UNRAVELLING A SELF-HEALING THERMO- AND HYDRODYNAMIC MECHANISM OF TRANSIENT PORE'S LATE-STAGE CLOSING IN VESICLES, AND RELATED SOFT-MATTER SYSTEMS, IN TERMS OF LIAISON BETWEEN SURFACE-TENSION AND BENDING EFFECTS*

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This study is devoted to reveal a simple self-healing, diffusive–dissolution-like mechanism of transient pore's closing in a model spherical vesicle. It is based on a novel thermodynamic mechanism invented in terms of structural flux–force relations, with Onsager's coefficients reflecting the main- and cross-effects of nearly one-micrometer-in-diameter pore formation (of linear cross sectional size r) immersed within the membrane of a spherical vesicle of at least several tens of micrometer in its radius (R). The closing nanoscopic limit is given by $r \to 0$. The pore's formation is envisaged as a kind of bending and excess-area bearing (randomly occurring) failure, contrasting with a homogenizing action of the surface tension, trying to recover an even distribution of the elastic energy accumulated in the membrane. The failure yields at random the subsequent transient pore of a certain

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characteristic length along which the solution leaks out, with some appreciable speed, until the passage is ultimately closed within a suitable time interval. Inside such a time span, the system relaxes back toward its local equilibrium and uncompressed state until which the pore dissolves, and the before mentioned excess area vanishes. The (slow and non-exponential) relaxation–dissolution behavior bears a diffusion fingerprint, and it can be related with varying osmotic-pressure conditions. Useful connotations with a qualitatively similar biolubrication mechanism in articulating (micelles-containing) systems, down to the nanoscale, have also been pointed out.

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1. Introduction

The vesicles are round, curvilinear and membranous systems of very wide application in research and biotechnology [1]. Recently, there is a huge interest in vesicular drug delivery systems enabling to control amount of substance transported to the specific disease site [2]. Moreover, in nature, they perform a variety of functions — vesicles are basic tools used by the cell for organizing cellular substances. Vesicles are also involved in metabolism, transport, and act as chemical reaction chambers, *etc.* They are merely composed of a multilayer membrane-type and sphere-like envelope, enclosing typically a polyelectrolyte inhomogeneous solution, capable of agitating dynamically the membrane to succeed in creating a temporary leakage, *i.e.* a transient pore [3]. (In Section 3.5, we argue that such pores can have a positive impact on lubricating properties of natural joints.) There are many possible mechanisms of pore opening/closure [4, 5] and these phenomena is a very complex problem.

There are many types of vesicles: vacuoles, lysosomes, transport and secretory (fusion) vesicles, *etc.*, differing with respect to structure and application. As concerns the membranous envelope's types already mentioned, and their roles played when forming the transient pores, occurring as a membrane-biomatter density fluctuation, one can generally assign them to two principal groups. The first group includes the unilamellar vesicles, whereas the second contains multilamellar (giant) vesicles — the latter is typically more robust and bigger, especially when accommodating to certain mechanical stress-strain and/or vigorous solution's flow conditions [6].

This work considers a case of vesicle's pore closure, *i.e.* when radius of a pore attains the nanoscopic limit of $r \to 0$, see Fig. 1, as conducted by a mechanism reminiscent of the one unveiled as the nucleus' diffusion–dissolution phenomenon [7]. The paper is structured as follows. In Section 2, the so-called Onsager's structural flux-force effects on the thermodynamics of the pore–vesicle system formation, involving linear mechanism coming

out from respective free-energy (or, entropy production) contributions, are considered. In Section 3, a simplified view of the pore's collapse when its aperture tends to zero, as argued in terms of membrane's surface-tension and bending cooperation, is discussed. Some comparison with an "inverse" process, that means a diffusion-controlled nucleus formation, is provided in the same section, in a sketchy way. The study ends with a summary, Section 4.

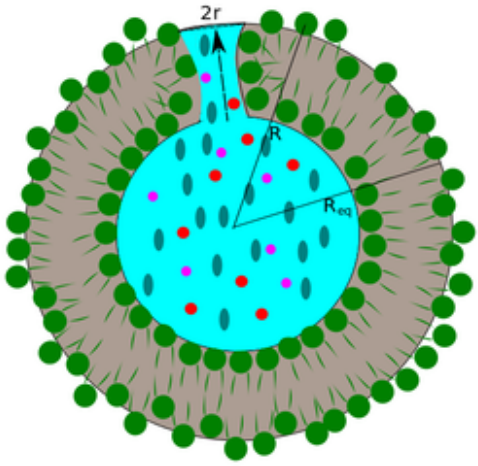

Fig. 1. (Color online) Artistic depiction of the system of interest. Vesicle is composed of phospholipid molecules (big circles/green) which form a curvilinear bilayer. The opening and closing of a randomly emerging pore is associated with a release of vesicle's core constituents such as: water dipoles (blue) and (merely small, *e.g.*, natrium- or hydrogen-) ions (small circles/red and pink).

