal{V}) + H_s(\mathcal{V}), \tag{15}$$

where [7]

$$H_c(\mathcal{V}) = \frac{1}{2}K_c\sum_{n=2}^{n_{\max}}\sum_{m=-n}^{n}(n-1)n(n+1)(n+2)\left(v_n^m\right)^2 \tag{16}$$

for the bending energy functional of the vesicle with nearly spherical geometry, and

$$H_s(\mathcal{V}) = \frac{1}{2}\frac{[\sigma(\mathcal{V})]^2}{K_s}S_0 \tag{17}$$

for the stretching energy functional, expressed via the membrane vesicle tension $\sigma(\mathcal{V})$; see Refs. [2,3,12,13].

We shall define the thermodynamic average of some quantity A with $H(\mathcal{V})$ in the standard way:

$$\langle A\rangle_{H(\mathcal{V})} = \{Z[H(\mathcal{V})]\}^{-1}\int D\{\mathcal{V}\}A\exp\left[-\frac{H(\mathcal{V})}{kT}\right], \tag{18}$$

where

$$Z[H(\mathcal{V})] = \int D\{\mathcal{V}\}\exp\left[-\frac{H(\mathcal{V})}{kT}\right] \equiv \exp\left\{-\frac{1}{kT}f[H]\right\} \tag{19}$$

is the statistical sum of the model and $f[H]$ is the Helmholtz free energy. Note that the correct definition of the measure $D\{\mathcal{V}\}$ is a subtle task in statistical mechanics of two-dimensional surfaces (see Ref. [7] and references therein). However, we do not need to go beyond the so-called normal gauge, which is known to be correct for small fluctuations [7]. At this level the proper measure is $D\{\mathcal{V}\} = \text{const}(d[v_2^{-2}], d[v_2^{-1}], \ldots, d[v_{n_{\max}}^{n_{\max}}])$, and the integration over v_n^m in Eq. (19) is carried out from 0 to ∞.

The term $H_s(\mathcal{V})$ due to its nonlinearity with respect to the squares of the amplitudes v_n^m causes some computational problems. To overcome this obstacle we linearize the Hamiltonian (17) using the Bogoliubov variational inequalities (for historical remarks and a list of different applications see, e.g., Ref. [26]).

The Bogoliubov inequalities in their most convenient form are given by

$$\langle H - H_{\text{app}}(X)\rangle_H \leqslant f[H] - f[H_{\text{app}}(X)] \leqslant \langle H - H_{\text{app}}(X)\rangle_{H_{\text{app}}(X)}, \tag{20}$$

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 $f[H]$. The following comment is in order here. The second of the inequalities (20) is known as Bogoliubov variational upper bound of the exact free energy [27]. The best approximation from above is obtained if the variational parameter X minimizes the variational free energy $f_{\text{var}}(X)$, defined as follows:

$$f_{\text{var}}(X) = f[H_{\text{app}}(X)] + \langle H - H_{\text{app}}(X)\rangle_{H_{\text{app}}(X)}. \tag{21}$$

This allows us to obtain the approximation from above (although sometimes quite crude) for the exact free energy of the studied physical system. The approach based on (21) is effectively used [28] in order to obtain a closed-form expression for the spectra of the thermal fluctuation of spherical vesicles incorporating nonlinear curvature elasticity terms.

We shall use another approach. If the left-hand side of (20) 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 right-hand side of (20). The use of inequalities (20) in the statistical mechanics of a lipid vesicle has been announced in Ref. [29].

C. The approximating Hamiltonian

In order to make the application of Bogoliubov variational inequalities more convenient, the model Hamiltonian $H(\mathcal{V})$ can be rewritten (up to an irrelevant constant) in an alternative form:

$$H(\mathcal{V}) = \mathcal{T}(\mathcal{V}) + [\mathcal{A}(\mathcal{V})]^2, \tag{22}$$

where

$$\mathcal{T}(U) = \frac{1}{2}K_c\sum_{n=2}^{n_{\max}}\sum_{m=-n}^{n}(n-1)(n+2)[n(n+1)+\overline{\sigma}_0]\left(v_n^m\right)^2 \tag{23}$$

and

$$\mathcal{A}(\mathcal{V}) = \sqrt{\frac{K_s}{2S_0}}\Delta S(\mathcal{V}). \tag{24}$$

Here and hereafter the bar over the quantity means dimensionless due to the multiplier R^2/K_c:

$$\overline{\sigma}_0 = \frac{R^2}{K_c}\sigma_0, \tag{25}$$

where

$$\sigma_0 = K_s\frac{4\pi R^2 - S_0}{S_0}. \tag{26}$$

It is important to note that if one skips the second term $[\mathcal{A}(\mathcal{V})]^2$ from the right-hand side of Eq. (22), a similar result to that of Milner and Safran for the mean-square values of the amplitudes v_n^m is obtained, as $\overline{\sigma}_0$ can be both positive and negative. In what follows the renormalization of $\overline{\sigma}_0$ due to this term is presented.

The second term in Eq. (22) may be presented in the form

$$[\mathcal{A}(\mathcal{V})]^2 = 2X\mathcal{A}(\mathcal{V}) - X^2 + [\mathcal{A}(\mathcal{V}) - X]^2, \tag{27}$$

where X is an arbitrary real parameter. We define the linearized Hamiltonian $H_{\rm app}(\mathcal{V}, X)$ as

$$H_{\rm app}(\mathcal{V}, X) = \mathcal{T}(\mathcal{V}) + 2X\mathcal{A}(\mathcal{V}) - X^2. \tag{28}$$

The last equation is obtained from Eq. (22) by removing the term $[\mathcal{A}(\mathcal{V}) - X]^2$ from the right-hand side. The Hamiltonian $H_{\rm app}(\mathcal{V}, X)$ defined in this way is linear with respect to $(v_n^m)^2$.

From Eqs. (23), (24), and (28) we obtain

$$H_{\rm app}(\mathcal{V}, X) = \sum_{n=2}^{n_{\max}}\sum_{m=-n}^{n} a_n(X)\left(v_n^m\right)^2 - X^2, \tag{29}$$

where

$$a_n(X) = \tfrac{1}{2}K_c(n-1)(n+2)[n(n+1) + \overline{\Sigma}_{\rm app}(X)], \tag{30}$$

and the dimensionless quantity $\overline{\Sigma}_{\rm app}(X)$ is defined as

$$\overline{\Sigma}_{\rm app}(X) = \overline{\sigma}_0 + \sigma_1 X \tag{31}$$

with $\overline{\sigma}_0$ from Eq. (25), and

$$\sigma_1 = \frac{R^2}{K_c}\sqrt{\frac{2K_s}{S_0}}. \tag{32}$$

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

$$\langle H(\mathcal{V}) - H_{\rm app}(\mathcal{V}, X)\rangle_{H(\mathcal{V})} = \langle[\mathcal{A}(\mathcal{V}) - X]^2\rangle_{H(\mathcal{V})} \geqslant 0. \tag{33}$$

Then Eqs. (20) and (33) imply that for each X:

$$0 \leqslant f[H(\mathcal{V})] - f[H_{\rm app}(\mathcal{V}, X)] \leqslant \langle[\mathcal{A}(\mathcal{V}) - X]^2\rangle_{H_{\rm app}(\mathcal{V},X)}. \tag{34}$$

We define $\widetilde{X}$ as the solution of the equation

$$\frac{\partial f[H_{\rm app}(\mathcal{V}, X)]}{\partial X} = 0. \tag{35}$$

It can be shown that this equation has only one solution, namely, $\widetilde{X}$, and $\widetilde{X}$ satisfies the condition

$$f[H_{\rm app}(\mathcal{V}, \widetilde{X})] = \max_X f[H_{\rm app}(\mathcal{V}, X)]. \tag{36}$$

From Eq. (34) it follows that

$$f[H_{\rm app}(\mathcal{V}, \widetilde{X})] \leqslant f[H(\mathcal{V})]. \tag{37}$$

Consequently, the free energy $f[H_{\rm app}(\mathcal{V}, \widetilde{X})]$ of the ensemble of not "interacting oscillators" is the best approximation from below of the free energy, corresponding to the model Hamiltonian $H(\mathcal{V})$.

