

Endocytosis analysis

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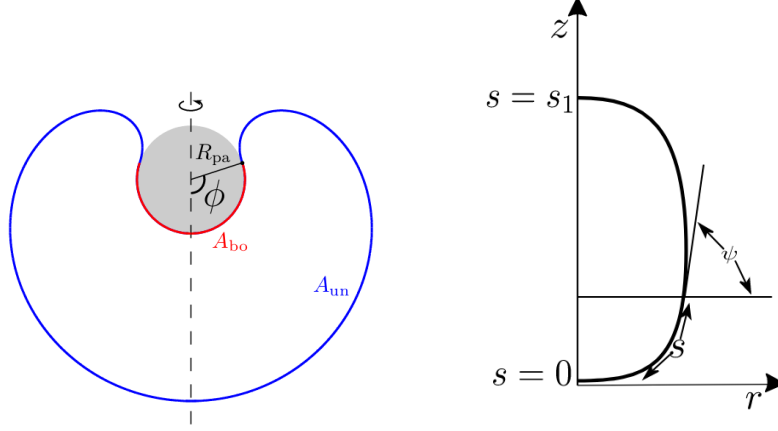
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1 Introduction

This part follows closely what has been done by the supplementary material of [1]. The code is adapted from [3] and from supplementary materials of [2]. The total free energy of the system will be composed by two contribution representing the bound and unbound segment:

$$E = E_{bo} + E_{un}$$



(a) image taken from supplementary material of [1]

The bound segment of the membrane will follow the particle contour but the unbound segment does not have a trivial shape.

E_{bo} has an adhesive and a bending energy contribution: [1]

$$E_{bo} = (-2\pi|W|R_{pa}^2 + 4\pi k(1+mR_{pa})^2)(1-\cos\phi) = (-2\pi|W|R_{pa}^2 + 4\pi k)(1-\cos\phi)$$

we are considering a vesicle bilayer with zero spontaneous curvature, ie $m = 0$.

In order to find the shape of the unbound segment that minimizes E_{un} , for a fixed value of contact angle ϕ , and satisfies the constraints on the total membrane area $A - A_{bo}$ and enclosed volume $V + V_{bo}$ of the vesicle, we must minimize the shape functional

$$F = E_{un} + \Sigma(A - A_{bo}) - \Delta P(V + V_{bo}) = \int_{A_{un}} dA 2kH^2 + \Sigma(A - A_{bo})$$

where $\int_{A_{un}} dA 2kH^2$ is the Helfrich energy integral.

In our simulations we dont have any control or constraint on the vesicle volume, we dont pay a cost to change the vesicle volume then we put the volume term equal to zero.

Assuming that the vesicle shape will be axis-symmetric around z-axis It is possible to rewrite F in terms of $s, \psi(s), x(s)$:

$$F = \int_{s_0}^{s^*} L(s, \psi(s), x(s)) ds$$

The mean curvature H is given by

$$H = \frac{1}{2}(C_1 + C_2)$$

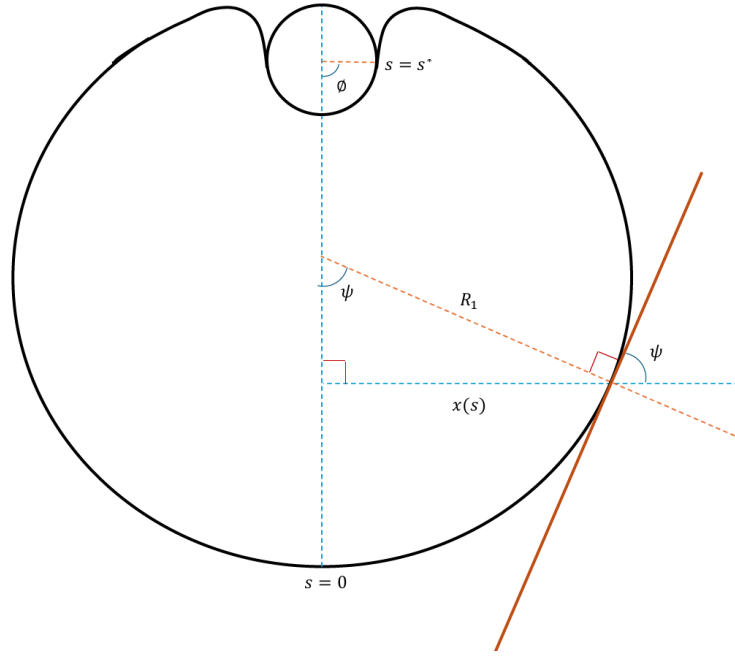


Figure 2: Visualization of the curvature

From figure 2 follows that:

