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Comment on "Thermodynamics of vesicle growth and instability"

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Fanelli and McKane [Phys. Rev. E **78**, 051406 (2008)] recently described the growth of vesicles due to the accretion of lipid molecules onto their surface in terms of linear irreversible thermodynamics. They calculated the critical radius at which the shape of a spherical vesicle becomes unstable. Their treatment is different from those previously put forward and, in the following, we explain why we regard their thermodynamic description to be deficient.

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Fanelli and McKane [1] considered the growth of a spherical vesicle by assuming that the increase in membrane area is exponential and that vesicle behavior is determined by the spontaneous curvature model. The latter model is characterized by the membrane elastic energy $W_b = \frac{\kappa}{2}\int dA(C_1+C_2-C_0)^2$, with C_1 and C_2 as the principal curvatures, C_0 the membrane spontaneous curvature, κ the membrane bending rigidity, and A the membrane surface area [2]. They sought the critical radius at which the shape of a spherical vesicle becomes unstable. Two cases were considered. In the simpler one a vesicle resides in a purely aqueous environment and its volume changes as a consequence of membrane hydraulic permeability. In a more general case solute, to which the membrane is also permeable, is included. The results of Fanelli and McKane on the critical radius differ from ours [3,4], which they ascribe to their consistent thermodynamic description. However, their results (Figs. 1 and 2 in [1]) cannot be correct, for the reason that they do not include the unavoidable deviation from spherical shape if the membrane grows at zero hydraulic permeability and therefore at constant vesicle volume. Fanelli and McKane also gave in Sec. II C an inadequate interpretation of our approach. Therefore we shall give a detailed description of its physical basis. We shall also indicate the main source of discrepancies between the two approaches.

To clarify the essential difference between the approach of Fanelli and McKane and our reasoning, it suffices to analyze the simpler of the two cases [3]. In Ref. [3] we assumed that changes in vesicle membrane area and volume are so slow that, at any moment, the vesicle attains its equilibrium shape corresponding to the minimum of the elastic energy of its membrane. In this approximation the transition from spherical to flaccid regimes of growth can be treated on the basis of the criteria for mechanical equilibrium. To elucidate the physical content of this transition we write the bending energy (reduced by being divided by the bending energy of the sphere for $C_0=0$, $w_b=W_b/8\pi\kappa$) as $w_b=w_{b0}(A)+\Delta w_b(v,A)$, where $w_{b0}(A)$ is the bending energy of a sphere with membrane area A and $\Delta w_b(v,A)$ is the difference between the bending energy and that of a sphere. v is the reduced volume ($v=6\sqrt{\pi}V/\sqrt{A^3}$ where V is vesicle volume). Figure 1 shows the dependence of $\Delta w_b(v,A)$ on v and the reduced membrane spontaneous curvature c_0 ($c_0=C_0R$ where $R=\sqrt{A/4\pi}$) in the region close to the sphere. For $v<1$ there is the pressure difference between the pressures outside and inside the vesicle defined as $\Delta p=-\partial W_b/\partial V|_A=-(6\kappa/R^3)\,\partial\Delta w_b/\partial v|_{c_0}$. In the spherical limit ($v\to 1$) this pressure difference is equal to the limiting pressure

$$\Delta p_l=\frac{2\kappa}{R^3}(6-C_0R) \tag{1}$$

that was shown to be at given C_0R the maximum pressure difference for which the sphere is stable [6]. Figure 1 can therefore be considered as a graphical representation of the sphere stability problem within the spontaneous curvature model. In relation to the approach of Fanelli and McKane [1] it is important to note that the stability problem involves membrane lateral tension (σ). Namely, the stability condition ($\Delta p<\Delta p_l$) is obtained by varying the bending energy with respect to vesicle volume and its membrane area independently [6]. The corresponding mechanical equilibrium is given by [6]

$$\Delta pR^3+2\sigma R^2-\kappa C_0R(2-C_0R)=0. \tag{2}$$

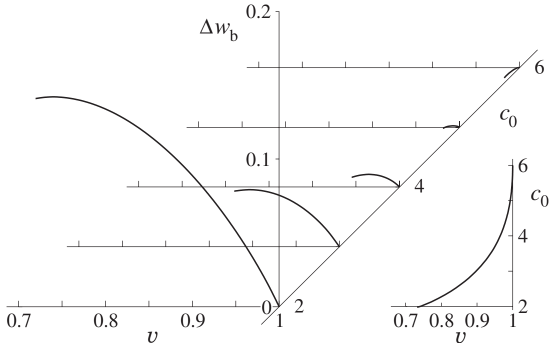

FIG. 1. The bending energy difference (Δw_b) as a function of the reduced vesicle volume (v) at given values of the reduced spontaneous curvature ($c_0=C_0R$). The curves were obtained by solving numerically the shape equation [5]. The inset shows the dependence of c_0 pertaining to the maximal bending energy ($\partial\Delta w_b/\partial v|_{c_0}=0$) on v.

