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GROWTH INSTABILITIES OF VESICLES

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ABSTRACT

We present a model for the growth of short-wavelength instabilities of membranes with small curvature energy based on the van der Waals interaction energy.

I. INTRODUCTION

As is well known, the macroscopic shape of lipid membranes is largely controlled by a combination of the curvature energy $K$, spontaneous curvature, temperature, and the interaction between membranes. Measured curvature energies are usually considerably in excess of $\beta^{-1} = k_B T$. The surface of the membrane is approximately flat on length scales less than the persistence length $\xi_p \sim \exp \beta K$. If we do reduce $\beta K$, then $\xi_p$ becomes smaller and smaller while the membrane becomes rougher and rougher. For $\beta K \leq 1$, membranes are believed to be unstable due to thermal fluctuations. The phase-transition between the $L_\alpha$ and $L_\beta$ phases may be an example of such an instability.

Recently, E. Evans devised an ingenious experiment which suggests an alternative scenario for the evolution of instabilities of low $K$ membranes. He dissolved the sub-surface protein scaffolding which had maintained the rigidity of a (spherical) vesicle and then watched the evolution. The initial curvature energy was quite low as testified by visible thermal fluctuations in the vesicle shape immediately following the dissolution. After a while, the vesicle grew "buds" which led to new smaller vesicles. The new vesicles were stable.

Most interestingly, he observed on occasion during this process tubular buds and these tubes showed a bead-like instability. In other words, the cross-section of the tube was modulated periodically. Instabilities of liquid cylinders are quite familiar since Rayleigh but there the driving force is the surface tension. For vesicles, the surface area is a fixed quantity because of the surfactant action of the lipid molecules. Spontaneous curvature effects can also be ruled out.

The instability would be understandable as the consequence of a long-range attractive interaction between the walls of the tube. A long-range
attractive force would favor a large number of small vesicles over a single large vesicle (with the same total area) since more sections of the membrane would be in close proximity in the former case. In that sense, an attractive force has an effect somewhat similar to surface tension. The observed Rayleigh-type instability would then also be understandable. This long-range attraction must compet with the curvature energy. If we transform a single spherical vesicle -- with no spontaneous curvature -- into $N$ smaller vesicles then the curvature energy is increased by roughly $(N-1)\Delta m (2K+\bar{K})$ with $\bar{K}$ the Gaussian curvature energy.

The dominant long-range attraction for membranes is provided by the van der Waals interaction. The attractive van der Waals energy between two flat parallel layers of thickness $\delta$ a distance $z$ apart is well known to be of order $W\delta^2/z^4$ with $W$ the Hamaker constant ($\sim 10^{-21} - 10^{-22}$ J). If we use for $\delta$ the membrane thickness ($\approx 50\text{A}$) then this attraction is minuscule compared to the curvature energy as long as $r(z) \gg \delta$. This would appear to be a fatal objection to the proposed explanation of the observed instability. However, for the experiment discussed earlier there is no reason for the dielectric constants of the solvents in the interior and exterior of the vesicle to be the same. Because of the dissolved protein scaffolding in the interior they could indeed be significantly different. The van der Waals interaction per unit area between two parallel sheets enclosing a medium of dielectric constant $\epsilon_A$ with a medium of dielectric constant $\epsilon_B$ on the outside is of order $W/z^2$. Here, $W$ is proportional to $(\epsilon_A - \epsilon_B)^2/(\epsilon_A + \epsilon_B)^2$. The attraction has increased by a factor $(z/\delta)^2$ compared to the direct interaction and can now be of the same order of magnitude as the curvature energy. In this article we will investigate the stability of a vesicle for which the van der Waals self-energy is comparable to the Helfrich curvature energy.
II. CURVATURE AND VAN DER WAALS ENERGIES.