IV. THE SELF-CONSISTENT EQUATION

A. The free energy

In order to present Eq. (35) in an explicit form we start from the Helmholtz free energy $f[H_{\rm app}(\mathcal{V}, X)]$:

$$f[H_{\rm app}(\mathcal{V}, X)] = -kT\ln\{Z[H_{\rm app}(\mathcal{V}, X)]\}, \tag{38}$$

where $Z[H_{\rm app}(\mathcal{V}, X)]$ is the partition function of the approximating system [see also the comment after Eq. (19)]

$$Z[H_{\rm app}(\mathcal{V}, X)] = \int D\{\mathcal{V}\}\left\{\exp\left[-\frac{H_{\rm app}(\mathcal{V}, X)}{kT}\right]\right\}. \tag{39}$$

Differentiating

$$f[H_{\rm app}(\mathcal{V}, X)] = -kT\ln\left\{\int D\{\mathcal{V}\}\exp\left[-\frac{\mathcal{T}(\mathcal{V}) + 2X\mathcal{A}(\mathcal{V})}{kT}\right]\right\} - X^2, \tag{40}$$

we obtain

$$\frac{\partial f[H_{\rm app}(\mathcal{V}, X)]}{\partial X} = 2[\langle\mathcal{A}(\mathcal{V})\rangle_{H_{\rm app}(\mathcal{V},X)} - X]. \tag{41}$$

Consequently, Eq. (35) can be written in the following equivalent form:

$$\langle\mathcal{A}(\mathcal{V})\rangle_{H_{\rm app}(\mathcal{V},X)} - X = 0. \tag{42}$$

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

The Hamiltonian [Eq. (29)] is a diagonal quadratic form in the real value functions $(v_2^{-2}, v_2^{-1}, \ldots, v_{n_{\max}}^{n_{\max}})$. As a result the multiple integral in (39) over u_n^m splits into a product of $N = \sum_{n=2}^{n=n_{\max}}\sum_{m=-n}^{m=n} = n_{\max}^2 + 2n_{\max} - 3$ one-dimensional Gaussian integrals. These integrals over v_n^m in (39) can be performed easily. Thus from Eqs. (38) and (39) we obtain the following expression for the free energy $f[H_{\rm app}(\mathcal{V}, \widetilde{X})]$ of the approximating system:

$$f[H_{\rm app}(\mathcal{V}, X)] = kT\sum_{n=2}^{n_{\max}}\frac{2n+1}{2}\ln\{(n-1)(n+2)[n(n+1) + \overline{\Sigma}_{\rm app}(X)]\} - (X)^2 + kT\frac{N}{2}\ln\left(\frac{K_c}{2\pi kT}\right), \tag{43}$$

with $X = \widetilde{X}$. Note that in Eq. (43) the dependence on K_s is hidden in the solution $\widetilde{X}$.

Hereafter, in order to be unambiguous we shall use notations linearized and approximating Hamiltonian for $H_{\rm app}(\mathcal{V}, X)$ and $H_{\rm app}(\mathcal{V}, \widetilde{X})$, respectively.

The mean-square amplitudes $\langle (v_n^m)^2 \rangle_{H_{\rm app}(\mathcal{V},X)}$, calculated by the linearized Hamiltonian $H_{\rm app}(\mathcal{V},X)$, are

$$\left\langle \left(v_n^m\right)^2 \right\rangle_{H_{\rm app}(\mathcal{V},X)} = \frac{kT}{K_c} \frac{1}{(n-1)(n+2)[n(n+1)+\overline{\Sigma}_{\rm app}(X)]}. \tag{44}$$

As can be seen after comparison with Eq. (6), the result for $\langle (v_n^m)^2 \rangle_{H_{\rm app}(\mathcal{V},X)}$ formally reproduces the result of Milner and Safran. However, a significant difference takes place. In their theory $\overline{\sigma}$ is introduced as a Lagrange multiplier, while in our theory $\overline{\Sigma}_{\rm app}(X)$ with $X = \widetilde{X}$ is obtained self-consistently by the application of statistical mechanics to the model Hamiltonian $H(\mathcal{V})$.

B. Analytical solutions of the self-consistent equation for some limiting cases

After differentiating Eq. (43) with respect to X we obtain Eq. (42) in an explicit form:

$$X = \frac{kT\sigma_1}{4} \sum_{n=2}^{n_{\max}} \frac{2n+1}{n(n+1)+\overline{\sigma}_0+\sigma_1 X}. \tag{45}$$

This equation is an analog in the case of spherical geometry of the equation, obtained in Refs. [3,9], for the renormalized surface tension of almost planar membranes. By multiplying both sides of Eq. (45) with $\overline{\sigma}_1$ [see Eq. (32)], adding to them $\overline{\sigma}_0$ [see Eq. (25)], and using the definition (31) we rewrite the self-consistent equation (45), from a physical point of view in a more convenient form:

$$\overline{\Sigma}_{\rm app} = \overline{\sigma}_0 + \overline{C} \sum_{n=2}^{n_{\max}} \frac{2n+1}{n(n+1)+\overline{\Sigma}_{\rm app}}, \tag{46}$$

where for clarity and conciseness the shorthand

$$\overline{\Sigma}_{\rm app} = \overline{\Sigma}_{\rm app}(\widetilde{X}) \tag{47}$$

and

$$\overline{C} = \frac{kT}{2} \frac{K_s}{S_0} \frac{R^4}{(K_c)^2} \approx \gamma K_s \frac{R^2}{K_c} \tag{48}$$

are used. Note that here and further in our computations sometimes we shall use the reasonable approximation $R^2/S_0 \approx 1/4\pi$.

In the general case, Eq. (46) can be solved only numerically to yield the solution $\overline{\Sigma}_{\rm app} = \overline{\Sigma}_{\rm app}(\overline{C}, \overline{\sigma}_0, N \approx n_{\max}^2)$.

Equation (46) shows that $\overline{\Sigma}_{\rm app}$ depends on K_s and K_c and geometrical parameters R and S_0 only in the combinations $\overline{C}$ and $\overline{\sigma}_0$. It can be shown that if

$$-\frac{\overline{\sigma}_0}{\overline{C}} \leqslant \sum_{n=2}^{n_{\max}} \frac{2n+1}{n(n+1)}, \tag{49}$$

this equation has only one solution, which belongs to the interval $[0,\infty)$. If the opposite inequality takes place, $\overline{\Sigma}_{\rm app}$ belongs to the interval $(-6, 0]$.