2. Small system irreversible thermodynamics of the relaxation of transient pores

Biological vesicles are always surrounded by a fluid in physiological conditions. Also in experiments, the behavior of different parameters and aspects of vesicles can be only observed when the system is in close relation with the heat bath, imposing on it the temperature, pressure and, in general, chemical conditions through the chemical potential. Due to this fact, the dynamics of transient pore, for instance, should be described by a theory able to cope with the coupling of the system with the surroundings.

Having in mind the increasing interest on vesicles as drug delivery systems, it is worth to examine how the dynamics of transient pores in the membrane of the vesicle can be controlled, as it may constitute a mecha-

nism for the capture or delivery of drugs. In this section, we will review the main aspects of irreversible thermodynamics of small systems recently proposed for the description of these phenomena [8].

The main question to consider is that the opening of a pore in the membrane of a vesicle introduces a new thermodynamic variable for describing the state of the vesicle, named, the radius of the pore, $r(t)$. Once formed the pore in a random fashion, experimental observations show that the radius of the vesicle, $R(t)$, decreases irrespective of the growth and collapse dynamics of the pore. Therefore, since the area, $A(r,R)$, and volume, $V(r,R)$, of the pore may be described in terms of the radius of the vesicle and of the radius of the pore for spherical-like vesicles, then, at constant temperature and total volume of the total system (vesicle plus bath), the dynamics of the variables $r(t)$ and $R(t)$ can be adequately described in terms of the Helmholtz free energy $F(r,R)$, that in the present case will be a function of both radii considered.

From equilibrium thermodynamics we know that, in the state of equilibrium, the total differential of the Helmholtz free energy $F(r,R)$ should vanish: $\mathrm{d}F = 0$. In contrast, for a nonequilibrium, relaxation process, the total differential of the Helmholtz free energy should be negative $\mathrm{d}F(r,R) < 0$. This condition is a consequence of the second law of thermodynamics for systems in constant volume, and it can be shown that $\mathrm{d}F(r,R) = -T\mathrm{d}_i S$, see Ref. [9], where $\mathrm{d}_i S$ is entropy produced during the infinitesimal transformations $\mathrm{d}r$ and $\mathrm{d}R$. Explicitly, these considerations lead to the general expression for the entropy production per unit time [8]

$$T\frac{\mathrm{d}_i S}{\mathrm{d}t} = -\frac{\mathrm{d}F}{\mathrm{d}t} = -\frac{\partial F}{\partial r}\frac{\mathrm{d}r}{\mathrm{d}t} - \frac{\partial F}{\partial R}\frac{\mathrm{d}R}{\mathrm{d}t}\,. \tag{1}$$

Assuming now that the thermodynamic fluxes $\mathrm{d}r/\mathrm{d}t$ and $\mathrm{d}R/\mathrm{d}t$ are proportional to the thermodynamic forces $\partial F/\partial r$ and $\partial F/\partial R$, the most general linear relationships that can be established are [10]

$$\frac{\mathrm{d}r}{\mathrm{d}t} = -L_{rr}\frac{\partial F}{\partial r} - L_{rR}\frac{\partial F}{\partial R}\,, \tag{2}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = -L_{RR}\frac{\partial F}{\partial R} - L_{Rr}\frac{\partial F}{\partial r}\,, \tag{3}$$

where the L_{ij}s are the so-called Onsager's phenomenological coefficients. Additionally, these coefficients also obey the Onsager's symmetry (tensorial) relations $L_{ij} = L_{ji}$. These relations are associated with both main- and cross-thermodynamic effects.

Choosing this coefficients as constants and neglecting cross effects leads to a previous model proposed in the literature, see Ref. [11]. In Ref. [8], it was shown by dimensional analysis that these coefficients should be inversely

proportional to a product of dynamical viscosity (taken from Newtons' law for the laminar flow) and certain specific lengths. Respectively, the lengths l_is, being included in the L_{ij}s, correspond formally to: (1) formation of the pore ($i \to r$ or $j \to r$); (2) formation of the vesicle ($i \to R$ or $j \to R$); (3) some *modus-vivendi* compromise of creating a pore of diameter $2r$ within the vesicle of radius R ($i \to rR$ or $i \to Rr$; or, *mutatis mutandis* the j subscript follows the latter rule); the scalar (and, constant) value of solution's viscosity complement the aforementioned product; for details, see [8].