The free energy of a closed vesicle with no spontaneous curvature is

$$F = \frac{1}{2} K \int d^2 \sigma \left\{ R_1^{-1} + R_2^{-1} \right\}^2 + \frac{W}{2 \pi^2} \int_{\text{exterior}} d^3 \mathbf{r} \int_{\text{interior}} d^3 \mathbf{r}' \frac{1}{|\mathbf{r} - \mathbf{r}'|^6}$$  (1)

The first term is the standard Helfrich curvature energy. We dropped the Gaussian curvature term as it is independent of the vesicle shape and we also assumed zero spontaneous curvature. The second term in Eq.1 is the non-retarded van der Waals self-energy in the de Boer-Hamaker approximation as discussed in the Appendix. We are implicitly assuming in Eq.1 that -- notwithstanding the different solvents -- there is no appreciable osmotic pressure difference between interior and exterior of the vesicle.

We now should minimize $F$ with respect to the vesicle shape for a given fixed surface area. From dimensional considerations we should expect for $K >> W$ to find a spherical shape since then the Helfrich term dominates.

For $K << W$, the van der Waals self-energy dominates. We saw in the introduction that two parallel flat sheets attract each other. If $K << W$ we thus should expect the vesicle to be crumpled in some way. The general minimization of $F$ with respect to shape is clearly a quite difficult problem. We will consider only a special case, motivated by Evans' experiment, namely that of a rotationally invariant vesicle.

Assume a tubular membrane with a position dependent radius $r(z)$ attached to a micron-size vesicle of radius $R >> r$ (see Fig.1) which acts as a reservoir. The length of the tube is $L$ and the $\hat{z}$ axis coincides with the tube. The free energy Eq.1 then simplifies to

$$F = \int_0^L dz \left \{ K \pi r(z) \left( \frac{d^2r}{dz^2} - \frac{1}{r(z)} \right)^2 - A r^{-1}(z) \right \}$$  (2)
with $A = \lambda W$. The derivation of the van der Waals term in Eq. 2 is given in the Appendix but it's form is obvious from dimensional considerations: for $r(z)$ constant, $F$ must be proportional to both $L$ and $W$ so $F \propto WL/r$. The second term in Eq. 2 is an obvious generalization of this.

Equation 2 is only valid for the non-retarded van der Waals interaction. If $r > \lambda$ with $\lambda$ the dominant adsorption wavelength of the solvent (~ 50 nm), then we must replace $Ar^{-1}$ by $Br^{-2}$ with $B = \lambda A$ (the retarded van der Waals interaction).

The qualitative features of $F$ are easily understood. For a cylindrical tube with $r(z) = r_0$, Eq. 2 gives $F = L(K\pi - A)/r_0$. For $K > A/\pi$, we can minimize $F$ by reducing $L$ and increasing $r_0$. For $K < A/\pi$, we minimize $F$ by reducing $r_0$ and increasing $L$. We thus expect that for $K > A/\pi$ the vesicle is stable while for $K < A/\pi$ it will spontaneously develop tubular protrusions. For $r_0 > \lambda$, $F = L(K\pi - B/r_0)/r_0$ so there is then a critical radius $R^* = 8B/3\pi K$ such that for $r_0 > R^*$ the tube will swell and vanishes while for $\lambda < r_0 < R^*$ it will shrink and elongate (the reason for the numerical factor $8/3$ will become clear later).

The necessary condition $\lambda \leq R^*$ for this instability is just $K \leq A/\pi$ as before. We conclude that $K^* = A/\pi$ marks the threshold of a growth instability which we will now proceed to investigate in more detail.

III. DYNAMICS

The growth-rate of the tube will be controlled by the flow of solvent material. To see why, assume we have a tube of length $L$ and uniform radius $r$.

As it shrinks, its total surface area $S \propto r(t)L(t)$ must remain (roughly) fixed. This means that the tube volume $V(t) \propto r^2(t)L(t)$ must decrease as $V(t) \propto Sr(t)$. This in turn implies that there must be flow from the tube into the vesicle.
As a result, the region where the tube is connected to the vesicle moves towards the vesicle (see Fig. 1). We will focus on this contact region and in particular look for "steady-state" solutions with the tube shape fixed but moving left.