For $\overline{\Sigma}_{\rm app} \gg 1$, it is possible to obtain an analytical solution of the Eq. (46), in terms of the Lambert function [see (A19) in the Appendix]. For large $\overline{\Sigma}_{\rm app}$, two different regimes have to be distinguished (see the Appendix):

(1)

$$\overline{\Sigma}_{\rm app} = \overline{C} \ln\left(\frac{N e^{\overline{\sigma}_0/\overline{C}}}{\overline{C}}\right), \quad \frac{N e^{\overline{\sigma}_0/\overline{C}}}{\overline{C}} \gg 1, \tag{50}$$

or

(2)

$$\overline{\Sigma}_{\rm app} = N e^{\overline{\sigma}_0/\overline{C}}, \quad \frac{N e^{\overline{\sigma}_0/\overline{C}}}{\overline{C}} \ll 1, \tag{51}$$

Concerning the dependence on K_s, the former has to be attributed to finite K_s, while the latter to the limit case $K_s \to \infty$. Note that the ratio $\overline{\sigma}_0/\overline{C}$ does not depend on K_s.

In our further studies it is convenient to include an auxiliary effective tension $\overline{\Sigma}_{\rm MS}$ related to a *reference vesicle with fixed area and volume* $A = S_0$, $V = \frac{4\pi}{3}R^3$ and with excess area α defined in Eq. (8) (i.e., with the same values as those of the vesicle considered in Sec. II which is the reason to use the same notation $\overline{\Sigma}_{\rm MS}$). Thus, the definitions Eqs. (7), (9), (25), and (48) employ the identity

$$-\frac{\alpha}{\gamma} = \frac{\overline{\sigma}_0}{\overline{C}}, \quad \overline{\sigma}_0 < 0. \tag{52}$$

Now it is possible to insert the value of $\overline{\Sigma}_{\rm MS}$ from Eq. (10) in Eqs. (50) and (51). One gets

(1′)

$$\overline{\Sigma}_{\rm app} = \overline{C} \ln\left(\frac{\overline{\Sigma}_{\rm MS}}{\overline{C}}\right), \quad \frac{N e^{\overline{\sigma}_0/\overline{C}}}{\overline{C}} \gg 1, \tag{53}$$

or

(2′)

$$\overline{\Sigma}_{\rm app} = \overline{\Sigma}_{\rm MS}, \quad \frac{N e^{\overline{\sigma}_0/\overline{C}}}{\overline{C}} \ll 1. \tag{54}$$

Thus, one obtains $1 \ll \overline{\Sigma}_{\rm app} \leqslant \overline{\Sigma}_{\rm MS}$. Equations (53) and (54) allow us to keep track of the two effective tensions, $\overline{\Sigma}_{\rm app}$ and $\overline{\Sigma}_{\rm MS}$, under the condition $e^{-\frac{\alpha}{\gamma}} \ll 1$, which validates the result (10).

It is worth noting that in the presented approach $\overline{\Sigma}_{\rm app}$ has a natural physical interpretation: Eq. (46) [recall the relations (12), (13), and (44)] implies

$$\overline{\Sigma}_{\rm app} = \frac{R^2}{K_c} K_s \frac{\langle S(\mathcal{V})\rangle_{H_{\rm app}(\mathcal{V},\widetilde{X})} - S_0}{S_0} = \frac{R^2}{K_c} \langle \sigma(\mathcal{V})\rangle_{H_{\rm app}(\mathcal{V},\widetilde{X})}, \tag{55}$$

where $\sigma(\mathcal{V})$ is the true (not normalized) tension of the membrane [see Eq. (14)].

Let us replace $\overline{\Sigma}_{\rm app}$ in favor of the other meaningful quantity: dimensionless excess area $\alpha(\overline{\Sigma}_{\rm app})$:

$$\alpha(\overline{\Sigma}_{\rm app}) \equiv \frac{\langle S(\mathcal{V})\rangle_{H_{\rm app}(\mathcal{V},\widetilde{X})} - 4\pi R^2}{4\pi R^2}. \tag{56}$$

From Eqs. (12), (13), and (44) (with $X = \widetilde{X}$) it follows that

$$\alpha(\overline{\Sigma}_{\rm app}) = \gamma \sum_{n=2}^{n_{\max}} \frac{2n+1}{n(n+1)+\overline{\Sigma}_{\rm app}}. \tag{57}$$

The transformation of the right-hand side of Eq. (57) with the help of Eq. (A15) in the Appendix shows that the following functional dependences take place:

$$\alpha(\overline{\Sigma}_{\rm app}) = \gamma \ln\left(\frac{N}{\overline{\Sigma}_{\rm app}}\right), \quad \frac{\overline{\Sigma}_{\rm app}}{N} \ll 1. \tag{58}$$

Now we are in the position to compare in an explicit form this result with the excess area obtained within the approach of Milner and Safran $\alpha(\overline{\Sigma}_{\rm MS})$; see Eq. (11). One gets

$$\alpha(\overline{\Sigma}_{\rm app}) - \alpha(\overline{\Sigma}_{\rm MS}) = \gamma \ln\left(\frac{\overline{\Sigma}_{\rm MS}}{\overline{\Sigma}_{\rm app}}\right) \geqslant 0 \tag{59}$$

under the conditions

$$\frac{\overline{\Sigma}_{\rm app}}{N} \leqslant \frac{\overline{\Sigma}_{\rm MS}}{N} \ll 1, \quad 1 \ll \overline{\Sigma}_{\rm app} \leqslant \overline{\Sigma}_{\rm MS}. \tag{60}$$

Moreover, provided the inequality $\overline{\Sigma}_{\rm app} \leqslant \overline{\Sigma}_{\rm MS}$ takes place, by comparing Eqs. (8) and (57) one may conclude that always $\alpha(\overline{\Sigma}_{\rm app}) \geqslant \alpha(\overline{\Sigma}_{\rm MS})$. Thus, according to Eqs. (8) and (57), a larger K_s value will result in a smaller excess area $\alpha(\overline{\Sigma}_{\rm app})$.

In order to check our model, it is instructive to estimate the constants in δ_0, $\overline{\sigma}_0$, and $\overline{C}$. We shall use the following typical numerical values of the quantities [30]:

$$\begin{aligned} K_s &\sim 100\ \text{erg/cm}^2 \\ K_c &\sim 10^{-12}\ \text{erg} \\ R &\sim 10^{-3}\ \text{cm} \\ S_0 &\sim 4\pi R^2 \sim 1.256\times 10^{-5}\ \text{cm}^2 \\ \overline{\sigma}_1 &\equiv (R^2/K_c)\sigma_1 = 4\times 10^9\ \text{erg}^{-0.5} \\ kT &\sim 4.10^{-14}\ \text{erg}. \end{aligned}$$

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

$$\begin{aligned} \alpha &\sim 10^{-2} \\ \gamma &\sim 10^{-3} \\ |\overline{\sigma}_0| &\sim 10^6 \\ \overline{C} &\sim 10^5. \end{aligned}$$

Evidently, the above constants obey the relation

$$\frac{\alpha}{\gamma} = \frac{|\overline{\sigma}_0|}{\overline{C}} \sim 10. \tag{61}$$

Thus, the inequality (49) holds, and Eq. (46) has a positive solution for $\overline{\Sigma}_{\rm app}$. Note that two regimes resulting from the inequality between $\overline{C}$ and N are possible: (1) given by Eq. (50) or (2) given by Eq. (51). In the above statement we accept also that the intermolecular distance λ is of the order of 10 Åand then $n_{\max} \sim 3\times 10^4$ and $N \sim 10^9$.

