International Journal of Applied Mechanics
Vol. 1, No. 2 (2009) 327–338

Imperial College Press
www.icpress.co.uk

PHENOMENOLOGICAL MODELING FOR PORE OPENING, CLOSURE AND RUPTURE OF THE GUV MEMBRANE

HUI FAN* and YAN CHEN

School of Mechanical and Aerospace Engineering
Nanyang Technological University
Singapore 639798, Republic of Singapore
**mhfan@ntu.edu.sg*

K. Y. SZE

Department of Mechanical Engineering
The University of Hong Kong, Pokfulam
Hong Kong SAR, P. R. China

Received 5 January 2009
Accepted 25 February 2009

In this paper, the pore opening and closure on the giant unilamellar vesicle GUV membrane are studied under different theoretical schemes. The opening process is considered as a dynamics process; while the closure process is considered as a quasi-static process. The opening criterion is set based on an energy release rate theory, similar to the Griffith theory for crack initiation. On the other hand, the closure process is described by a non-equilibrium thermodynamic theory. When the size of initial pore is smaller than a critical value, the pore is stable, and followed by the closure process. Otherwise, the pore is unstable, which leads to the rupture of the vesicle.

Keywords: GUV; irreversible thermodynamics; energy rate.

1. Introduction

The giant unilamellar vesicle (GUV) has been considered as a promising drug delivery system. A comprehensive review for various research interests on GUV was conduced by Dobereiner.[1] Among all the configurations, opening and closure of pores on the vesicle is related to releasing drug inside of the vesicle. Creating a pore on a vesicle can be made via mechanical loading, optical approaches or others. There are all kinds of research attempts from various aspects for the pore opening and closure, which include experimental observation,[2] analytical phenomenological modeling,[3] and also mechanism modeling.[4] It is our objective of the present paper to study the pore opening and closure process based on a continuum physics approach.

*Corresponding author.

The size of GUV in the order of tens of micro meters, which is much smaller than its capillary length,[5] $L_c = \sqrt{\sigma/(\rho g)}$, where σ is the surface tension of the membrane and ρ is the mass density of the vesicle. Hence, the gravity is negligible and the geometric change of the vesicle is governed by the surface tension of the membrane, rather than by volume associated energy such as elastic deformation within the vesicle. Therefore, fundamental understanding on the physical response of the vesicle membrane is the primary task in the research of GUV deformation. The vesicle membrane is made of bi-layer lipid which was considered as a kind of liquid. The surface tension, or sometimes called surface energy, of the vesicle membrane, was simplified to be constant during the deformation for some preliminary studies. However, recent experimental and analytical modeling on the GUV pore opening phenomenon[6] indicated that the surface tension should be a variable during the deformation of the membrane.

In this paper, we consider a geometric configuration of the pore opening and closure process on a vesicle membrane as shown in Fig. 1. The surface tension, σ_0, is associated with a reference configuration. During the deformation, the change of the surface tension is given by

$$\Delta\sigma = \sigma - \sigma_0 = E\Delta\varepsilon = -E\frac{\Delta A}{A_0}, \tag{1.1}$$

where E is introduced as tension modulus, which is phenomenological constant of the membrane. The strain is related to the change of surface area of the vesicle. ΔA is the pore area and A_0 is the area of the spherical vesicle just before the opening of the pore. Indicative order of magnitudes of the $E = 200\,\text{mN/m}$ and $\sigma = 10\,\text{mN/m}$ are given by Ly.[2] Some of the researchers prefer the reference state

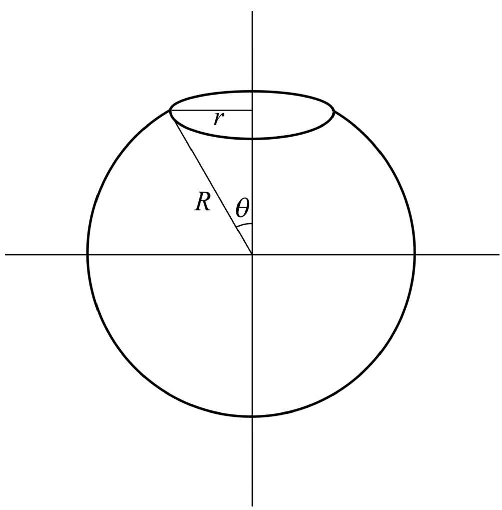

Fig. 1. The geometric configuration of a pore opened on a spherical GUV.