There will be contributions to the viscous energy-dissipation by the solvent flow both from the vesicle interior and exterior. Viscous losses from the interior will dominate because of the velocity gradients imposed by the boundary conditions at the vesicle surface. As our boundary condition on the flow velocity $\mathbf{v}$, we will set $\mathbf{v} = 0$ at the membrane. This is again because the membrane has a fixed surface area. If we wish to maintain, or even increase, the length of the tube during the flow, then the membrane molecules cannot be carried along by the flow towards the vesicle so $\mathbf{v}$ must be zero at the surface of the tube. We also will assume that there is no solvent transport across the membrane.

Let $\mathbf{v}(p,z)$ be the solvent flow velocity. To compute $\mathbf{v}$, we use the Poiseuille approximation:

$$
\eta \frac{\partial^2 \mathbf{v}}{\partial p^2} = \frac{\partial P}{\partial z} \tag{3}
$$

with $P(z,p)$ the pressure in the tube and $\eta$ the viscosity. We assumed in Eq. 3 $r(z)$ to be a slowly varying function of $z$. As a consequence $\mathbf{v}$ is roughly parallel to the tube axis $\hat{z}$ ("lubrication approximation") and $\frac{\partial^2 \mathbf{v}}{\partial p^2} \gg \frac{\partial^2 \mathbf{v}}{\partial z^2}$. The solution of Eq.3 is then

$$
\mathbf{v}(p,z) \approx \frac{1}{2\eta} \frac{\partial P}{\partial z} (r^2 - p^2) \tag{4}
$$

Finally, we demand mass conservation:
Using Eq.4 in Eq.5 gives
\[
\frac{3}{8} (\pi r^2) + \frac{1}{2} \left\{ r(z) \int_0^{2\pi} v(\rho, z) d\rho \right\} = 0
\] (5)

\[
\frac{3}{8} \frac{d}{dt} \left( \pi r^2 \right) + \frac{1}{2} \left\{ \frac{3}{8} \frac{d}{dz} \left( \int_0^{2\pi} v(\rho, z) d\rho \right) \right\} = 0
\]

(6)

where we performed a suitable average of \( P(z, \rho) \) over \( \rho \).

The pressure in Eq.6 receives contributions from both curvature \( (P_H) \) and van der Waals \( (P_{vdw}) \) energies. We start with the "Helfrich" pressure \( P_H \). On physical grounds we can identify at least two contributions to \( P_H \):

(i) For \( r(z) = r_0 \) independent of \( z \), the curvature energy per unit area of a tube is \( K/2 r_0^2 \). The chemical potential of surfactant molecules at the tube surface is thus larger than at the vesicle surface. This chemical potential difference would lead to transport of surfactant molecules from vesicle to tube. Local equilibrium requires a negative count-pressure -- of order \( K/r_0^3 \) -- to prevent swelling of the tube.

(ii) Recall that across a curved surface of a fluid with surface tension \( \sigma \) there is a pressure drop \( \sigma \nabla^2 h \) with \( h \) the height profile (Young-Laplace pressure). This pressure drop is the variational derivative \( \delta F/\delta h \) of the interfacial energy. For membranes we would expect by analogy a pressure \( \delta F/\delta h \approx K \nabla^2 h \) which would contribute a term \( Kd^4 r/dz^4 \).

We define the Helfrich pressure \( P_H = 3F_H/3V = \frac{1}{2\pi r} \frac{\delta F_H}{\delta r} \). The positive sign is required because \( P_H \) is the counter-pressure required for local equilibrium. Using Eq.2,

\[
P_H = K \left\{ \frac{d^4 r}{dz^4} + \frac{2}{r} \frac{d r}{dz} \frac{d^2 r}{dz^2} + \frac{3}{2r} \left( \frac{d^2 r}{dz^2} \right)^2 - \frac{1}{2 r^3} \right\}
\]
which contains the expected terms.