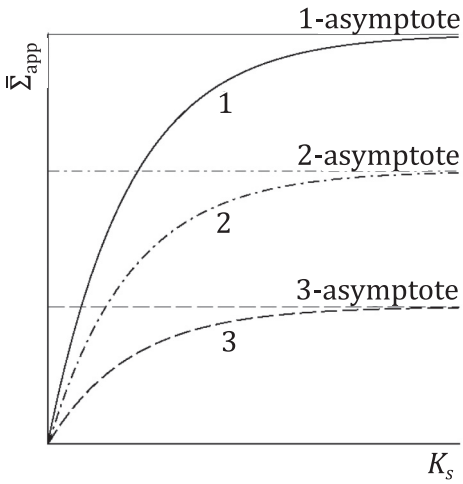

FIG. 1. Schematic representation of the dependence of the vesicle tension $\overline{\Sigma}_{\rm app}$ [see Eq. (46)] on its stretching elasticity K_s. The three curves 1, 2, and 3 refer to three vesicles with identical radii R, bending elasticities K_c, and temperature T and with different tension-free areas S_0 of their membranes. S_0 of curve 1 is greater than that of curve 2, which is greater than that of curve 3. When K_s tends to ∞, the dependences of this kind tend to horizontal asymptotes: $\overline{\Sigma}_{\rm app} = \overline{\Sigma}_{\rm MS}$ (see below). In the present case the asymptotes, corresponding to the curves 1, 2, and 3, are denoted as the 1-asymptote, 2-asymptote, and 3-asymptote, respectively.

C. The relation between $\overline{\Sigma}_{\rm app}$ and K_s

Using effective tension $\overline{\Sigma}_{\rm MS}$ defined through Eq. (8) (with $A = S_0$), Eq. (46) can be presented in the following form:

$$\overline{\Sigma}_{\rm app} = \overline{C}(\overline{\Sigma}_{\rm MS} - \overline{\Sigma}_{\rm app}) \times \sum_{n=2}^{n_{\max}} \frac{(2n+1)}{[n(n+1)+\overline{\Sigma}_{\rm app}][n(n+1)+\overline{\Sigma}_{\rm MS}]}. \tag{62}$$

Equation (62) shows the dependence of $\overline{\Sigma}_{\rm app}$ as a function of K_c and K_s for different values of $\overline{\Sigma}_{\rm MS}$ (respectively S_0) at fixed R and T. This dependence in an explicit form, for $\overline{\Sigma}_{\rm app} \gg 1$, in terms of the Lambert function is obtained in the Appendix; see Eq. (A21). For three different values of S_0, $\overline{\Sigma}_{\rm app}(K_s)$ is schematically presented in Fig. 1.

The simple dependence of $\overline{\Sigma}_{\rm app}$ as a function of K_s prompts Eq. (62) to be inverted to yield K_s as a function of $\overline{\Sigma}_{\rm app}$:

$$\frac{R^2}{K_c}K_s = F_s(\overline{\Sigma}_{\rm MS}, \overline{\Sigma}_{\rm app}), \tag{63}$$

where

$$F_s(\overline{\Sigma}_{\rm MS}, \overline{\Sigma}_{\rm app}) = \frac{\overline{\Sigma}_{\rm app}}{\overline{\Sigma}_{\rm MS} - \overline{\Sigma}_{\rm app}} \left\{ \gamma \sum_{n=2}^{n_{\max}} \frac{(2n+1)}{[n(n+1)+\overline{\Sigma}_{\rm MS}][n(n+1)+\overline{\Sigma}_{\rm app}]} \right\}^{-1}. \tag{64}$$

Note that by definition the quantity K_s must be positive. Since negative values of $\overline{\Sigma}_{\rm MS}$ are allowed [7] the following two possibilities depending on the sign of $\overline{\Sigma}_{\rm MS}$ in the above formula are relevant:

(a) If $-6 < \overline{\Sigma}_{\rm MS} < 0$, then $\overline{\Sigma}_{\rm MS} < \overline{\Sigma}_{\rm app} < 0$

(b) If $\overline{\Sigma}_{\rm MS} > 0$, then $\overline{\Sigma}_{\rm MS} > \overline{\Sigma}_{\rm app} > 0$.

The obtained result allows to determine the values of $\overline{\Sigma}_{\rm app}(K_s)$ 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

$$\lim_{K_s \to 0} \overline{\Sigma}_{\rm app}(K_s) = 0. \tag{65}$$

The analogous case in the Milner and Safran approach is the case when $\overline{\sigma} = 0$ [see Eqs. (4) and (5)].

Since $\overline{\Sigma}_{\rm MS}$ does not depend on K_s, from the rhs of Eq. (64) it follows that when $\overline{\Sigma}_{\rm app} \to \overline{\Sigma}_{\rm MS}$, $K_s \to \infty$. The second limit is exactly the tension of the reference uncompromisable vesicle $\overline{\Sigma}_{\rm MS}$ [see also Eq. (A21)]:

$$\lim_{K_s \to \infty} \overline{\Sigma}_{\rm app}(K_s) = \overline{\Sigma}_{\rm MS}. \tag{66}$$

The theory of Milner and Safran is adequate within regimes in which K_s is not relevant. Equations (65) and (66) suggest that it is a limit case of our theory.

One of the key points of this work is the elucidation of the role of the self-consistent equation. We showed that this equation allows us to obtain the stretching elasticity modulus K_s via experimentally accessible quantities.

Note that it is possible to obtain $\overline{\Sigma}_{\rm app}(K_c, K_s)$ from Eq. (46) and after that to calculate the dependence of $\langle (v_n^m)^2 \rangle_{H_{\rm app}(\mathcal{V},\widetilde{X})}$ on K_c, K_s and using $\overline{\Sigma}_{\rm app}(K_c, K_s)$, (i.e., to obtain $\langle (v_n^m)^2 \rangle_{H_{\rm app}(\mathcal{V},\widetilde{X})}$ from Eq. (44), with $X = \widetilde{X}$, $\langle (v_n^m)^2 \rangle_{H_{\rm app}(\mathcal{V},\widetilde{X})}[K_c, \overline{\Sigma}_{\rm app}(K_c, K_s)]$).

D. The fitting function

Another point to discuss is the straightforward connection of our theory with experimental studies of vesicle fluctuations by the technique of flicker-noise measurement. In the case when the fluctuations of quasispherical vesicles can be observed by phase contrast microscopy, our formula, Eq. (44), for the mean-square amplitudes $\langle (v_n^m)^2 \rangle_{H_{\rm app}(\mathcal{V},X)}$ can in principle be used as a tool to extract information from the experimental data.

In the general case $\overline{\Sigma}_{\rm app}$ depends on K_c, K_s, R, and S_0. If the last two parameters can be calculated or measured by independent methods and are not correlated with K_c and K_s, then, by fitting $\langle (v_n^m)^2 \rangle_{H_{\rm app}(\mathcal{V},\widetilde{X})}$ with K_c and K_s, we can determine them from the analysis of the thermal fluctuations of the vesicle shape.

But to present the needed fitting parameters in an explicit form is not trivial, at least, not straightforward, since as was mentioned, they are hidden in the solution $\overline{\Sigma}_{\rm app}$ of the self-consistent equation.