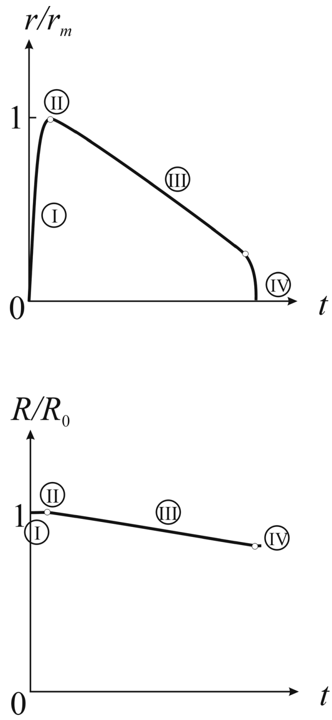

Fig. 2. The four stages of the pore opening and closure process.

as the "zero" surface tension configuration, which makes no difference of making theoretical analysis but rather increase the difficulty of experimental measurement.

According to experimental observation,[3] there are four stages during pore opening and closure as shown in Fig. 2. Stage I is the rapid opening; Stage II is stop of growth at its maximum radius; Stage III is the slow closure; and Stage IV is the fast closure. We will try to establish certain theoretical analyses for each of the stages in the following sections. Some numerical demonstrations and parametric study are carried out incorporated with membrane material constant published in various experimental references.

2. Energy Release Rate Consideration

Based on the experimental observation,[6] the processes of the pore opening was so fast that the radius of the vesicle did not change during the pore opening interval, and the fluid inside of the vesicle did not have time for leaking. The process started with increasing the surface tension of the vesicle by various optical or mechanical approaches. When the surface tension reached its critical value, the vesicle broke a "hole" to release the energy. The pore reached its maximum size and stopped. This process is very much similar to a brittle solid specimen under uni-axial displacement-controlled tensile test. The stress reaches a critical value when a macro-crack starts propagating from micro-defects. Since the tensile loading is displacement-controlled, therefore, the stress is released during the crack propagation until it stops. The crack propagation was described by Griffith's energy release rate theory.[7] We see the similarity between crack propagation and pore opening. It may be possible to apply the energy rate concept to the pore opening process.

It is noticed that the pore is not gradually growing from zero-dimension to an equilibrium size. Instead, the pore is formed by coalesce of the many micro-defects and reaches a macroscopic size.[6] When the pore formed with size of r_i, its stability needs to be examined based the energy release rate theory.[7] Upon its stability, we can conclude whether pore will be closed under the thermodynamic forces or totally ruptured. We used subscript "i" here, because this is the "initial" pore of closure or rapture.

Let us consider the energy and energy rate in the system of the vesicle with inside liquid different from outside liquid. There are two energies in the system, namely line tension energy $2\pi r\tau$ and the surface energy σA (surface tension times the surface area of the vesicle). Referring to the geometric configuration of Fig. 1, we can write the change of the line tension energy as the pore size changes as

$$\frac{\partial(2\pi r\tau)}{\partial\theta} = \frac{\partial(2\pi R\sin\theta\tau)}{\partial\theta} = 2\pi R_0\tau\cos\theta, \tag{2.1}$$

where we adopted the fact that the radius of the spherical vesicle does not change during the dynamic opening process, i.e. $R = R_0$.