The van der Waals pressure is highly inhomogeneous as discussed in the Appendix. For the present purpose, we note that the van der Waals self-energy would in Eq.2 lead to collapse of the tube unless there is a positive counter-pressure.

\[
P_{\text{VDW}} = \begin{cases} 
\frac{A}{2\pi r^2} & r \leq \lambda \\
\frac{B}{\pi r^4} & r > \lambda 
\end{cases}
\]  

Near the membrane the true pressure considerably exceeds \(P_{\text{VDW}}\) (see Appendix) but since \(v\) is restricted to the interior of the tube, we will simply use \(P_{\text{VDW}}\). Since \(r(z)\) decreases as we enter the tube, \(P_{\text{VDW}}\) increases with \(z\). The resulting pressure gradient in Eq.6 is responsible for the flow into tube.

We shall look for solutions of Eq.6 of the form \(r(z, t) = r(z+Ut)\), i.e. solutions for which the growing tube maintains a stationary shape while moving to the left. Here, \(U\) is the growth velocity which should be of the order of 1 micron/second. In a frame moving with a velocity \(U\), where \(r\) only depends on \(x = z + Ut\), Eq.6 becomes

\[
8\eta U \frac{dr}{dx} = \frac{1}{r^4 \frac{dP}{dx}} \frac{d}{dx} \left( r^4 \frac{dP}{dx} \right)
\]

This equation has a first integral

\[
\frac{dP}{dx} - \frac{4\eta U}{r^2} = \text{const.}
\]

We will assume that deep inside the vesicle, the pressure gradients are very small so the integration constant in Eq.10 is also very small (of order \(\eta U/R^2\)). We will set it to zero. This means that in the tube \(dP/dx\) is everywhere non-zero so \(dr/dx\) must be non-zero as well. Tubes with uniform cross-section are
thus only possible for \( U = 0 \). We will only allow solutions with \( \frac{dr}{dx} < 0 \).

For large \( r \), we can neglect the van der Waals pressure in Eq.10 as well as the \( 1/r^2 \) contribution to \( P_H \). Equation 10 then reads:

\[
K \frac{d}{dx} \left\{ \frac{d^4r}{dx^4} + \frac{2}{r} \frac{d^3r}{dx^3} + \frac{3}{2r} \left( \frac{d^2r}{dx^2} \right)^2 \right\} = \frac{4nU}{r^2} \tag{11}
\]

We will look for solutions of increasing \( r \) as \( x \) becomes more negative. The Ansatz \( r(x) = c(-x)^3 \) is a solution of Eq.11 if

\[
r(x) = \left( \frac{18nU}{SK} \right)^{1/3} (-x)^{2/3} \tag{12}
\]

For \( x \sim -R \), \( r(R) \) must be of order \( R \). Using Eq.12, this gives an expression for the growth velocity \( U \):

\[
U \sim \frac{K}{\eta R^2} \tag{13}
\]

The unexpected aspect of Eq.13 is that the growth velocity does not depend on the magnitude of the van der Waals attraction (which is providing the driving force for the growth). We will return to this point later. For a typical vesicle with \( R \sim 10^{-3} \) cm, we find \( U \sim 10^{-4} \) cm/sec if \( \eta = 10^{-2} \) Poise (water) and \( K \sim k_B T \). The order of magnitude of \( U \) is thus in a reasonable range.