One way to obtain an approximating fitting function is to replace $\overline{\Sigma}_{\rm app}$ in the right-hand side of Eq. (44) by the expression given in Eq. (53); this gives

$$\left\langle \left(v_n^m\right)^2 \right\rangle_{H_{\rm app}(\mathcal{V},X)} = \frac{8\pi\gamma}{(n-1)(n+2)\{n(n+1) + \gamma \overline{K}_s[\ln \overline{\Sigma}_{\rm MS} - \ln(\gamma \overline{K}_s)]\}}, \tag{67}$$

where $\overline{K}_s = \frac{R^2}{K_c} K_s$ is the dimensionless area compressibility modulus. Let us recall that the above equation becomes valid provided that the condition

$$\frac{\overline{\Sigma}_{\rm MS}}{\gamma \overline{K}_s} \gg 1 \tag{68}$$

is fulfilled. Note that, as follows from (54), the opposite strong inequality provides the case considered by Milner and Safran:

$$\left\langle \left(v_n^m\right)^2 \right\rangle_{H_{\rm app}(\mathcal{V},X)} = \frac{8\pi\gamma}{(n-1)(n+2)\{n(n+1) + \overline{\Sigma}_{\rm MS}\}}. \tag{69}$$

These expressions for the mean-square amplitudes could be used to determine experimentally K_s, K_c, and parameter $\overline{\Sigma}_{\rm MS}$ (instead of S_0) in the fitting procedure in the flicker spectroscopy method.

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

Taking into account Eq. (34), the correlator $C(\widetilde{X})$ in the right-hand side of the Bogoliubov inequalities (20) may be presented as

$$C(\widetilde{X}) \equiv \langle [\mathcal{A}(\mathcal{V}) - \widetilde{X}]^2 \rangle_{H_{\rm app}}(\mathcal{V}, \widetilde{X}). \tag{70}$$

Obviously, we have

$$\langle [\mathcal{A}(\mathcal{V}) - \widetilde{X}]^2 \rangle_{H_{\rm app}(\mathcal{V},\widetilde{X},\sigma_0)} = \langle [\mathcal{A}(\mathcal{V})]^2 \rangle_{H_{\rm app}(\mathcal{V},\widetilde{X},\sigma_0)} - 2\langle \mathcal{A}(\mathcal{V}) \rangle_{H_{\rm app}(\mathcal{V},\widetilde{X},\sigma_0)} \widetilde{X} + (\widetilde{X})^2. \tag{71}$$

From Eqs. (24), (32), and (44) we obtain

$$\langle \mathcal{A}(\mathcal{V}) \rangle_{H_{\rm app}(\mathcal{V},\widetilde{X})} = \frac{kT\sigma_1}{4} \sum_{n=2}^{n_{\max}} \frac{2n+1}{[n(n+1) + \overline{\Sigma}_{\rm app}]}. \tag{72}$$

From Eqs. (42) it follows that

$$\langle \mathcal{A}(\mathcal{V}) \rangle_{H_{\rm app}(\mathcal{V},\widetilde{X})} \equiv \widetilde{X}. \tag{73}$$

But Eqs. (13) and (24) imply

$$\langle [\mathcal{A}(\mathcal{V})]^2 \rangle_{H_{\rm app}(\mathcal{V},\widetilde{X})} = \frac{K_s}{2S_0} \frac{R^4}{4} \sum_{n=2}^{n_{\max}} \sum_{m=-n}^{n} \sum_{n'=2}^{n_{\max}} \sum_{m'=-n'}^{n'} (n-1)(n+2) \times (n'-1)(n'+2) \left\langle \left(v_n^m\right)^2 \left(v_{n'}^{m'}\right)^2 \right\rangle_{H_{\rm app}(\mathcal{V},\widetilde{X})}. \tag{74}$$

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

$$\left\langle \left(v_n^m\right)^4 \right\rangle_{H_{\rm app}(\mathcal{V},\widetilde{X})} = 3\left[\left\langle \left(v_n^m\right)^2 \right\rangle_{H_{\rm app}(\mathcal{V},\widetilde{X})}\right]^2. \tag{75}$$

Hereafter in our final results it is more instructive to use $\overline{\Sigma}_{\rm app}$ instead of $\widetilde{X}$ [see Eq. (31)]. After some tedious but simple calculations we get

$$\langle [\mathcal{A}(\mathcal{V})]^2 \rangle_{H_{\rm app}(\mathcal{V},\widetilde{X})} = [\langle \mathcal{A}(\mathcal{V}) \rangle_{H_{\rm app}(\mathcal{V},\widetilde{X})}]^2 + \frac{K_s}{S_0}\frac{R^4}{4}\left[\frac{kT}{K_c}\right]^2 \sum_{n=2}^{n_{\max}} \frac{2n+1}{[n(n+1)+\overline{\Sigma}_{\rm app}]^2}. \tag{76}$$

Recalling the relation

$$\overline{\Sigma}_{\rm app} \equiv \overline{\sigma}_0 + \sigma_1 \widetilde{X}, \tag{77}$$

finally we have

$$C(\widetilde{X}) = \langle [\mathcal{A}(\mathcal{V}) - \widetilde{X}]^2 \rangle_{H_{\rm app}(\mathcal{V},\widetilde{X})} = \frac{K_s}{S_0}\frac{R^4}{4}\left[\frac{kT}{K_c}\right]^2 \sum_{n=2}^{n_{\max}} \frac{2n+1}{[n(n+1)+\overline{\Sigma}_{\rm app}]^2}. \tag{78}$$

In the above expression $\overline{\Sigma}_{\rm app}$ is the solution of the self-consistent equation (46) at fixed kT, K_c, K_s, R, and S_0.

If the correlator is a small quantity in some sense, then due to the inequalities [Eq. (34)] the thermodynamics of the model system [Eq. (22)] is well approximated by the approximating Hamiltonian $H_{\rm app}(\mathcal{V}, \widetilde{X})$.

Let us consider the behavior of the correlator (78) at the extreme values of K_s (0 and ∞). From Eq. (65) it follows that when $K_s \to 0$ at fixed kT, K_c, R, and S_0, the correlator in Eq. (78) also tends to zero. If $K_s \to \infty$, $\overline{\Sigma}_{\rm app}$ tends to $\overline{\Sigma}_{\rm MS}$ [see Eq. (66)], and the correlator tends to ∞.