2.1. Free energy contribution and the linear form of elementary vesicle's area change

The general laws given by Eqs. (2) and (3) can be written explicitly after considering that the free energy change of the system has four contributions: $\mathrm{d}F = \mathrm{d}F_V + \mathrm{d}F_\sigma + \mathrm{d}F_B + \mathrm{d}F_l$ coming from volume (F_V), surface tension (F_σ), bending curvature (F_B) and edge tension (F_l),

$$\mathrm{d}F = -\Delta P \mathrm{d}V_{\mathrm{in}} + \tilde{\sigma}\mathrm{d}A + \gamma \mathrm{d}l\,, \tag{4}$$

where $\tilde{\sigma} = \sigma + \frac{\kappa_B}{R^2}$ is total effective surface tension, κ_B is bending free energy (σ — surface tension), γ is pore's edge tension, and $l = 2\pi r$ is the pore contour length, V_{in} is a volume inside the vesicle (see Fig. 1), ΔP is a difference between inside and outside pressure of the vesicle caused by curvature of the membranous envelope. For the case of small pore's radius $r/R \ll 1$, the free energy differential can be expressed as a function of r and R as follows

$$\mathrm{d}F = 4\pi R\left(2\tilde{\sigma} - R\Delta P\right)\mathrm{d}R + 2\pi\left(\gamma - \tilde{\sigma} r\right)\mathrm{d}r\,. \tag{5}$$

From [8], after employing a Maxwell's relation, one provides $\sigma = \left(\frac{\partial F_\sigma}{\partial A}\right)_{T,V} = \sigma_{\mathrm{c}}\left(\frac{A}{A_{\mathrm{eq}}} - 1\right)$; σ_{c} stands for the characteristic (and, constant) surface tension of the vesicle. After making use of $A \equiv A(R,r) = A(r,R) = 4\pi R^2 - \pi r^2$, one can obtain

$$\sigma = \sigma_{\mathrm{c}}\left[\frac{R^2}{R_{\mathrm{eq}}^2} - \frac{r^2}{4R_{\mathrm{eq}}^2} - 1\right]. \tag{6}$$

In this study, we confront ourselves to the case in which a nearly constant surface tension of the vesicle's surface is to be approached, deciphering this way a close-to-equilibrium state (at $R \approx R_{\mathrm{eq}}$) prone to a small excess area to be assigned to the vesicle's envelope. Therefore, we take in Eq. (6) and just for its right-hand side parenthesis involved there that the expression in it is going to approach unity. It immediately results in the following

$$\frac{R^2}{R_{\mathrm{eq}}^2} - \frac{r^2}{4R_{\mathrm{eq}}^2} = 2 \Rightarrow R^2 = \left(\frac{r}{2}\right)^2 + 2R_{\mathrm{eq}}^2\,, \tag{7}$$

which also expresses the late-stage vesicle formation; note that $R > R_{\rm eq}$ even though the pore's aperture $r \to 0$. In addition, notice that the elementary change in vesicle's area is a linear differential form of both R and r, namely $\mathrm{d}A(R,r) \equiv \mathrm{d}A(r,R) = 8\pi R\mathrm{d}R - 2\pi r\mathrm{d}r$. This mathematical observation suits very well to the linear Onsager thermodynamic framework, Eqs. (2)–(3).

In order to see how the global late stage dynamics of the vesicle with the effect of inclusion of its transient pore in a collapsing state of interest are developed, we will further base on hydrodynamic stationary Navier–Stokes-type approach, which results in specifying the corresponding osmotic pressure difference as $\Delta P = -\frac{3\eta_{\rm s}R^2}{r^3}\dot{R}$, see [8].

Using these results in equations (2) and (3) for the thermodynamic fluxes one obtains the final coupled non-linear evolution equations for the pore and vesicle radii

$$\frac{\mathrm{d}r}{\mathrm{d}t} = 2\pi L_{rr}\left(\tilde{\sigma}r - \gamma\right) - 4\pi R L_{rR}\left(2\tilde{\sigma} - R\Delta P\right), \tag{8}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = -4\pi R\left(2\tilde{\sigma} + R\Delta P\right) + 2\pi\left(\tilde{\sigma}r - \gamma\right). \tag{9}$$