Also, we assume that the shape of the vesicle during the opening of the pore can be approximated as a sphere with a constant radius. Thus, the area of the membrane is calculated as

$$A = A_0 - \Delta A = 4\pi R_0^2 - 2\pi R_0^2(1-\cos\theta) = 2\pi R_0^2(1+\cos\theta). \tag{2.2}$$

Noting that the surface tension is related to the reference value, σ_0, the critical surface tension is

$$\sigma = \sigma_0 - E\frac{\Delta A}{A_0}, \tag{2.3}$$

when the vesicle is broken.[2]

Considering Eq. (2.2), we have

$$\sigma = \sigma_0 - \frac{E}{2}(1-\cos\theta). \tag{2.4}$$

From Eqs. (2.2) and (2.4), the energy release rate of the surface energy is calculated as

$$\frac{\partial(\sigma A)}{\partial\theta} = -2\pi R_0^2\sin\theta(\sigma_0 + E\cos\theta). \tag{2.5}$$

In order to continuously open the pore, the released energy rate from the surface energy given by Eq. (2.5) must be larger than that from the line tension energy given by Eq. (2.1). Therefore, the energy release rate condition during the pore opening is

$$-\frac{\partial(\sigma A)}{\partial\theta} \geqslant \frac{\partial(2\pi r\tau)}{\partial\theta}. \tag{2.6}$$

The critical size of the pore is given by

$$R\sin\theta(\sigma_0 + E\cos\theta) = \tau\cos\theta, \tag{2.7}$$

or, in a dimensionless form,

$$\sin\theta(1 + \alpha\cos\theta) = \beta\cos\theta, \tag{2.8}$$

where $\alpha = E/\sigma_0$ and $\beta = \tau/(\sigma_0 R_0)$. From the experimental data,[2] we see that α is in the order of 20, while β remains unknown.

We are looking for a *stable solution* within the range of $\theta \in (0, \pi/2)$. The so-called *stable solution* means that for the pore size larger than the solution, the energy rate released by surface tension is less than the energy rate needed for expanding line tension energy. Hence, the dynamic process stops. Otherwise, the solution is said to be unstable.

For the solution of Eq. (2.8), θ_d, the pore radius

$$r_d = R_0\sin\theta_d \tag{2.9}$$

is considered as a system constant. The subscript "*d*" stands for the value obtained via the dynamic consideration. The full range solution presented in Fig. 3 shows that

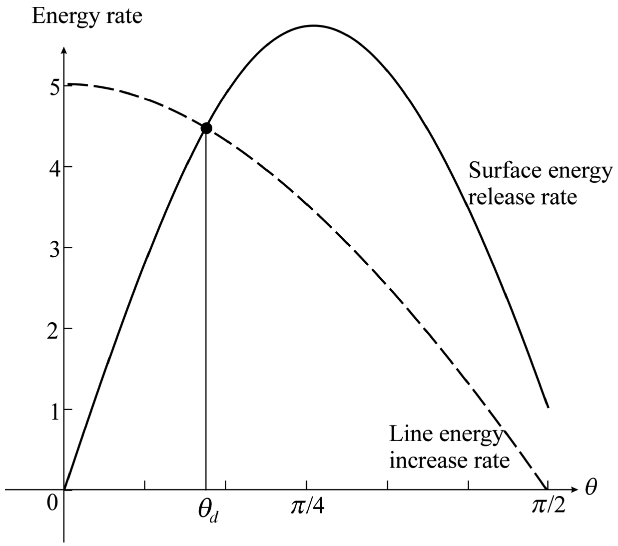

Fig. 3. θ_d from the surface energy release rate and line energy increase rate for $\alpha = 10$ and $\beta = 5$.

there is only one solution within $\theta \in (0, \pi/2)$ in general. Comparison of the initial size of the pore, r_i, to the above system constant, r_d, gives us following possibilities.

(i) $r_i < r_d$, the pore is stable. A closure process will be followed, which is discussed in the next section.
(ii) $r_i > r_d$, the pore is unstable, the rupture of the vesicle is expected.