The sum in the right-hand side of the Eq. (78) has an asymptotic behavior in N given by Eq. (A7) (see the Appendix) in which $\overline{\Sigma}_{\rm app}$ must be replaced with its value from Eq. (50) or (51). As a result, it is easily seen that if $N \to \infty$ then $C(\widetilde{X}) \to 0$, 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 a function of K_s. Here 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 to be 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 $\overline{\Sigma}_{\rm app}$ and K_s as given by Eq. (63). In other words due to the specific form of this relation it is more convenient instead of K_s to use as an open parameter $\overline{\Sigma}_{\rm app}$. To this end we substitute the variable $\widetilde{X}$ by $\overline{\Sigma}_{\rm app}$ in the Bogoliubov inequalities (20) using the relation (31). Thus, the Bogoliubov inequalities may be rewritten in the form

$$0 \leqslant \frac{f[H] - f[H_{\rm app}(\overline{\Sigma}_{\rm app})]}{f[H_{\rm app}(\overline{\Sigma}_{\rm app})]} \leqslant R(\overline{\Sigma}_{\rm app}), \tag{79}$$

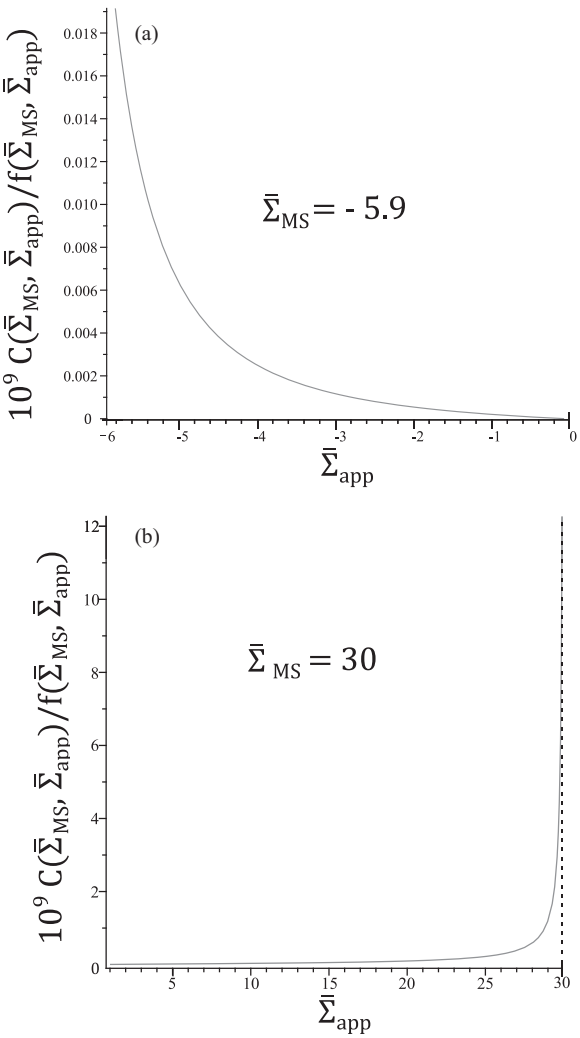

FIG. 2. The dependence of the ratio $\frac{C(\overline{\Sigma}_{\rm app}, \overline{\Sigma}_{\rm MS})}{f[H_{\rm app}(\overline{\Sigma}_{\rm app}, \overline{\Sigma}_{\rm MS})]}$ on the normalized tension $\overline{\Sigma}_{\rm app}$ is shown. To emphasize the dependence on $\overline{\Sigma}_{\rm MS}$ it is explicitly written as an additional argument of the functions. The numerical results are obtained with the typical numerical values given above of the quantities $K_c = 10^{-12}$ erg, $R = 10^{-3}$ cm, $kT \sim 4\times10^{-14}$ erg and for two concrete values of $\overline{\Sigma}_{\rm MS}$: (a) $\overline{\Sigma}_{\rm MS} = -5.9$ and (b) $\overline{\Sigma}_{\rm MS} = 30$. In Eq. (43) for $f[H_{\rm app}(\mathcal{V}, \widetilde{X})]$,with the help of Eq. (31), we replace the variable $\widetilde{X}$ with $\overline{\Sigma}_{\rm app}$ [see the comment in the text concerning inequalities (79)].

where

$$R(\overline{\Sigma}_{\rm app}) \equiv \frac{C(\overline{\Sigma}_{\rm app})}{f[H_{\rm app}(\overline{\Sigma}_{\rm app})]} \tag{80}$$

is the relative error. The function $R(\overline{\Sigma}_{\rm app})$ for some fixed $\overline{\Sigma}_{\rm MS}$ is presented in Fig. 2. Our numerical analysis shows that $R(\overline{\Sigma}_{\rm app}) \ll 1$, and therefore the used approximation provides a very good relative accuracy for any solution $\overline{\Sigma}_{\rm app}$ of the self-consistent equation which belongs to the *open* interval $(-6, \infty)$.

VI. MONOLAYERS: RESULTS AND CONCLUSIONS

In the case of a nonelastic impermeable membrane the volume and the area of a vesicle can be considered as constants.

In most of the theoretical studies the membrane area constraint is guaranteed by a Lagrange multiplier σ conjugate to the real area $S(\mathcal{V})$ [7,8,14,16,25]. The Lagrange multiplier fixes the mean area $\langle S(\mathcal{V})\rangle_{H(\mathcal{V})}$ of the vesicle and is known also as "intrinsic tension" [16] or "internal tension" [25]. Its value cannot be measured directly and is experimentally determined thorough the temperature and the excess area [7,8]. Contrary to the apparent simplicity of this issue, the relation of σ to the other generic definitions of membrane surface tension is a matter of a longstanding debate (see, e.g., Refs. [14,16,25] and references therein). The method, involving a Lagrange multiplier, allows easier analytical calculations (the corresponding integrals in the partition function and thermodynamic mean values are Gaussian) in comparison with the other method that exactly fixes the membrane area by a δ function [7,8,11,24]. The latter requires use of the integral representation of the δ function, and the calculations can be performed using the method of the steepest descent in the corresponding integral. This approach becomes exactly valid in the thermodynamic limit [7,8,11,12].

Although the two approaches model two different statistical ensembles, it is widely assumed that they give equivalent results in the thermodynamic limit, i.e., the ensembles are equivalent in the limit of infinitely large membranes [16,25]. However, it is questionable whether this equivalence holds for all characteristics of the system. The problem resembles the well-known problem for the equivalence of spherical and of mean spherical models of ferromagnetism which belong to different ensembles. It is well known that in the latter case these two ensembles are, in general, statistically inequivalent (for a discussion and list of references see Chapter 3 of the monograph [26]). In the membrane fluctuation theories the above mentioned equivalence problem should be carefully reconsidered. In addition, there is one more profound obstacle, namely, that an infinitely large membrane at finite tension is an object not at thermodynamic equilibrium [19], and thus, the description in different ensembles should not give equivalent results.

In the present paper, our consideration avoids all these problems being in the realm of statistical mechanics of finite-size systems. We study a quite different physical situation in which the membrane of the vesicle is treated as a stretchable or 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 σ in the formulas of Milner and Safran for the mean-square amplitudes and excess area, or more precisely, of the quantities which appear instead. In particular, this should allow us to include the experimental determination of the stretching elasticity modulus K_s in the scenario of 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 $H(\mathcal{V})$ becomes nonlinear with respect to the squares $(v_n^m)^2$ of the amplitudes v_n^m, due to the nonlinearity of $H_s(\mathcal{V})$. To solve this problem one can follow the common approach based on the Habbard-Stratonovich transformation, with the subsequent use of the saddle-point approximation [11,13,17]. It turns out that the problem is exactly solvable (only) in the thermodynamic limit [11,13,16,17]. Let us recall that this aspect of the membrane fluctuation theory has been already discussed in the context of the spherical model of phase transitions in 1976 [3].