Deep inside the tube, \( r(z) \) varies little. The dominant contribution to the Helfrich pressure is the \( 1/r^2 \) term in Eq.7. Neglecting the other terms in \( P_H \) but including \( P_{VDW} \) gives for Eq.10:

\[
\frac{dr}{dx} = \frac{6}{3} \frac{nU}{(K - \frac{A}{\eta})} r^2 \quad (r \leq \lambda) \tag{14a}
\]
\[
\frac{dr}{dx} = \frac{4nU}{\left[ \frac{3}{2}K - \frac{4}{\pi} R \right]} r^2 \quad \text{[} r \geq \lambda \text{]} \quad (14b)
\]

Only solutions with \(dr/dx < 0\) are allowed so for \(r \geq \lambda\) we must demand that \\
\[K < \frac{8R}{3\pi r} \quad (\text{i.e. } r \leq R^*) \text{ while for } r \leq \lambda, \text{ we must demand } K < \frac{A}{\pi}.\] \\

The shape of the tube for \(r \geq \lambda\) is given by the solution of Eq.14b:

\[
r(x) = \frac{4B}{n} \left[ \frac{3}{2}K + \left( \frac{9}{4}K^2 + \frac{32B}{\pi} nU(x + x_0) \right) \right]^{1/2} \quad \left[ R^* \leq r \leq \lambda \right] \quad (15)
\]

with \(x_0\) an integration constant. To determine \(x_0\), we match Eq.15 with Eq.12 around \(r(x) \sim R^*\), i.e. around \(x = -x_0\) since \(R^* \sim B/K\). The result is that \\
\[x_0 \sim -(R^* R^2)^{1/3}\], using Eq.13.

For \(r \leq \lambda\), we must use Eq.14a:

\[
r(x) = \frac{3(\lambda - K)}{8nU} \left( \frac{1}{x + x'} \right) \quad \left[ r \leq \lambda \right] \quad (16)
\]

with \(x_0'\) determined by matching Eqs.15 and 16 around \(r = \lambda\).

The tube-shape described by Eqs.15 and 16 has a cross-section of order \(R^*\) over a rather large distance. Using Eq.15, \(r\) is of the order of \(R^*\) for \(x \leq R^2/R^*\) using Eq.13. Since \(R \gg R^*\), the tube length would be quite large compared to \(R\). Actually, the tube length is unlikely to get that large. The vesicle is not really a reservoir into which we can pump just any amount of solvent.

Because of its fixed surface area a vesicle can swell by only a small amount. Eventually the vesicle will be perfectly spherical and further flow from the tube is prevented (barring mass transport across the membrane). In the absence of flow, we saw that there can be no further increase in \(L\) or decrease in \(r\). The maximal extension of the tube will depend on how "wrinkled" the initial surface is of the vesicle because of thermal fluctuations. Another limitation
on L is set by the Rayleigh instability which we will discuss now.

IV. RAYLEIGH INSTABILITY FOR MEMBRANES

To investigate whether membranes can exhibit a Rayleigh instability, we start with a cylindrical vesicle of radius $R > \lambda$. The internal pressure in the tube is assumed to be adjusted to compensate for curvature and van der Waals forces. Now add a small perturbation in the tube radius:

$$r(z,t) = R + \epsilon(z,t)$$  \hspace{1cm} (17)

Since the surface area must be kept fixed, the average value $R$ of $r$ is unchanged. The induced pressure variation is then (see Eqs. 7 & 8):

$$P(\epsilon) = K \frac{d^4\epsilon}{dz^4} - \left[ \frac{4B}{\pi R^3} - \frac{3K}{2R^4} \right] \epsilon$$  \hspace{1cm} (18)

Inserting Eq.17 in Eq.6 gives

$$\frac{\partial \epsilon}{\partial t} = \frac{R^3}{8\eta} \left\{ K \frac{d^6\epsilon}{dz^6} + \left( \frac{3K}{2R^4} - \frac{4B}{\pi R^3} \right) \frac{d^2\epsilon}{dz^2} \right\}$$  \hspace{1cm} (19)

A periodic modulation $\epsilon(z,t) = e^{i\omega_\kappa t} \cos kz$ is a solution if

$$\omega_\kappa = \frac{R^3}{8\eta} K \left\{ \frac{4B}{\pi R^3} - \frac{3K}{2R^4} - Kk^4 \right\}$$  \hspace{1cm} (20)

By maximizing $\omega_\kappa$ we find the most rapidly growing mode. Setting $\partial \omega_\kappa / \partial k^* = 0$ gives for the associated wavevector

$$k^* = \left( \frac{3(\frac{R^*}{R} - 1)}{R} \right)^{1/4}$$  \hspace{1cm} (21)
with $R^* = 8B/3\pi$ as before. The wavelength of the instability is thus of order $R^* = 8B/3\pi$ just as for the "true" Rayleigh instability. Note that $k^{-1}$ diverges as $R$ approaches $R^*$. For $R > R^*$ there is no instability.