3. Non-Equilibrium Thermodynamic Framework for Pore Closure

From experimental observation schematically shown in Fig. 2,[3] there are four stages in pore opening and closure history. It is seen that the rapid opening stage only takes about 2% of the total time of the whole opening-closure process. Stage II and Stage III are very slow in comparison with Stage I. Hence, a quasi-static thermodynamic scheme, which has been applied to many other similar processes, such as droplet spreading on the substrate,[8] is presented here for describing the pore closure after the dynamic opening.

3.1. *Geometric configuration changes*

Let us consider a vesicle with a pore shown in Fig. 1. The non-equilibrium thermodynamics requires that the system (surface and line) changing is the process of reducing the system Gibbs free energy towards its minimum value. The free energy consists of the surface energy and line tension energy, denoted by U, and the negative work supply W to the system by the external actions. We have

$$G(R(t), r(t)) = U - W \tag{3.1}$$

with

$$U = \sigma A + \tau L \tag{3.2}$$

and t denotes time. From Eqs. (3.1) and (3.2), the free energy change of the vesicle system can be expressed by

$$\delta G = \sigma\delta A + A\delta\sigma + \tau\delta L + L\delta\tau - \delta W. \tag{3.3}$$

The variations of $\delta\sigma$ and $\delta\tau$ in the right hand-side of above equation are taken under the condition of no-change of A and L at certain moment. Note that the surface tension change only contributed via area change and line length change in our derivation, i.e.

$$\sigma = \sigma(R(t), r(t)), \tag{3.4a}$$

$$\tau = \tau(r(t)). \tag{3.4b}$$

When the geometric parameters $R(t)$ and $r(t)$ remain unchanged, the surface and line tensions follow, i.e. $\delta\sigma = 0$ and $\delta\tau = 0$. Eq. (3.3) is then rewritten as:

$$\delta G = \sigma\delta A + \tau\delta L - \delta W. \tag{3.5}$$

To evaluate the change of the free energy given in Eq. (3.5), we need to find the geometric change of surface area and line length. For the membrane, the sum of the two principal curvatures of surface is given by

$$\kappa = \frac{1}{R_1} + \frac{1}{R_2}, \tag{3.6}$$

where R_1 and R_2 are the principal radii of curvature, taken to be positive for a convex surface. On the one hand, associated with the virtual motion, δR_n (virtual displacement in the outward normal direction), the area of the membrane varies by

$$\delta A = \iint \kappa \delta R_n \, \mathrm{d}A. \tag{3.7}$$

On the other hand, associated with the virtual motion of the pore line, δr, the area of the membrane changes by

$$\delta A = \oint_L \delta r \cos\theta \, \mathrm{d}l, \tag{3.8}$$

without changing of curvature in Eq. (3.2). Also, we have

$$\delta L = \oint_L \frac{\delta r}{r} dl. \tag{3.9}$$

3.2. *Driving forces*

Having the aforementioned virtual motions, we can define the thermodynamic force on the membrane, f_S, and the force on the line, f_L. As the free energy decreases with respect to the virtual motions, we have

$$\oint_L f_L \delta r \mathrm{d}l + \iint_S f_S \delta R_n \mathrm{d}A = -\delta G. \tag{3.10}$$

Since the virtual motion δR_n is an arbitrary function of the position on the membrane and the δr is also an arbitrary function of the position on the line L, Eq. (3.10) uniquely defines the quantity f_S at every point on the membrane, S, and the f_L at every point along the pore boundary L. The above-defined thermodynamics force f_S has a unit of stress (force/area) and f_L has a unit of surface tension (force/length). They are called driving forces of the dynamic system.