These equations, derived on the basis of a combination of Onsager–Prigogine non-equilibrium thermodynamics constitute an adequate working version for describing the kinetics of the collapse of transient pores in giant vesicles. In figure 2, we show the numerical solution of Eqs. (8) and (9). In particular, figures 2 (a) and (b) show the time evolution of both, the pore $r(t)$ and the vesicle $R(t)$ radii. Several curves are represented showing the dependence of the relaxation time on the viscosity of the solvent in which the vesicle is immersed and, as a consequence, how the shape of the corresponding kinetics become affected. As observed by Dimova and collaborators [12], vesicles in low viscosity fluids present relaxation times lower than a second. Here, we compared the predictions for the viscosities shown in figure 2. A viscosity corresponding to $\eta = 32\,\mathrm{cP}$, *cf.* Table I, is similar to the one used in the experiments of reference [11]. Figures 2 (c) and (d) show the evolution in time of the surface tension and the pressure difference. Once again, the evolution is slower for a larger viscosity of the medium. These results are relevant because they show one of the possible forms in which the small system, the vesicle, is coupled to the heat bath, that is, the characteristic relaxation times of the variables involved for describing the state of the system depend, in turn, on the characteristic dissipation mechanism — in the present case, the one based on viscosity of the solvent.

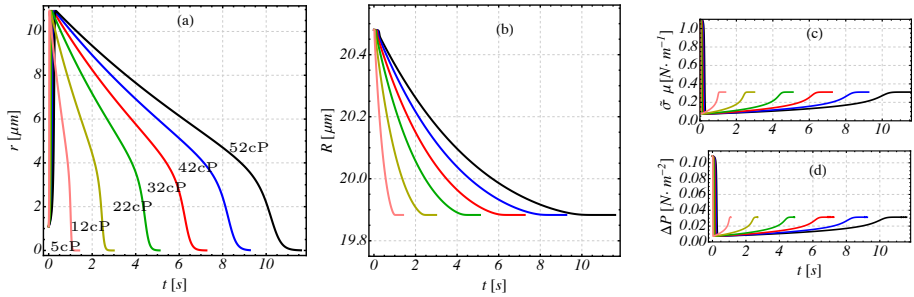

Fig. 2. Time evolution of the different parameters used to characterize the state of the vesicle during the collapse of a transient pore. (a) The radius of the pore for different values of the viscosity of the solvent. (b) The radius of the vesicle for the same set of viscosity values as in (a). (c) Time evolution of the effective surface energy (bending energy and surface tension) and (d) time evolution of the pressure difference between the inner and outer fluid.

TABLE I

The physical quantities used correspond to fittings of the experimental data reported in [1]. The viscosity η_0 takes the values $\eta_0 = 5, 12, 22, 32, 42$ and 52 cP to illustrate how the kinetics of the pore becomes retarded when increasing the friction with the host fluid. $R_{\rm eq}$ is the initial equilibrium value of the non-stressed vesicle and R_0 is the initial radius of the vesicle in the stressed condition, that is, just before the initiation of the pore rupture.

$\eta_{\rm s}$ [cP]	$R_{\rm eq}$ [μm]	κ_B [10^{-20}J]	$\sigma_{\rm c}$ [10^{-5}N·m]	γ [pN]	r_0 [μm]	R_0 [μm]
η_0	19.6	29	2.9	0.92	1.10	20.5

3. Simplified picture of the pore's closing when its aperture tends to zero as viewed in terms of membrane's surface-tension and bending cooperation

Let us rewrite Eq. (9) to the form, after using previously defined parameters as

$$\frac{{\rm d}R}{{\rm d}t} = -4\pi R L_{RR}\left[2\left(\sigma_{\rm c}+\frac{\kappa_B}{R^2}\right)+3R\eta_{\rm s}\frac{r^2}{R^3}\frac{{\rm d}R}{{\rm d}t}\right]+2\pi L_{Rr}\left[r\left(\sigma_{\rm c}+\frac{\kappa_B}{R^2}\right)-\gamma\right]. \tag{10}$$

Let us then assume the case of pore closure, namely that a nanoscopic limit of $r \approx 0$ applies, then from Eq. (7), we can obtain that $R^2 \simeq 2R_{\rm eq}$ and thus from the equation

$$\frac{{\rm d}R}{{\rm d}t} = -8\pi L_{RR}\frac{\sigma_{\rm c}R_{\rm eq}^2+\kappa_B}{R} \tag{11}$$

after integration, one obtains

$$\frac{1}{2}R^2(t) = \frac{1}{2}R_{\mathrm{eq}}^2 - \frac{8\pi}{\eta_{\mathrm{s}}\widetilde{\lambda}_R}\left(\sigma_{\mathrm{c}}R_{\mathrm{eq}}^2 + \kappa_B\right)(t - t_{\mathrm{eq}})\ . \tag{12}$$

In order to avoid a singularity in the effective surface tension conditions, the line-tension term, involved in the right-hand side of Eq. (10), has to vanish at the limit of $r \to 0$ too. In other words, at the limit, the energy ascribed to the pore's line tension has to be absorbed completely by the effective surface tension of the vesicle.