$$C_1 = \frac{1}{R_1} = \frac{\sin \psi}{x(s)}$$

C_2 is given by the definition of curvature: the rate at which ψ changes with respect to the arc length s , which gives:

$$C_2 = \frac{d\psi}{ds}$$

Note: I think that C_1 defines the curvature straight into (or out of) the paper, and C_2 defines the curvature in the direction of s . These two curvatures together give the mean curvature:

$$H^2 = \frac{1}{4} \left(\frac{d\psi}{ds} + \frac{\sin \psi}{x(s)} \right)^2$$

Now we will parameterize F in terms of $s, \psi(s), x(s)$

$$F = \int_{A_{un}} dA \, 2kH^2 + \Sigma A_{un} = \int_{s_0}^{s^*} L(s, \psi(s), x(s)) \, ds$$

For this step we need to rewrite an integral in terms of dA to an integral in terms of s . To do this we use the following formula:

$$dA = 2\pi x(s) ds$$

applying this formula to F gives:

$$F = \int_{A_{un}} dA \, 2kH^2 + \Sigma A_{un} = \int_{s_0}^{s^*} 2\pi x(s) ds \, 2kH^2 + \Sigma \int_{s_0}^{s^*} 2\pi x(s) ds$$

Now we will add the two integrals together and fill in H :

$$F = 2\pi k \int_{s_0}^{s^*} \frac{x(s)}{2} \left(\dot{\psi} + \frac{\sin \psi}{x(s)} \right)^2 + \frac{\Sigma}{k} x(s) ds$$

To make sure the relation between x and ϕ is satisfied, a Lagrange multiplier is added to the integral.

$$F = 2\pi k \int_{s_0}^{s^*} \frac{x(s)}{2} \left(\dot{\psi} + \frac{\sin \psi}{x(s)} \right)^2 + \frac{\Sigma}{k} x(s) + \gamma(\dot{x} - \cos \psi) ds$$

It is identical to the L that you have except for the k , so maybe I made a mistake somewhere

$$L(s, \psi, \dot{\psi}, x, \dot{x}, \gamma) = \frac{x}{2} \left(\dot{\psi} + \frac{\sin \psi}{x} \right)^2 + \Sigma x + \gamma(\dot{x} - \cos \psi)$$

$\gamma(s)$ is a Lagrange multiplier function that ensure the relation between x and ψ is satisfied.

We want to minimize the functional F using a variational approach $\delta F = 0$. δF denotes variation with respect to the shape of the vesicle and Σ and P are adjusted in order to guarantee the prescribed area and volume. After the minimization you end up with a system of differential equations that once solved it will describe the vesicle shape.

To draw a parallelism it is the same procedure of minimizing the action functional in classical mechanics respect to a trajectory.

More formally: The solution of the minimization of functional F is given by the Euler-Lagrange equations (see https://en.wikipedia.org/wiki/Euler%E2%80%93Lagrange_equation). In general, given a functional I :

$$I = \int_{x_a}^{x_b} L(x, f_1(x), f_2(x), \dots, \dot{f}_1(x), \dot{f}_2(x), \dots)$$

where $\dot{f}_i(x) = \frac{df_i}{dx}$ the Euler-Lagrange equations are:

$$\frac{d}{dx} \left[\frac{\partial L}{\partial \dot{f}_i} \right] - \frac{\partial L}{\partial f_i} = 0$$

In our case, the equations will be:

$$\frac{d}{ds} \left[\frac{\partial L}{\partial \dot{\psi}}(s, \psi, \dot{\psi}, x, \dot{x}, \gamma) \right] - \frac{\partial L}{\partial \psi}(s, \psi, \dot{\psi}, x, \dot{x}, \gamma) = 0$$