The growth rate of the instability is of order $B/R^4\eta$. For $R \sim .1$ micron, this is of order $10^2$ sec$^{-1}$ — relatively rapid. Of course, for later times we cannot really use linear stability analysis but by analogy with the Rayleigh instability we expect eventually to find an array of spherical vesicles with a radius of order $R$.

V. SUMMARY AND CONCLUSION

We can summarize our main results as follows:

(i) Vesicles are unstable against the growth of tubular protrusions if $K \leq A/\pi$.

(ii) The characteristic size of the protrusions is $R^* = 8B/3\pi K$ while the growth velocity is $U \sim K/\eta R$ — with $R$ the vesicle radius.

(iii) A tube with a radius $r_0 \leq R^*$ has a Rayleigh-type instability with a wavelength of order $r_0$.

Our result (ii) gives $R^* \approx .1$ micron and $U \approx 1$ micron/second both of which have the right order of magnitude. The stiffness constant was not known in Evans' experiment so (i) cannot be checked but for typical stable membranes, $K \approx 10^{-19}$ J. which easily obeys the stability criterion $K \geq A/\pi$. Concerning (iii), the observed wavelength of the Rayleigh-type instability was indeed of the order of the tube radius. These results show that membranes which form a boundary between solvents of different dielectric constants, have "short-wavelength" instabilities at low $K$ not driven by thermal fluctuations but instead by competition between curvature energy and van der Waals self-energy.

Despite these encouraging results, it is important to emphasize that we
made a number of rather serious approximations and simplifications. First of all, we used the Helfrich curvature free energy (Eq. 1). During our discussion, we actually were investigating the short-distance behavior of membranes. In general, there will be for small radius \( r \) correction terms to Eq.7 proportional to \( 2mr \left( \frac{1}{r^2} \right) \) with \( p = 2, 4, \ldots \). For small \( r \), such terms will eventually exceed the van der Waals attraction, say at a distance \( d \). Obviously, if \( d > R^* \) our instability mechanism fails. These same non-linear terms could also stabilize small-size vesicles. Estimating \( d \) seems rather difficult and we implicitly assumed \( d \) to be of a molecular size.

We have made a number of other simplifications:

1. We neglected electrostatic forces and hydration forces which could overcome the van der Waals attraction at short distances;
2. We only constructed steady-state solutions for the growing tube. We did not provide a nucleation mechanism. The nucleation barrier which must be overcome should not be large compared to \( k_B T \).
3. We neglected thermal fluctuations. The fact that \( W \sim K \) is an important threshold for the growth process suggests similarities with the unbinding transition of lamellar membranes where \( W \sim 10 K \) provides a threshold.\(^9\) Thermal fluctuations play a very important role in that case. The effect of thermal fluctuations in our case would crudely be to make the stiffness constant \( K \) dependent on the tube radius \( r \) and to provide a repulsive force for small \( r \).

Using standard arguments, we expect \( K(r) = K_R - k_B T \ln (r/R) \) with \( K_R \) the stiffness constant of the vesicle. The stiffness constant thus increases as the tube size decreases. The stiffness constant \( K_R \) of a vesicle with \( R < \xi \) is expected to be of order \( K_R = K_0 - k_B T \ln \left( R/a_0 \right) \) with \( a_0 \) a microscopic length and \( K_0 \) the "bare" curvature energy. Assume now \( K_0 \gg A/\pi \). Vesicles with \( K_R < A \) can grow tubes with \( r(z) > d \) where
The tube radius can however not shrink to zero since for \( r < d \), \( K(r) \) will exceed \( A \) even if \( K_R \) does not. Large thermal fluctuation could, as mentioned, lead to competing long-wavelength instabilities.\(^1\) On the basis of Evans' observations we concentrated on short-distance instabilities and ignored this possibility.