After multiplying both sides of Eq. (12) by 8π, we obtain an excess surface term ΔA provided in the course of a time span $\Delta t = t - t_{\mathrm{eq}}$. Note that $\Delta E_{\sigma\kappa_B} = \sigma_{\mathrm{c}}R_{\mathrm{eq}}^2 + \kappa_B$ which provides that

$$\frac{\Delta A}{\Delta E_{\sigma\kappa_B}} \approx \frac{\Delta t}{\eta_{\mathrm{s}}\widetilde{\lambda}_R} \tag{13}$$

applies. It is equivalent to claim that

$$4\pi R^2(t) \simeq 4\pi R_{\mathrm{eq}}^2 - 64\pi^2\Delta A \tag{14}$$

with a certain ΔA to be specified with an aid of Eq. (13) in the following subsection.

3.1. Excess vesicle-membrane local area as an unveiling factor of transient pore's formation

After suitably rearranging Eq. (13), with the help of the so-defined velocity of solution's outflow through the narrow transient pore, namely

$$\widetilde{v}_R = \frac{\widetilde{\lambda}_R}{\Delta t}\,, \tag{15}$$

with $\widetilde{\lambda}_R$ — pore's length, one defines ΔA, within a certain accuracy range, by means of a simple energy-flow formula

$$\Delta A \approx \frac{\Delta E_{\sigma\kappa_B}}{\eta_{\mathrm{s}}\widetilde{v}_R}\,. \tag{16}$$

From Eq. (16), it follows that the local excess area ΔA is inversely proportional to the product of solution's dynamic viscosity (η_{s}) and the velocity ($\widetilde{v}_R$) of solution's outflow through the narrowing transient pore, and its creation, as stated above, is provided thanks to the energy contribution $\Delta E_{\sigma\kappa_B} = \sigma_{\mathrm{c}}R_{\mathrm{eq}}^2 + \kappa_B$, being a sum of equilibrium surface tension and bending energetic contributions. It is due to the bending contribution that the

pore is formed, what qualitatively explains its local curvilinear character, going in parallel with the notion of the Gaussian curvature, attributable to the surface tension modification here, the latter staying, according to Kelvin–Laplace law, in close relation with the mean vesicle's curvature, *cf.* [13, 14].

3.2. Effect of liaison between membrane's surface tension and bending as causing the bending structural failure viewed as the pore's hydrodynamic formation

Thus, after accepting the rationale provided by the preceding subsection, a definite pore's closing appears to be effective if the nanoscale-geometric condition of $r \to 0$ goes in parallel with the diffusion–dissolution process of the vesicle, as clearly suggested either by Eq. (14) or, more apparently, by the analytical solution of $R(t)$ presented by Eq. (12).

Since the overall pore's (diffusive) collapsing effect goes by a nonequilibrium thermodynamic mechanism, which yields, according to Eq. (16), a primary energetic contribution to the area excess $\Delta E_{\sigma\kappa_B}$, the pore closure might go via an obvious limiting relation that $\Delta A \to 0$, suggesting that $\Delta E_{\sigma\kappa_B} \to 0$ too. It implies, as it has been already expected [8, 15], that the energetic excess, available due to former liaison of surface tension and bending, goes to zero. Following, in turn, relation (16), it would implicate that the product of $\eta_s \widetilde{v}_R$ but reversed, appears to be really small in such small-Re conditions (the Reynolds number can even be taken as $\mathrm{Re} \sim 10^{-3}$), and its depends upon the channel's local curvatures *viz.* internal nanostructural corrugations. After employing a definition of Re number [16], it can be estimated that the hydrodynamic part of the quotient, involved at the right-hand side of Eq. (16), obeys a proportionality relation

$$\frac{1}{\eta_s \widetilde{v}_R} \propto \mathrm{Re} \frac{r^2}{\widetilde{p}_R}\,, \tag{17}$$

wherein $\widetilde{p}_R$ is a Bernoulli-type dynamic pressure of the nano-flow, being of the form of $\widetilde{p}_R = (1/2)\rho_{\mathrm{fluid}} \widetilde{v}_R^2$ (ρ_{fluid} — (*e.g.*, synovial or physiological [17]) fluid density), and assumed to be still of appreciable (albeit moderate) value within the narrowing pore.