Let v_L be the actual velocity of the pore edge line L and v_S^n be the normal velocity of the membrane S, respectively. Under the framework of thermodynamics, the actual velocities are taken to be functions of the driving forces. In the present study, the velocity is assumed to be linearly proportional to the driving force,[9] i.e.

$$v_L = M_L f_L \tag{3.11}$$

$$v_S^n = M_S f_S. \tag{3.12}$$

In the above equation, M_L and M_S are called the ***mobilities*** of the pore boundary and the membrane, respectively. These two quantities are used as phenomenological parameters of the system, to be determined by comparing theoretical predictions with experimental measurements.[10] Since the thermodynamics requires that the evolution leads to a reduction of the free energy of the system, both M_L and M_S are positive. Equations (3.11) and (3.12) are called the kinetic laws for the pore boundary and the liquid/vapor interface. It should be noted that the kinetic laws (3.11) and (3.12) are linear relations and the velocity at a point only depends on the forces at this point, namely, a local relations. In general, the kinetic laws can be generalized to non-linear and non-local relationship if the linear law fails to give a good predication of the experimental result.

3.3. *Evolution equations*

Noting that the external work changes is given by

$$\delta W = \iint_S \Delta p \delta r_n \mathrm{d}A, \tag{3.13}$$

where Δp is the pressure difference across the membrane, which is the so-called Laplace pressure, we rewrite Eq. (3.5) as

$$\delta G = \oint_L \sigma \delta r \cos\theta \ \mathrm{d}l + \oint_L \frac{\tau}{r} \delta r dl + \iint_S \sigma \kappa \delta R_n \ \mathrm{d}A - \iint_S \Delta p \delta R_n \ \mathrm{d}A. \tag{3.14}$$

A comparison of Eq. (3.10) and (3.14) gives the expressions of the driving forces

$$f_L = \sigma \cos\theta - \frac{\tau}{r} \tag{3.15}$$

and

$$f_S = \Delta p - \sigma \kappa. \tag{3.16}$$

Substitution of Eqs. (3.15), (3.16) into (3.11) and (3.12) leads to

$$v_L = \frac{\delta r}{\delta t} = M_L \left(\sigma \cos\theta - \frac{\tau}{r} \right), \tag{3.17}$$

for the edge line of the pore, and

$$v_S^n = \frac{\delta R}{\delta t} = M_S (\Delta p - \sigma \kappa), \tag{3.18}$$

for the membrane. When a Laplace pressure is assumed, the evolution of vesicle radius and size of the pore can be fully simulated via Eqs. (3.17) and (3.18). We knew that Laplace pressure depends on the leaking process which involves a lot of assumptions.[3] Actually, we suggest that based on the experimental observation on R and r as shown in Fig. 2, Eqs. (3.17) and (3.18) could provide necessary information for the Laplace pressure.

4. Discussion with Numerical Demonstrations

There are four stages in pore opening and closure process[3] as shown in Fig. 2, in which R_0 is the original radius of the vesicle without the pore, and r_m is the maximum radius of the pore. Stage I is the rapid opening; Stage II is stop of growth at its maximum radius; Stage III is the slow closure; and Stage IV is the fast closure.

Stage I is the rapid opening of the pore, which is a dynamic process and modeled by energy release rate theory in Sec. 2.

Stage II is the stop of growth and adjustment of the pore radius at its maximum. At this moment, the thermodynamic force in Eq. (3.15) vanishes and

$$\sigma \cos\theta - \frac{\tau}{r} = 0. \tag{4.1}$$

Substituting surface tension by Eq. (2.4), a critical value of pore size based on static force balance condition is given by

$$R\left(\sigma_0 - \frac{E}{2}(1-\cos\theta)\right)\cos\theta\sin\theta = \tau. \tag{4.2}$$

With dimensionless parameter defined in Eq. (2.8), we can rewrite Eq. (4.2) as

$$\left(1 - \frac{\alpha}{2}(1-\cos\theta)\right)\cos\theta\sin\theta = \beta. \tag{4.3}$$

The solution obtained from Eq. (4.3) is under quasi-static force balance, and is denoted as

$$\theta_s = \theta_s(\alpha, \beta),$$

which is also considered as a system constant. The subscript "s" stands for the quasi-static value.