Hamiltonian function: It is possible to define an "Hamiltonian function":

$$H = -L + \dot{\psi} \frac{\partial L}{\partial \dot{\psi}} + \dot{x} \frac{\partial L}{\partial \dot{x}} = \frac{x}{2} \left[\dot{\psi}^2 - \frac{\sin^2 \psi}{x} \right] - \Sigma x + \gamma \cos \psi$$

H is conserved because $\frac{\partial L}{\partial s} = 0$. It also leads to the boundary condition for $\gamma(s)$ see eqs 3.7 from [4].

This Hamiltonian is an "energy" function too.

1.1 Physical quantity of the system

The following ones are the physical quantities or the constitutive relations involved in our system of interest:

- R_{pa} particle radius

- $|W|$ adhesive energy density for area unit
- R_{ve} radius of vesicle
- k bending rigidity

We can describe the system using two adimensional quantity:

$$r_{pa} = \frac{R_{pa}}{R_{ve}}$$

$$w = \frac{|W|R_{pa}^2}{k}$$

2 Shape ODE system

The following is the set of differential equation needed to describe the equilibrium shape of a membrane that interacts with an external particle. This system of equation is:

- ordinary because the independent variable is always \bar{s} .
- First order because all the derivatives are first derivative
- Non linear because of non linear terms like squares or trigonometric functions.
- it is a system because the dependent variables are coupled.

$$\begin{cases} \frac{d\psi}{ds} = u \\ \frac{du}{ds} = \left[-\frac{u}{x} \cos \psi + \frac{\cos(\psi) \sin(\psi)}{x^2} + \frac{\gamma \sin \psi}{2\pi k x} \right] \\ \frac{d\gamma}{ds} = \left[\pi k \left(u^2 - \frac{\sin^2 \psi}{x^2} \right) + 2\pi \Sigma \right] \\ \frac{dx}{ds} = \cos \psi \end{cases} \quad (1)$$

2.1 Non-dimensionalization step

$$R_{ve} = \sqrt{\frac{A}{4\pi}}$$

Given R_{ve} as length scale, k as basic energy scale and s^\star as the bound arc length we can rewrite our equation in a unitless form:

The dash symbols are the unitless quantities. **write in a better way, maybe in a table**

$$\bar{\psi} = \psi$$

$$\bar{u} = uR_{ve}$$

$$\bar{x} = \frac{x}{R_{ve}}$$

$$\bar{\gamma} = \gamma R_{ve}$$

$$\bar{\Sigma} = \Sigma \frac{R_{ve}^2}{k}$$

$$\bar{A} = \frac{A}{4\pi R_{ve}^2}$$

$$\bar{V} = \frac{3V}{4\pi R_{ve}^3}$$

$$\bar{s} = \frac{s}{s^\star}$$

$$s^\star = \frac{s^\star}{s^\star} = 1$$

$$\Omega = \frac{s^\star}{R_{ve}}$$

Substitute in the system we get:

$$\begin{cases} \frac{d\bar{\psi}}{d\bar{s}} = \Omega \bar{u} \\ \frac{d\bar{u}}{d\bar{s}} = \Omega \left[-\frac{\bar{u}}{\bar{x}} \cos \bar{\psi} + \frac{\cos(\bar{\psi}) \sin(\bar{\psi})}{\bar{x}^2} + \frac{\bar{\gamma} \sin \bar{\psi}}{2\pi k \bar{x}} \right] \\ \frac{d\bar{\gamma}}{d\bar{s}} = \Omega \left[\pi k (\bar{u}^2 - \frac{\sin^2 \bar{\psi}}{\bar{x}^2}) + 2\pi \bar{\Sigma} k \right] \\ \frac{d\bar{x}}{d\bar{s}} = \Omega \cos \bar{\psi} \end{cases} \quad (2)$$

2.2 Initial conditions and parameters

We ended up with 5 ODEs, we have five boundary conditions at the South Pole ($s = 0$):

$$\psi(s = 0) = 0, u(s = 0) = u_0, \gamma(s = 0) = 0$$

$$x(s = 0) = 0, A(s = 0) = 0$$

Explanation of BCs: Hamiltonian $H(s = 0) = 0$ and substituting the value for ψ, x I obtain $\gamma(s = 0) \cos(\psi(s = 0)) = 0$ and then $\gamma(s = 0) = 0$.