The self-healing mechanism of the pore's closing, as anticipated here, rests then upon a liaison of thermodynamic (energetic) and hydrodynamic natural co-factors driving together the cessation of the pore's dynamics. It is self-evident when inspecting again the small-Re conditions in the context of Eq. (17), largely assisted here by the thermodynamic-geometric precondition of closure, *i.e.* $r \to 0$.

3.3. Temporal behavior of the vesicle radius upon restituting its local equilibrium state — a relaxation effect with diffusion fingerprint

Here, a comparison to the diffusion-limited dissolution process, as studied in [7] is legitimate to occur. The authors [7] considered an interface-hydrodynamic model as applied to sub-micrometer droplet's evaporation. They have got a solution to the problem, qualitatively of the same form as ours, rearranged accordingly

$$R^2(t) = R_{\rm eq}^2 + \frac{16\pi}{\eta_{\rm s}\widetilde{\lambda}_R}\left(\sigma_{\rm c}R_{\rm eq}^2 + \kappa_B\right)t_{\rm eq} - \frac{16\pi}{\eta_{\rm s}\widetilde{\lambda}_R}\left(\sigma_{\rm c}R_{\rm eq}^2 + \kappa_B\right)t\,, \tag{18}$$

cf. Section III in [7]. The process of their interest has been the thermal conductance of the vapor through the interface, for which the thermal gradient played the role of thermodynamic driving force. In our case, the corresponding pressure difference $\Delta P = -\frac{3\eta_{\rm s}R^2}{r^3}\dot{R}$ conducts the solution through the pore. Its solely confirmed depiction is given by the hydrodynamic quotient of Eq. (17), being largely damped, however, at the pore-closure stage.

3.4. Helpful (reverse) analogy with structural stability analysis of growing spherical nuclei immersed in a diffusion field

Mullins–Sekerka instability problem concerns emergence and growth of a spherical nucleus in a diffusion regime. The evolution of the spherical nucleus, given in terms of its radius, $R_n(t)$, assumed that the surface perturbation (very small) amplitudes die out in the long times' domain [13, 14, 19, 20], is well approximated by

$$\frac{{\rm d}R_n}{{\rm d}t} = D\frac{\sigma_{\rm ss}}{R_n}\,, \tag{19}$$

wherein $\sigma_{\rm ss}$, being the non-dimensional supersaturation [14], approaches a constant value; formally, it is then presented as $\sigma_{\rm ss} = (c_\infty - c_0)/(C - c_0)$ with c_∞ — a far-distant concentration of the solution, c_0 stands for the equilibrium concentration at the fairly flat (for $R_n \to \infty$) nucleus' interface, whereas C provides the (nearly) constant density of the diffusively growing nucleus. D is the diffusion coefficient.

It is a matter of very simple one-quadrature inspection that Eq. (19) has to be solved by

$$R_n^2(t) = R_n^2(t=0) + 2D\sigma_{\rm ss}t\,, \tag{20}$$

uncovering asymptotically the well-known diffusion regime by means of $R_n(t) \sim t^{1/2}$. Note, however, that because of the plus sign at the right-hand side of Eq. (20), the nucleus does not dissolve but grows (by the

incoming mass [14]) in time t — an inverse process as compared to the diffusion–dissolution mechanism revealed here, or in an analogous, though less simplified manner (as in here) by [7].