While the solution obtained from Eq. (2.8) is under the dynamic energy release rate consideration, it is denoted as

$$\theta_d = \theta_d(\alpha, \beta)$$

where the subscript "d" stands for the dynamic value.

The initial pore radius θ_i related to θ_s and θ_d leads to various possibilities. Let us take some representative numbers to demonstrate various situations. Firstly, let us take $\alpha = 10$ (indicated by Ly[2]) and $\beta = 5$ (parametric study). There is only one solution of θ_d as shown in Fig. 3. There is no solution for θ_s shown in Fig. 4, which implies that quasi-static closure is possible for all θ_i. For any θ_i corresponding to the initial radius of the pore for Stage II (after Stage I obtained in Sec. 2), if $\theta_i < \theta_d$, the pore is stable and will proceed to the closure stage. If $\theta_i > \theta_d$, the pore is unstable, and will proceed to the rupture of the vesicle. Secondly, let us see the case that β is very small, such as $\beta = 0.1$ (again $\alpha = 10$). There are two solutions for θ_s as shown in Fig. 5. It is seen that $\sigma r\cos\theta > \tau$ when $\theta_{s1} < \theta < \theta_{s2}$. It means that the pore can be enlarged under quasi-static mechanism in this region. However, θ_d is always smaller than θ_{s1} as shown in Fig. 6. Therefore, for any stable $\theta_i < \theta_d < \theta_{s1}$, condition $\sigma r\cos\theta < \tau$ is always satisfied. In turn, the pore is in the closure process.

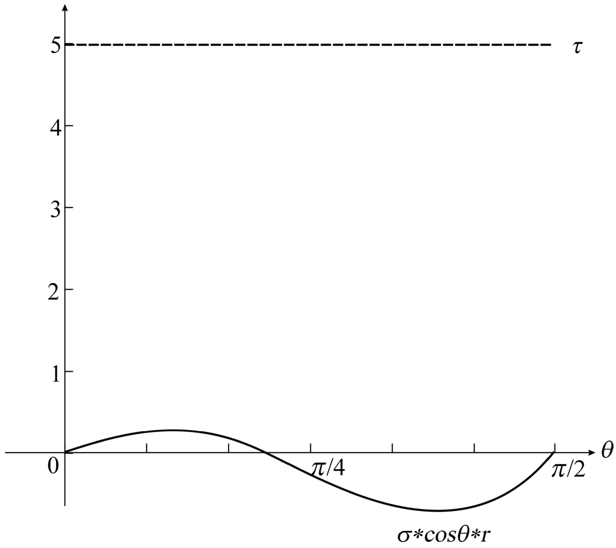

Fig. 4. θ_s from the surface energy and line energy for $\alpha = 10$ and $\beta = 5$.

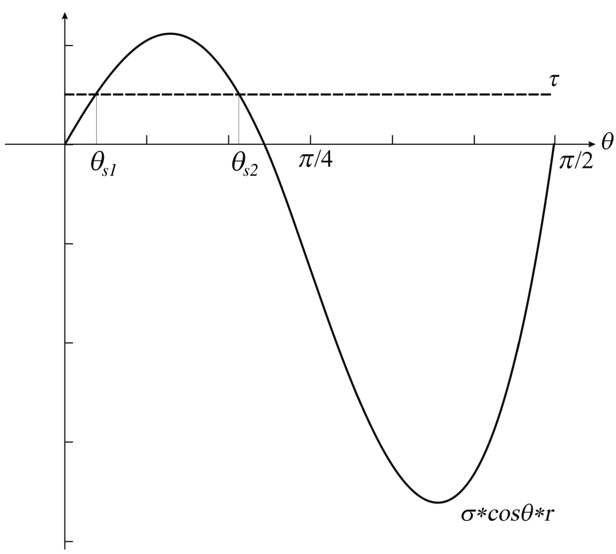

Fig. 5. θ_s from the surface energy and line energy for $\alpha = 10$ and $\beta = 0.1$.