Our discussion of membrane stability was patterned on the theory of precursor spreading.\(^8\) Precursors are thin films spreading out of drops of fluid on a substrate which is wetted by the fluid. As in the present case, the van der Waals force is believed to lie at the origin of the precursor instability. Our peculiar result that the growth velocity \( U \) is independent of the Hamaker constant was also found to be true for precursor spreading. The reader is referred to Ref.\(^8\) for a further discussion of this strange fact. An important difference with precursor spreading is that in that case the van der Waals force thickens the film while in our case it led to a thinning of the tube.

The most easily experimentally accessible predictions concern the growth velocity \( U \) (Eq.13) and the wavevector \( k^* \) of the membrane analog of the Rayleigh instability. In particular, it would be very interesting if \( \Delta \varepsilon = \varepsilon_A - \varepsilon_B \) could be varied since the growth velocity \( U \) is predicted to be independent of the Hamaker constant which is proportional to \( \Delta \varepsilon^2 \). On the other hand, by tuning \( \Delta \varepsilon \) one could adjust the stability condition \( A < K \). One could even speculate whether the budding instability occurs in biological vesicles with \( \Delta \varepsilon \) as the control parameter.
ACKNOWLEDGMENTS

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Fig. 1 Tubular instability appearing on the surface of spherical vesicle of radius R. The bud is rotationally invariant around the z axes. The tube grows by a flow $\mathbf{v}(\rho, z)$ from the tube into the vesicle.
APPENDIX A: Van der Waals Interaction

Assume we have a closed vesicle of arbitrary shape. Let "A" denote interior solvent molecules and "B" exterior solvent molecules. The non-retarded van der Waals energy of the vesicle in the de Boer-Hamaker approximation is:

\[
F_{\text{vdw}} = -\frac{W_{AA}}{2} \int_A d^3r_1 \int_A d^3r_2 \frac{1}{|r_1 - r_2|^6} - \frac{W_{BB}}{2} \int_B d^3r_1 \int_B d^3r_2 \frac{1}{|r_1 - r_2|^6} - \frac{W_{AB}}{2} \int_A d^3r_1 \int_B d^3r_2 \frac{1}{|r_1 - r_2|^6}
\]

with \(W_{AA}\), \(W_{AB}\), and \(W_{BB}\) the appropriate energy scales for respectively AA, BB and AB interaction. All integrals must be evaluated with a cut-off \(|r_1 - r_2| > d\) where \(d\) is a molecular length. Define

\[
C(d) = \int_{|r| > d} d^3r \frac{1}{|r|^6}
\]

and rewrite Eq. A1 as

\[
F_{\text{vdw}} = - \left( \frac{W_{AA}}{2} V_A + \frac{W_{BB}}{2} V_B \right) C(d) + \left( \frac{W_{AA}}{2} + \frac{W_{BB}}{2} - W_{AB} \right) \int_A d^3r_1 \int_B d^3r_2 \frac{1}{|r_1 - r_2|^6}
\]

with \(V_A\) the total volume of A solvent and \(V_B\) that of B solvent. We thus can interpret \(-\frac{W_{AA}}{2} C(d)\) and \(-\frac{W_{BB}}{2} C(d)\) as contributions to the chemical
potentials of the solvent molecules inside and outside the vesicle. By assumption there is no osmotic pressure drop across the membrane so we can drop them.