3.5. Virtual connotations with a mesoscopic biolubrication mechanism in articulating systems

Let us address the obtained results in terms of mechanism of facilitated lubrication in articular cartilage (AC) [17, 21]. According to [22], phospholipids in their micellar aggregates may influence overall mechanism of lubrication in natural joints. Synovial fluid (SF) is composed of water (60–70%) and other aggregates, such as: hyaluronic acid (HA), surface active phospholipids (SAPLs), *etc.* AC shows very low friction coefficient which can be $\mu \approx 10^{-3} \div 10^{-2}$, and a lubrication is to be considered of hydrodynamic nature [18]. There is a growing amount of recent papers [17, 22–27] that indicate the role of vesicles in biolubrication. They propose, at least at the laboratorial scale, that the mechanism of biolubrication can be explained in terms of vesicles' response to both: loading and (small) shearing force factors. The basic notion staying behind this mechanism is proposed to be the hydration repulsion, possibly assisted by laminae shearing over one another [23, 27]. The overall name coined for the mechanism is the hydration lubrication. What in our opinion turns out to be a certain drawback of the mechanism is that the vesicles involved in it have to suffer from creation and annihilation of transient pores in the vesicles' membranes. Those pores can occur while vesicle is inhomogenously compressed [24]. Therefore, pore creation and annihilation is a vivid subject that should be intensively studied. Based on knowledge of previously studied systems, we wish to argue the self-healing, thermodynamic character of the transient pore occurring virtually during friction *vs.* lubrication effects. Based on our studies of the role of micelles of facilitated lubrication in articular joints, we came into conclusion that at least at the (sub)micrometer level, the pores are necessary to supplement a dynamic separation of the opposing (nano)surfaces by means of available ionic streams, such as the hydrogen ones, coming out from hydrogen bond breakage in the aqueous milieu. Then, the corresponding Grotthuss mechanism of hydrogen ions transport is possible [28]. As a consequence, the facilitated lubrication can be obtained due to superdiffusive transport of hydrogen ions [26], complemented by the overall action of screened electrostatics [29]. The leakage of the water and dissolved ions [22, 26] accompanying H-bond breakage may cause a proton streams cascades' creation. The Re number is higher in nanochannels as confinement grows [16, 30], thus, such revealed mechanism seems to be an important factor in systems with facilitated lubrication.

Regarding, in turn, the model hydration–lubrication system [24] of multilamellar vesicular character, one can foresee a relevant circumstance of its virtual deconstruction [31, 32]. Namely, a type of (lipid) vesicle's disintegration may occur, depending on pH, lipid concentration (and the corresponding osmotic pressure) as well as near physiologic temperature conditions. Though such disintegration is less probable for micelles, it is plausible to occur for layer-by-layer grown multilamellar vesicles. Moreover, some biomolecular inclusions, mostly of protein-type, might cause the vesicles to deconstruct into two-dimensional films; such an instance would apply preferrably at as-achieved (minute) electrical neutrality conditions [31]. Returning comparatively to micelles [22], and their roles played in the biolubrication mechanism, it appears when the kinetic friction coefficent is about to reach its appreciably high value, out of the facilitated lubrication regime [26]. It implies that the (pores-affecting) self-healing mechanism does not apply, and the layers reform at suitable surfaces of articulating system. This, in turn, forces somehow the system to make use of the shear involving part of the hydration–lubrication event: the layers may slide then one over another [25, 27]. The self-healing phenomenon does not preserve any longer until the curvilinearly shaped micelle- or vesicle-type soft object eventually rebuilds.

Moreover, it has previously been shown in Ref. [15] that the elastic contribution to the free energy of the membrane that forms a vesicle may be, depending on the properties of the membrane itself (bending constant and linear tension of the pore), a bistable function. For giant spheres (with a radius bigger than 50 nm), the free energy has a minimum at the spherical configuration and, therefore, the formation of the vesicle takes place as a transport process from planar membrane to a closed sphere. In this case, there is no critical size of the pore for which the vesicle disintegrates. In contrast, for small enough vesicles, the formation has to overcome a free energy barrier. In this circumstance, it is appropriate to ascertain that the critical radius of the pore, r_c, over which the pore never collapses again is determined, in the first approximation, by the relation $r_c \simeq R_{eq}^2 \gamma/\kappa_B$. For a prestressed vesicle, this relation can be approximated, in turn, by $r_c \simeq \gamma/\sigma_0$ with σ_0 — the initial value of the effective surface tension, see Ref. [8]. Here, the competition between the closing force (γ) and the opening force (σ_0) are the main parameters controlling the size of this critical value of the pore's radius.

4. Summary

The presented work can be summarized concisely as follows:

— The new approach (based on Onsager theory) of irreversible thermodynamics of small systems gives very useful formalism for description of the process of vesicular pore creation and annihilation. Numerical solutions of Fig. 2 show one of the possible forms in which the considered system is coupled to the heat bath — the characteristic relaxation times of the system's variables are dependent on the viscosity of the solvent as expected from experiment.

— Presented model does not look at molecular level of pore creation and annihilation in vesicle. To look into detail one has to use experimental methods as well as computer modeling. Presented approach gives, however, an impression on how this so revealed mechanism may occur and thus gives a possible control in *e.g.* drug delivery systems. One may expect that due to electrostatic interactions between lipids' heads, the Coloumbic interactions may play a crucial role in our system in molecular detail. However, in aqueous solutions, the phospholipid membranes acquire a net negative charge. At physiological concentrations, the Debye length is quite short (less then 1 nm) and the electrostatic interactions are strongly screened. Therefore, electrostatics is not expected to play a crucial role in revealed mechanism.