Assuming that H is conserved ([how to verify?](#)), $H(s = s^*) = 0$ but I cannot solve the system of eq (4 unknown, 1 equation).

What I get is

$$\gamma^* = \frac{1}{2} \frac{1}{\cos \psi^*} (\sin^2 \psi^* + 2\Sigma x^* - u_{\star}^2 x^*)$$

We also have 5 boundary conditions at the North Pole $s = s^*$, the first three are known:

$$\bar{\psi}(s^*) = \pi + \phi$$

$$\bar{x}(s^*) = \frac{R_{pa}}{R_{ve}} \sin \phi = r_{pa} \sin \phi$$

$$\bar{u}(s^*) = \frac{R_{ve}}{R_{pa}} = \frac{1}{r_{pa}}$$

Oss: We dont have an equation for the volume because in simulation we are not constraining it and there is no energy cost in changing vesicle internal volume.

Then, we have 3 unknown parameters ("randomly" guessed at the beginning of the integration procedure):

$$\Sigma, s^*, u_0$$

3 Numerical protocol

3.1 How (Pietro thinks) it works

- assuming that the constitutive relations of the system r_{pa} and w are given and we know its values.
- you will choose a value for ϕ the wrapping angle and you will know the A_{bo} this is actually what concern me more, I would like to include the wrapping angle not as a given parameter!!
- now you have everything to calculate the bound free energy E_{bo}
- shooting method for the unbound shape:
 - you will start with choosing random free parameters Σ , s^* and u_0
 - you will integrate the ODE system having the initial conditions for ψ, u, γ, x, A
 - after the integration you calculate the residuals as the error between the boundary conditions at $s = s^*$
 - the idea is to iterate the integration procedure to minimize the residuals and finding the optimal value of the free parameters.
- calculate the total free energy of the system
- establish if the total free energy is a minimum/stable state for the chosen combination of constitutive relations and contact angle ϕ .

Oss: the values obtained for the free parameters changes when you change the angle ϕ . in the same way the free parameters changed in the Felix paper when he changed m and ν .

4 Expansion at the South pole

At $s = 0$ $x(s)$ goes to zero and it appears as denominator and it leads to divergences causing numerical instability. An easy way to solve this is to regularize the functions at the "South pole" when $s = 0$. Regularization means Taylor expansion of all functions around $s = 0$.

First you need to expand $x(s), \psi(s), u(s), \gamma(s)$ and substitute the expansion in each equation (both sides) of the system. Then equating the coefficient of the polynomials you can get the series coefficient.

$$u(s) = u(0) + u_1 s + \frac{u_2}{2} s^2 + \frac{u_3}{6} s^3 + \frac{u_4}{24} s^4 + O(s^4)$$

$$\cos(\psi(s)) = 1 - \frac{\psi(s)^2}{2} + \frac{\psi(s)^4}{24} = 1 - \frac{1}{2} U_0^2 s^2 + \frac{U_0 \psi_2}{2} s^3 + \left(\frac{\psi_2^2}{8} + \frac{U_0 \psi_3}{6} \right) s^4 + O(s^4);$$

Considering the simplest (and not trivial) equation from our system $\frac{dx}{ds} = \cos \psi$ and performing this substitution we'll get the coefficients for x expansion:

$$x_1 = 1, \quad x_2 = 0, \quad x_3 = -u_0^2, \quad x_4 = 0$$

$$x(s) = s - \frac{s^3 u_0^2}{6};$$

The another equations from the system are quite challenging to deal on pen and paper and for that we have used a Mathematica script to perform the expansion. The final values for the coefficient are:

$$x_1 = 1, \quad x_2 = 0, \quad x_3 = -u_0^2, \quad x_4 = 0$$

$$\begin{aligned} \psi_1 &= u_0, \quad \psi_2 = 0, \quad \psi_4 = 0 \\ \psi_3 &= \frac{3\gamma_1 u_0 - 4\pi k u_0^3}{2\pi k} = \frac{6\pi \Sigma u_0 - 4\pi k u_0^3}{2\pi k} \end{aligned}$$

$$\gamma_1 = 2\pi \Sigma, \quad \gamma_2 = 0$$

$$\gamma_3 = \frac{4}{3} k \pi \psi_3 u_0 = 4\pi \left(\Sigma u_0 - \frac{2}{3} k u_0^3 \right), \quad \gamma_4 = 0$$