However, to linearize the Hamiltonian in Eq. (17) we shall follow a different approach based on the Bogoliubov variational inequalities. In our opinion this yields a clearer picture of the proposed approximation. Moreover, the approximation is not related to the notion of the thermodynamic limit. The problem is reduced to solving the self-consistent equation (45) for the auxiliary variable X in a finite-size system. At $X = \widetilde{X}$ this equation has a simple physical interpretation, if it is presented in the form

$$\left[\frac{1}{2}\sum_{n=2}^{n_{\max}}\sum_{m=-n}^{n}(n-1)(n+2)\left\langle\left(v_n^m\right)^2\right\rangle_{H_{\rm app}(\mathcal{V},\widetilde{X})}+4\pi\right]R^2 = A(\widetilde{X}), \tag{81}$$

where

$$A(\widetilde{X}) = 4\pi R^2 + \sqrt{\frac{2S_0}{K_s}}\widetilde{X}. \tag{82}$$

Comparing with the approach where the microscopic area of the vesicle is fixed in the partition function through the δ function [see, e.g., Eq. (47) in Ref. [7] and Eq. (15) in Ref. [11]], we see that the equality (81) (valid for membrane parameters S_0, K_s, K_c, R, and temperature T) imposes a "soft" constraint on the amplitudes of the shape fluctuations of the vesicle. It ensures that the mean area of the membrane [left-hand side of Eq. (81)] is equal to the area $A(\widetilde{X})$ [right-hand side of Eq. (81)]. Since X has been introduced to linearize the Hamiltonian (22), the quantity $\overline{\Sigma}_{\rm app}(\widetilde{X})$ is not *a priori* a direct experimentally measurable quantity. Hereafter, if $\overline{\Sigma}_{\rm app}(\widetilde{X})$ is considered as a fitting parameter, then Eq. (44) for $\langle(v_n^m)^2\rangle_{H_{\rm app}(\mathcal{V},X)}$ can be used to determine not only the bending elasticity modulus K_c, but also the stretching elasticity modulus K_s. This is achieved by using the measurable shape fluctuations of the vesicles. In order to extract the vesicle's contours, phase contrast microscopy combined with fast image processing can be used [5].

In other words, in the present paper we showed that the approach proposed in refs. [4,7], based on the Bogolyubov inequalities, can be utilized also for vesicles with a compressible thin film membrane. Our consideration reveals the principal possibility to extract the value of the stretching elasticity modulus K_s in conjunction with the estimation of the exactness of the used approximation from analysis of the shape fluctuations. It was proven that there is an interval of values for the vesicle membrane tension treated as a fitting parameter, for which the application of this method gives precise enough results. The degree of exactness can be obtained by estimating the correlator in the right-hand side of the Bogoliubov inequalities [see Eq. (78)]. This estimation can be applied for finite membranes as well. We note that the correlator tends to zero when the stretching elasticity K_s of the membrane tends to zero as well.

VII. BILAYERS: POSSIBLE GENERALIZATIONS

So far, we have restricted ourself to the case when the vesicle membrane is a *compressible 2D monolayer* immersed in fluids having the same viscosity on either side of the membrane. However, many studies have actually considered the effects of interlayer coupling in a fluctuating bilayer membrane. A review of the results, both experimental and theoretical, that have played seminal roles in the field can found in Refs. [31,32]. We shall point out also Refs. [15,33–36], where the theoretical description is in terms of the discrete spherical harmonics and which are of interest for our consideration. It is of a huge interest from the point of view of real membranes to consider bilayer structures involving a nonlinear area-elasticity effects and to focus on the effects of relative displacement of the membrane monolayers.

An important consequence of the membrane bilayer structure is that bending deformation always accompanies stretching of one monolayer(the outer) and compression of the other (the inner). To take into account this effect, 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, as evidenced in papers cited above, the significant impact has physical processes that are the 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, some dynamical degrees of freedom related with the lipid density difference between the two monolayers in conjunction with quasispherical geometry have been incorporated in the theory more or less on a phenomenological level [15,33–35,37] or on the basis of some fundamental principles [35,36]. 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 an intermonolayer friction. In the comments below it is not our aim to extend our theory on the case of bilayers. Rather, we do advocate that it is possible to point 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 Ref. [37]. Explicit relations for the fluctuations of the form of a quasispherical vesicle, influenced by the mutual displacements of the monolayers, comprising its bilayer, for arbitrary values of the fluctuation wave vector, have been obtained in Ref. [33]. Later it was proved [34] that in the case of a bilayer membrane, the bending elasticity participating 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 [33,34] reproduce in form the result of Milner and Safran [see Eq. (6) in the present study] for the mean-square values of the amplitude $u(\theta, \varphi, t)$, indeed, with a richer physical meaning of the corresponding effective bending elasticity modulus and effective surface tension. In order to be more concrete the comparison of Eq. (6) with the result obtained in Ref. [34] shows that K_c and σ must be replaced by the free flip-flop bending elasticity K_c^{fr} and $\sigma + \epsilon$, respectively. The crucial point is the obtained dependence of ϵ on the free flip-flop bending elasticity K_c^{fr}, blocked flip-flop bending elasticity K_c^{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 ξ; see Eq. (29) in Ref. [34]. 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. (23) of our model Hamiltonian (22), 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. (59), whether values of $\alpha(\overline{\Sigma}_{\rm app})$ might legitimately be larger or smaller from $\alpha(\overline{\Sigma}_{\rm MS})$ the first is we need to have an estimation of the difference between the values of K_c^{fr} and K_c^{bl}. The second remark concerns the solution $\overline{\Sigma}_{\rm app}$. It must be obtained in a self-consistent way. The solutions of the former and the latter problems are a difficult task.

A step in this direction, however, beyond a self-consistent theory, has been done in Refs. [15,34], where the effects related with the *stretching elasticity* of the bilayer in conjunction with lateral monolayer displacement in a 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, having a rigor based on some fundamental principles, has to be done in the framework of the theory proposed in Ref. [35] involving, however, the *nonlinear* elasticity energy of the bilayer, i.e., term of the type (17).

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 Ref. [35] 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 degrees of freedom, two more fields are needed in addition to $u(\theta, \varphi, t)$ [in our notations to $v(\theta, \varphi, t)$: $\phi^+(\theta, \varphi, t)$] and $\phi^-(\theta, \varphi, t)$, representing the local surface (number) densities of the outer and inner monolayer, respectively, and defined with respect to the surface described by $\mathcal{R}(\theta, \varphi, t)$. As was pointed out in Ref. [35] 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 be taken into account. This might be a part of the general and complicated problem of the correct construction of statistical ensembles of

surfaces [38]. 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. (20). Moreover, the very solution of the variational problem will be more complicated. It is obvious that the case of a fluctuating quasispherical bilayer involving a *nonlinear area elasticity* is still waiting for an exact theoretical development.

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APPENDIX: LIMIT CASE ANALYTICAL SOLUTIONS OF EQS. (8) AND (46)

Equations (8), (46), and (72) could be analyzed by replacing the summation in its right-hand side with integration. In order to validate the corresponding approximations we shall use the Euler-McLaurin summation formula

$$\sum_{n=0}^{n_{\max}-1} F(n+1/2) = \int_0^{n_{\max}} F(t+1/2)\,dt - \frac{1}{2}[F(n_{\max}+1/2) - F(1/2)] + \frac{1}{12}[F'(n_{\max}+1/2) - F'(1/2)] + \cdots, \tag{A1}$$

where

$$F(x) = F_1(x) = \frac{2x}{x^2+\Sigma-1/4} \tag{A2}$$

with $\Sigma = \overline{\Sigma}_{\rm MS}$ in (8) and $\Sigma = \overline{\Sigma}_{\rm app}$ in (46), and

$$F(x) = F_2(x) = \frac{2x}{[x^2+\Sigma-1/4]^2} \tag{A3}$$

with $\Sigma = \overline{\Sigma}_{\rm app}$ in (72).