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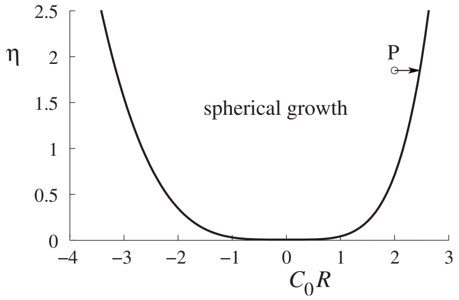

FIG. 2. The transition line defining the region of the stability of spheres in the parameter plane (C_0R, η) obtained from condition (3) by applying the equality sign. The point P $(C_0R=2, \eta=1.85)$ is the starting point of a self-reproducing vesicle [3]. The arrow indicates the direction of spherical growth.

When vesicle grows as a sphere, vesicle volume and membrane area are interrelated. Such growth can only occur if the inflow of water is synchronized with the increase in membrane area. The pressure difference must attain the value that is needed to overcome the membrane resistance to water flow; i.e., it adjusts to $\Delta p=(dV/dt)/L_pA$, where L_p is the membrane hydraulic permeability. The equilibrium [Eq. (2)] is preserved by an adjustment of the membrane tension. The sphere instability problem is represented as in Fig. 1 of Ref. [1] by defining the region of sphere stability in the parameter plane (C_0R, η) where $\eta=L_pT_d\kappa C_0^4$, with T_d as the membrane area doubling time. T_d appears in the expression for the exponential increase in the membrane area $(A=A_0 2^{t/T_d}$ where A_0 is the membrane area at $t=0)$. By applying the condition that $\Delta p=(dV/dt)/L_pA<\Delta p_l$ we get for the criterion for the spherical growth

$$\eta > \frac{C_0^4R^4 \ln 2}{4(6-C_0R)}. \qquad (3)$$

The region of vesicle spherical growth obtained on the basis of condition (3) is presented in Fig. 2.

In Fig. 2 we also indicate the direction of vesicle growth at a given value of η with point P as the starting point. This vesicle increases its radius by remaining spherical until it hits the transition line. After then it grows in a nonspherical manner. The smaller the membrane hydraulic permeability and consequently the parameter η, the larger Δp is needed to drive the water through the membrane, and spherical growth ends sooner. The result of Fanelli and McKane [1] presented in their Fig. 1 is the opposite. It indicates that below $\eta_{\min}=17.74$ there is no transition into a nonspherical vesicle growth. Thus a vesicle would grow as a sphere also at zero hydraulic permeability. In our view the reason that Fanelli and McKane [1] obtained this unrealistic prediction is the omission of the lateral tension term in their free-energy functional. In the formulation of the effective pressure (Eq. (3) in Ref. [1]) for the case of spherical growth the lateral tension term is indispensable.

In Ref. [3] we sought the conditions for vesicle self-reproduction. Therefore we followed how vesicle shape evolves also in nonspherical regime. We found that the parameter η, at which the vesicle during the membrane area doubling time doubles its volume and concomitantly attains the shape that is a composition of two equal spherical parts, is equal to 1.85. For the reason that this value is below their $\eta_{\min}$ Fanelli and McKane [1] expressed doubt about its correctness. However, point P in Fig. 2 representing the self-reproducing vesicle resides within the region of spherical growth and this confirms the consistency of the obtained value of η.

Fanelli and McKane [1] also criticized our approach in which we analyzed the effect of solute permeability on vesicle self-reproduction [4]. In our model we made the simplifying assumption that transport pathways for water and solute through the membrane are separate. In this way we did not need to consider the reflection coefficient, which is a necessary concept in the case of a common channel for the two entities [7]. There are certainly known cases of separate water and solute pathways [8], which indicates that our approach does not contradict reality as a whole. We agree that in treating different specific cases consideration may have to include other properties of the system such as the reflection coefficient.

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[1] D. Fanelli and A. J. McKane, Phys. Rev. E **78**, 051406 (2008).
[2] W. Helfrich, Z. Naturforsch. C **28**, 693 (1973).
[3] B. Božič and S. Svetina, Eur. Biophys. J. **33**, 565 (2004).
[4] B. Božič and S. Svetina, Eur. Phys. J. E **24**, 79 (2007).
[5] U. Seifert, K. Berndl, and R. Lipowsky, Phys. Rev. A **44**, 1182 (1991).
[6] Ou-Yang Zhong-can and W. Helfrich, Phys. Rev. A **39**, 5280 (1989).
[7] O. Kedem and A. Katchalsky, Biochim. Biophys. Acta **27**, 229 (1958).
[8] F. W. Kleinhans, Cryobiology **37**, 271 (1998).