In the end the values for area and volume are not needed because we are not considering ODE for area and volume

$$A_1 = 0, A_2 = 2\pi, A_3 = 0, A_4 = -2\pi u_0^2$$

$$V_1 = 0, V_2 = 0, V_3 = 0, V_4 = 6\pi u_0$$

Then if you want to reconstruct the series:

$$x(s) = x_1 s + \frac{x_2}{2} s^2 + \frac{x_3}{6} s^3 + \frac{x_4}{24} s^4 = s - \frac{u_0^2}{6} s^3$$

$$A(s) = \pi s^2 - \frac{\pi u_0^2}{12} s^4$$

$$V(s) = \frac{\pi u_0}{4} s^4$$

$$\gamma(s) = 2\pi \Sigma s + \frac{2}{9} k \pi \psi_3 u_0 s^3 = 2\pi \Sigma s + \frac{1}{9} u_0 (6\pi u_0 \Sigma - 4k u_0^3) s^3$$

$$\psi(s) = u_0 s + \frac{3\Sigma u_0 - 2k u_0^3}{6k} s^3$$

$$\begin{aligned} u(s) &= u(0) + u_1 s + \frac{u_2 s^2}{2} + \frac{u_3 s^3}{6} + \frac{u_4 s^4}{24} = u_0 + \psi_2 s + \frac{\psi_3 s^2}{2} + \frac{\psi_4 s^3}{6} + \frac{\psi_5 s^4}{24} \\ &= u_0 + \frac{3\Sigma u_0 - 2k u_0^3}{2k} s^2 \end{aligned}$$

This expansions still need to be non-dimensionalized.

4.1 Non-dimensionalization of the expansion

Again the dash symbols are the unitless quantities and we applied the same trasformations previously used.

$$\bar{x}_1 = \Omega, \bar{x}_3 = -\Omega^3 \bar{u}_0^2$$

$$\bar{\psi}_1 = \Omega \bar{u}_0$$

$$\bar{\psi}_3 = (3\bar{\Sigma}\bar{u}_0 - 2\bar{u}_0^3)\Omega^3$$

$$\bar{u}_0 = \bar{u}_0$$

$$\bar{u}_1 = \frac{\Omega^2}{2}(3\bar{u}_0\bar{\Sigma} - 2\bar{u}_0^3)$$

$$\gamma_1 = 2\pi\bar{\Sigma}k\Omega$$

$$\gamma_3 = \frac{4}{3}\pi k\bar{u}_0\Omega^3(3\bar{\Sigma}\bar{u}_0 - 2\bar{u}_0^3)$$

$$\bar{V}_4 = \frac{9}{2}\bar{u}_0\Omega^4$$

$$\bar{A}_2 = \frac{1}{2}\Omega^2, \bar{A}_4 = -\frac{1}{2}\bar{u}_0^2\Omega^4$$

4.2 Expansion at North Pole

Our problem is different from [3] because we are not integrating from South-pole $s = 0$ to the Northpole where we have again divergence caused from the radius $x(s = 1) = 0$.

In our problem we will integrate from $s = 0$ to the contact point between particle and vesicle. this contact point is not that close to the z-axis (rotational simmetry axis) such that $x(s^*) \neq 0$ and not leading to any divergence.

It should be enough to just check after having set the constitutive relation if $x(s^*)$ is big enough to not lead to divergences. Felix sets this threshold around 0.035.

4.3 Doubts and Questions

Reasonable values for r_{pa} and w : How can I choose them ????

Rank of the least squares system?? check how many free parameters and/or initial conditions I should have to have well posed problem for least squares

South expansion for u : how can we assume that $u(0) = 0$ if we dont know the value u_0 ???