For two plates separated by a distance \( \ell \), Eq.A3 is easy to evaluate:

\[
F_{\text{VDW}}/S = \frac{\pi}{6} \left( \frac{W_{AA}}{2} + \frac{W_{BB}}{2} - W_{AB} \right) \left\{ \frac{1}{d^2} - \frac{1}{\ell^2} \right\}
\]

with \( S \) the surface area. This must reduce to the well known result

\[
F_{\text{VDW}}/S = -\frac{W}{12\pi \ell^2} + \text{constant}
\]

with \( W \) the Hamaker constant. We thus identify

\[
\frac{W_{AA}}{2} + \frac{W_{BB}}{2} - W_{AB} = W/2\pi^2
\]

Approximately, \( W_{AA} \propto \varepsilon_A^2 \), \( W_{BB} \propto \varepsilon_B^2 \) and \( W_{AB} \propto \varepsilon_A \varepsilon_B \) while \( W \propto (\varepsilon_A - \varepsilon_B)^2 \).

Next we go to a tube of cross-section \( r \), length \( L \). Then

\[
\frac{F_{\text{VDW}}}{L} = \int_0^L 2\rho d\rho f(\rho)
\]

with

\[
f(\rho) = \frac{W}{2\pi^2} \int_0^{2\pi} \int_0^r \rho^2 d\rho d\phi\left[ \rho^2 + \rho^2 - 2\rho \rho' \cos(\phi) + z^2 \right]^{-3}
\]

the energy density. This integral is a hypergeometric function, so is difficult to obtain \( F_{\text{VDW}} \) in closed form. Numerical evaluation cannot be used because the integral in Eq.A7 is strongly divergent at \( \rho=r \). To circumvent
this problem, we expand first \( f(p) \) in powers of \( p \):

\[
f(p) \equiv \frac{W}{r^3} \left\{ \frac{1}{8} + \frac{15}{32} \left( \frac{p}{r} \right)^2 + \mathcal{O} \left[ \left( \frac{p}{r} \right)^4 \right] \right\}
\]

The series contains only even powers. Next, for \( p \) close to \( r \) it is easy to show that \( f(p) \) reduces to the standard expression of Derjaguin:

\[
f(p) \equiv \frac{W}{12\pi} \frac{1}{(r - p)^3} + \cdots
\]

Equation A10 is not of the analytic form indicated by the power series Eq.A9 as it contains odd powers of \( p/r \). It is simple to rewrite Eq.A10 to avoid this problem:

\[
f(p) \equiv (2/3\pi) \frac{W}{r^3} \left\{ C + \left( \frac{1}{1 - (p/r)^2} \right)^3 \right\}
\]

with \( C \) an undetermined constant. We choose \( C \) by demanding that \( f(0) = W/8r^3 \) (see Eq.A9) so \( C = (3\pi/16 - 1) \). Now, \( f(p) \) has the limiting form of Eq.A10 without violating the form imposed by Eq.A9. If we expand Eq.A11 in powers of \( p/r \) then we find that coefficient \( 2/\pi \) of the \( (p/r)^2 \) term is close to the correct value \( 15/32 \). The coefficient of the zero order term is the correct \( 1/8 \) by construction. We conclude that Eq.A11 is a reasonable approximation to \( f(p) \) for all \( p \) in the range \( 0 \) to \( r \).

Performing the integral in Eq.A7 gives:

\[
\frac{F_{\text{vdw}}}{L} = C' \frac{W}{d^2} - (1-\pi/8) \frac{W}{r}
\]

with \( C' \) a constant.
The first term in Eq. A12 is proportional to the surface area \( L_r \). It is thus a contribution to the surface energy. The total surface tension is assumed zero so we can drop the term. The remaining term is the second term of Eq. 2 where we assumed \( r(z) \) to be slowly varying with \( z \) on a scale of order \( r \).

The reason why the van der Waals pressure is inhomogeneous follows from the condition of hydrostatic equilibrium

\[
\frac{\partial P}{\partial \rho} = - \frac{\partial f}{\partial \rho} \tag{A18}
\]

with our free energy density. It follows from Eq. A11 that \( P \) is very large near \( \rho = r \).