Let us ignore the higher order terms in (A1) and approximate $F(x) \approx F(0) + xF'(0)$ in the interval $[0, 1/2]$. In our case, the approximations made are consistent only for large $\overline{\Sigma}_{\rm app} \gg 1$ since then the relative change of $F(x)$ is small when $n \to n+1$. With these approximations the Euler-Maclaurin formula (A1) reduces to

$$\sum_{n=0}^{n_{\max}} F(n+1/2) \approx \int_0^{n_{\max}+1/2} F(x)\,dx + \frac{1}{24}F'(0) + \frac{1}{2}\left[F(n_{\max}+1/2) + \frac{1}{6}F'(n_{\max}+1/2)\right] \tag{A4}$$

[cf. with Eq. (59.10), Ref. [39], p. 173]. Using (A4) the summation in (8) and (46) can be performed easily. This leads to

$$\sum_{n=2}^{n_{\max}} F_1(n+1/2) \approx \ln\frac{N+N^{1/2}+\Sigma}{\Sigma-1/4} + \frac{1}{12}\frac{1}{\Sigma-1/4} + \frac{1}{2}\frac{2N^{1/2}+1}{N+N^{1/2}+\Sigma} - \frac{1}{6}\frac{N+N^{1/2}-\Sigma+1/2}{(N^2+N^{1/2}+\Sigma)^2} \tag{A5}$$

and for our purposes to

$$\sum_{n=2}^{n_{\max}} F_1(n+1/2) \approx \ln\frac{N}{\Sigma} + \frac{\Sigma}{N} + O\left(\frac{1}{N^{1/2}}\right) + O\left(\frac{1}{\Sigma}\right) + O\left(\left[\frac{\Sigma}{N}\right]^2\right) \tag{A6}$$

in Eqs. (8) and (46) and

$$\sum_{n=2}^{n_{\max}} F_2(n+1/2) \approx \frac{1}{\overline{\Sigma}_{\rm app}} - \frac{1}{\overline{\Sigma}_{\rm app}+N} + O\left(\frac{1}{\overline{\Sigma}_{\rm app}^2}\right) \tag{A7}$$

in Eq. (78). In the above expressions it is used that $n_{\max}$ is of the order of the square root of the number of molecules N in the vesicle membrane.

1. Solution of Eq. (8)

Using (A6) and the definition of $\overline{\sigma}_0$ [see Eq. (25)] Eq. (8) may be presented (up to the used approximations) in the form

$$x_0 e^{x_0} = -e^{-\frac{\alpha}{\gamma}}, \tag{A8}$$

where

$$x_0 = -\frac{\overline{\Sigma}_{\rm MS}}{N}. \tag{A9}$$

Equation (A8) can be solved in terms of the Lambert function $\mathbf{W}(x)$.

Recall that by definition $\mathbf{W}(xe^x) = x$ [40,41]. $\mathbf{W}(x)$ can take two possible real values for $-\frac{1}{e} \leqslant x \leqslant 0$. Values satisfying $\mathbf{W}(x) \geqslant -1$ belong to the principal branch denoted as $\mathbf{W}_0(x)$, while values satisfying $\mathbf{W}(x) \leqslant -1$ belong to the $\mathbf{W}_1(x)$ branch. The two branches meet at the branch point for $x = -\frac{1}{e}$, where $\mathbf{W_0}(-\frac{1}{e}) = \mathbf{W}_{-1}(-\frac{1}{e})$. All values of $\mathbf{W}$ for $x \geqslant 0$ belong to the principal branch $\mathbf{W}_0(x)$.

The solution of Eq. (A8) now reads

$$x_0 = \mathbf{W}\left(-e^{-\frac{\alpha}{\gamma}}\right) \tag{A10}$$

or finally

$$\overline{\Sigma}_{\rm MS} = -N\mathbf{W}\left(-e^{-\frac{\alpha}{\gamma}}\right). \tag{A11}$$

In the interval $-e^{-1} \leqslant -e^{-\frac{\alpha}{\gamma}} < 0$ the equation has two solutions given by $\mathbf{W}_0$ and $\mathbf{W}_{-1}$, respectively.

For large x, $\mathbf{W}(x)$ is approximated by

$$\mathbf{W}(x) = \ln x - \ln\ln x + o(1). \tag{A12}$$

The Taylor series around $x = 0$ is given by

$$\mathbf{W}(x) = x - x^2 + \cdots. \tag{A13}$$

The first few terms of the series expansion of $\mathbf{W}(x)$ near the branching are

$$\mathbf{W}(x) = -1 + p - \tfrac{1}{3}p^2 + \cdots, \tag{A14}$$

where $p = \pm\sqrt{2(ex+1)}$ for $\mathbf{W}(x)_{0,1}$.

Thus, using (A13) for $x = e^{-\frac{\alpha}{\gamma}} \ll 1$, one gets Eq. (10):

$$\overline{\Sigma}_{\rm MS} = Ne^{-\frac{\alpha}{\gamma}}. \tag{A15}$$

Using the expansion near the branching point of the Lambert function, i.e., $x = e^{-\frac{\alpha}{\gamma}} \approx e^{-1}$, one obtains

$$\overline{\Sigma}_{\rm MS} = N\left[1 - \sqrt{2\left(1 - e^{-\frac{\alpha}{\gamma}+1}\right)}\right]. \tag{A16}$$

2. Solution of Eq. (46)

It is evident that Eq. (46) can be treated in the same way (for $\overline{\Sigma}^0_{\rm app} \gg 1$). Using (A6) it may be presented (up to the used approximations) in the form

$$xe^x = \left(\frac{1}{\overline{\overline{C}}} - \frac{1}{N}\right)Ne^{\overline{\sigma}_0/\overline{C}}, \tag{A17}$$

where

$$x = \left(\frac{1}{\overline{\overline{C}}} - \frac{1}{N}\right)\overline{\Sigma}_{\rm app}. \tag{A18}$$

In terms of the Lambert $\mathbf{W}(x)$ function the solution reads

$$\overline{\Sigma}_{\rm app} = \left(\frac{1}{\overline{\overline{C}}} - \frac{1}{N}\right)^{-1}\mathbf{W}\left[\left(\frac{1}{\overline{\overline{C}}} - \frac{1}{N}\right)Ne^{\overline{\sigma}_0/\overline{C}}\right]. \tag{A19}$$

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

With the help of both expansions (A12) and (A13) one easily obtains Eqs. (50) and (51). Note that if

$$-\frac{\alpha}{\gamma} = \frac{\overline{\sigma}_0}{\overline{\overline{C}}}, \tag{A20}$$

combining Eqs. (A19) and (A8), the more general relation takes place:

$$\overline{\Sigma}_{\rm app} = \left(\frac{1}{\overline{\overline{C}}} - \frac{1}{N}\right)^{-1}\mathbf{W}\left[\left(\frac{1}{\overline{\overline{C}}} - \frac{1}{N}\right)\overline{\Sigma}_{\rm MS}\exp\left(-\frac{\overline{\Sigma}_{\rm MS}}{N}\right)\right]. \tag{A21}$$

From the above result immediately follows Eq. (66), where use has been made of the definition of the Lambert function.

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