Stage III is the slow closure of the pore which can be treated as quasi-static process as we modeled in Sec. 3. The numerical simulations based on Eqs. (3.17) and (3.18) should show the vesicle radius and pore radius changing with time linearly (shown in Fig. 2). This stage is not the subject issue of the present paper. Interested readers may refer to Fan[8] for the detailed process of numerical simulations.

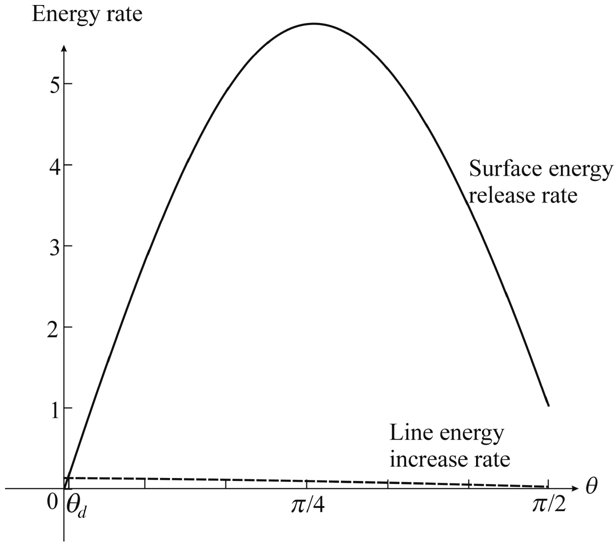

Fig. 6. θ_d from the surface energy release rate and line energy increase rate for $\alpha = 10$ and $\beta = 0.1$.

Finally at Stage IV, the pore undergoes fast closure. When the pore radius becomes very small, the leak-out is negligible.[3] Based upon Eq. (3.18), the radius of vesicle does not reduce significantly, and neither of the surface tension. Then, from Eq. (3.17), the change rate of the pore radius is proportional to $1/r$. So the pore can be closed very fast until $r = 0$.

5. Concluding Remarks

In the present paper, we distinguished the pore opening and pore closure as two totally different dynamic processes. The opening of the pore is fast and analogy to the failure of micro-cracked solids under displacement loading. That is why we conducted an "energy release rate" analysis similar to the fracture mechanics.[7] The closure of the pore is described by an irreversible thermodynamics framework,[8] in which there are two new membrane constants, namely the mobilities of the pore boundary line and membrane surface (M_L and M_S), are needed to be determined from the experimental calibrations.

References

1. H. Dobereiner, Properties of giant vesicles, *Current Opinion in Colloid & Interface Science* **5** (2000) 356–263.
2. H. V. Ly, Effect of short-chain alcohols on elasticity, stability and phase transition of lipid membrane, Ph.D thesis, University of California at Davis, 2003.
3. F. Brochard-Wyart, P. G. de Gennes and O. Sandre, Transient pores in stretched vesicles: Role of leak-out, *Physica A* **278** (2000) 32–51.

4. O. Farago and C. D. Santangelo, Pore formation in fluctuating membranes, *J. Chemical Physics* **122** (2005) 044901.
5. P. G. de Gennes, Wetting: Statics and dynamics, *Reviews of Modern Physics* **57**(3) (1985) 827–863.
6. E. Karateikin, O. Sandre and F. Brochard-Wyuart, Transient pores in vesicle, *Polymer International* **52** (2003) 486–493.
7. A. A. Griffith, The phenomena of rupture and flow in solids, *Phil. Trans. Roy. Soc. London A* **221** (1921) 163–197.
8. H. Fan, Liquid droplet spreading with line tension effect, *J. Physics: Condensed Matters.* **18** (2006) 4481–4488.
9. Z. Suo, Motions of microscopic surface in materials, *Advances in Applied Mechanics* **33** (1997) 193–294.
10. H. Fan, X. Y. Gao and X. Y. Huang, Thermodynamics modeling for moving contact line in gas/liquid/solid system: Capillary rise problem revisited, *Physics of Fluids* **13**(6) (2001) 1615–1623.