— The self-healing mechanism of the pore's closing rests upon a cooperation of thermodynamic (energetic) and hydrodynamic natural cofactors driving together the cessation of the pore's dynamics. It is self-evident when inspecting again the small-Re conditions in the context of Eq. (17), largely assisted here by the thermodynamic — geometric precondition of closure. A possible application to facilitated lubrication due to vesicles/micelles interactions enabling ions to go through so-called ion channels. Among all ions, protons have the highest charge-to-mass ratio in physiological solutions (such as SF), therefore, their role in decreasing friction between AC surfaces is of high importance due to Grotthuss mechanism. Our future studies will focus on mechanism of proton conduction in so-called proton intermicellar channels.

— Simultaneously membrane rupture occurs, which results in the release of the encapsulated substance into the liposome-surrounding compartment. The reason for the rupture at the lower pH is the transition from lamellar to hexagonal HII phase. Liposomes also ruptured following adsorption when providing poor high-pressure lubrication.

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REFERENCES

[1] E. Karatekin *et al.*, *Biophys. J.* **84**, 1734 (2003).
[2] R. van der Meel *et al.*, *J. Contr. Release* **195**, 72 (2014).
[3] A. Iglic (Ed.), *Advances in Planar Lipid Bilayers and Liposomes*, Academic Press Vol. 14, Amsterdam 2014.
[4] Y. Levin, M.A. Idiart, *Physica A* **331**, 571 (2004).
[5] I. Goychuk, *Phys. Rev. E* **92**, 042711 (2015).
[6] G. Cevc, D. Marsh, *Phospholipid Bilayers: Physical Principles and Models*, Wiley-Interscience, New York 1987.
[7] V. Babin, R. Hołyst, *J. Phys. Chem. B* **109**, 11367 (2005).
[8] L. Martínez-Balbuena, E. Hernández-Zapata, I. Santamaría-Holek, *Eur. Biophys. J.* **44**, 473 (2015).
[9] D. Kondepudi, I. Prigogine, *Modern Thermodynamics*, John Wiley&Sons, England, 2007.
[10] L. Onsager, *Phys. Rev.* **37**, 405 (1931).
[11] F. Brochard-Wyart *et al.*, *Physica A* **278**, 32 (2000).
[12] T. Portet, R. Dimova, *Biophys. J.* **99**, 3264 (2010).
[13] A. Gadomski, C. Trame, *Acta Phys. Pol. B* **30**, 2571 (1999).
[14] A. Gadomski, J. Łuczka, Z.J. Grzywna, *IMA Preprint Series* No. 869, 1991.
[15] L. Martínez-Balbuena, E. Hernández-Zapata, I. Santamaría-Holek, *J. Biol. Phys.* **35**, 297 (2009).
[16] R. Jaeger *et al.*, *Appl. Phys. Lett.* **101**, 184102 (2012).
[17] A. Gadomski *et al.*, *Math. Biosci.* **244**, 188 (2013).
[18] K. Wierzcholski, *Int. J. Appl. Mech. Engin.* **11**, 515 (2006).
[19] A. Gadomski, *Vacuum* **50**, 79 (1998).
[20] A. Gadomski *et al.*, *Acta Phys. Pol. B* **36**, 1537 (2005).
[21] Z. Pawlak, A. Oloyede, *Biosystems* **94**, 193 (2008).
[22] A. Gadomski, Z. Pawlak, A. Oloyede, *Tribol. Lett.* **30**, 83 (2008).
[23] R. Goldberg *et al.*, *Biophys. J.* **100**, 2403 (2011).
[24] R. Sorkin *et al.*, *Biomaterials* **34**, 5465 (2013).
[25] R. Goldberg, J. Klein, *Chem. Phys. Lip.* **165**, 374 (2012).

[26] A. Gadomski *et al.*, *Acta Phys. Pol. B* **44**, 1801 (2013).
[27] Z. Pawlak *et al.*, *Biointerphases* **11**, 019002 (2016).
[28] N. Agmon, *Chem. Phys. Lett.* **244**, 456 (1995).
[29] A. Cherstvy, *Phys. Chem. Chem. Phys.* **13**, 9942 (2011).
[30] I. Santamaría-Holek *et al.*, *J. Non-Eqilib. Thermodyn.* **37**, 273290 (2012).
[31] Z. Gui *et al.*, *J. Mater. Chem.* **20**, 1467 (2010).
[32] D.E. McAlduff, Y.M. Heng, F.P. Ottensmeyer, *J. Microsc.* **205**, 113 (2002).