Volume ODE : why or why not having a diff equation for volume???

A Jacobian Matrix

This ODE system now is written in the standard form:

$$\frac{d}{d\bar{s}}\mathbf{Y} = \mathbf{f}(\mathbf{Y})$$

where

$$\mathbf{Y} = (\bar{\psi}, \bar{u}, \bar{\gamma}, \bar{x}, \bar{A}, \bar{V})$$

and

$$\mathbf{f} : \mathbb{R}^6 \rightarrow \mathbb{R}^6$$

The Jacobian is needed for the algorithm used by Felix but in principle with Runge-Kutta methods is not needed because it is calculated by finite difference method.

Oss: Now the following quantities are not dashed but they are already in their adimensional form, so consider for example $\psi(s)$ as $\bar{\psi}(\bar{s})$.

However:

$$\mathbf{J} = \begin{bmatrix} \frac{\partial f_1}{\partial \mathbf{Y}} \\ \frac{\partial f_2}{\partial \mathbf{Y}} \\ \vdots \\ \frac{\partial f_n}{\partial \mathbf{Y}} \end{bmatrix} = \begin{bmatrix} \frac{\partial f_1}{\partial \bar{\psi}} & \frac{\partial f_1}{\partial \bar{u}} & \frac{\partial f_1}{\partial \bar{\gamma}} & \cdots & \cdots \\ \frac{\partial f_2}{\partial \bar{\psi}} & \frac{\partial f_2}{\partial \bar{u}} & \frac{\partial f_2}{\partial \bar{\gamma}} & & \\ \vdots & \vdots & & & \\ \frac{\partial f_n}{\partial \bar{\psi}} & \frac{\partial f_n}{\partial \bar{u}} & \frac{\partial f_n}{\partial \bar{\gamma}} & \cdots & \cdots \end{bmatrix}$$

$$\mathbf{J} = \begin{bmatrix} 0 & a_{12} & 0 & 0 & 0 & 0 \\ a_{21} & a_{22} & a_{23} & a_{24} & 0 & 0 \\ a_{31} & a_{32} & 0 & a_{34} & 0 & 0 \\ a_{41} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & a_{54} & 0 & 0 \\ a_{61} & 0 & 0 & a_{64} & 0 & 0 \end{bmatrix}$$

$$a_{12} = \frac{df_\psi}{du} = \Omega$$

$$a_{21} = \frac{df_u}{d\psi} = \Omega \left(\frac{u}{x} \sin \psi + \frac{1}{x^2} \cos^2 \psi - \frac{1}{x^2} \sin^2 \psi \frac{\gamma}{2\pi k x} \cos \psi \right)$$

$$a_{22} = \frac{df_u}{du} = -\frac{\Omega}{x} \cos \psi$$

$$a_{23} = \frac{df_u}{d\gamma} = \Omega \frac{\sin \psi}{2\pi k x}$$

$$a_{24} = \frac{df_u}{dx} = \Omega \left(\frac{u}{x^2} \cos \psi - 2 \frac{\cos \psi \sin \psi}{x^3} - \frac{\gamma \sin \psi}{2\pi k x^2} \right)$$

$$a_{31} = \frac{df_\gamma}{d\psi} = \Omega \left(-\pi k \frac{\cos \psi}{x^2} \right)$$

$$a_{32} = \frac{df_\gamma}{du} = \Omega \pi k 2u$$

$$a_{34} = \frac{df_\gamma}{dx} = 2\Omega \pi k \sin \psi \frac{1}{x^3}$$

$$a_{41} = \frac{df_x}{d\psi} = -\Omega \sin \psi$$

$$a_{54} = \frac{df_A}{dx} = \Omega$$

$$a_{61} = \frac{df_V}{d\psi} = \Omega \frac{3}{4} x^2 \cos \psi$$

$$a_{64} = \frac{df_V}{dx} = \frac{3}{2} \Omega x \sin \psi$$

References

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- [4] Udo Seifert, Karin Berndl, and Reinhard Lipowsky. Shape transformations of vesicles: Phase diagram for spontaneous- curvature and bilayer-coupling models. 44(2):1182–1202.