In memory of V.B. Prieszhev

On statistical mechanics of closed membranes (vesicles)

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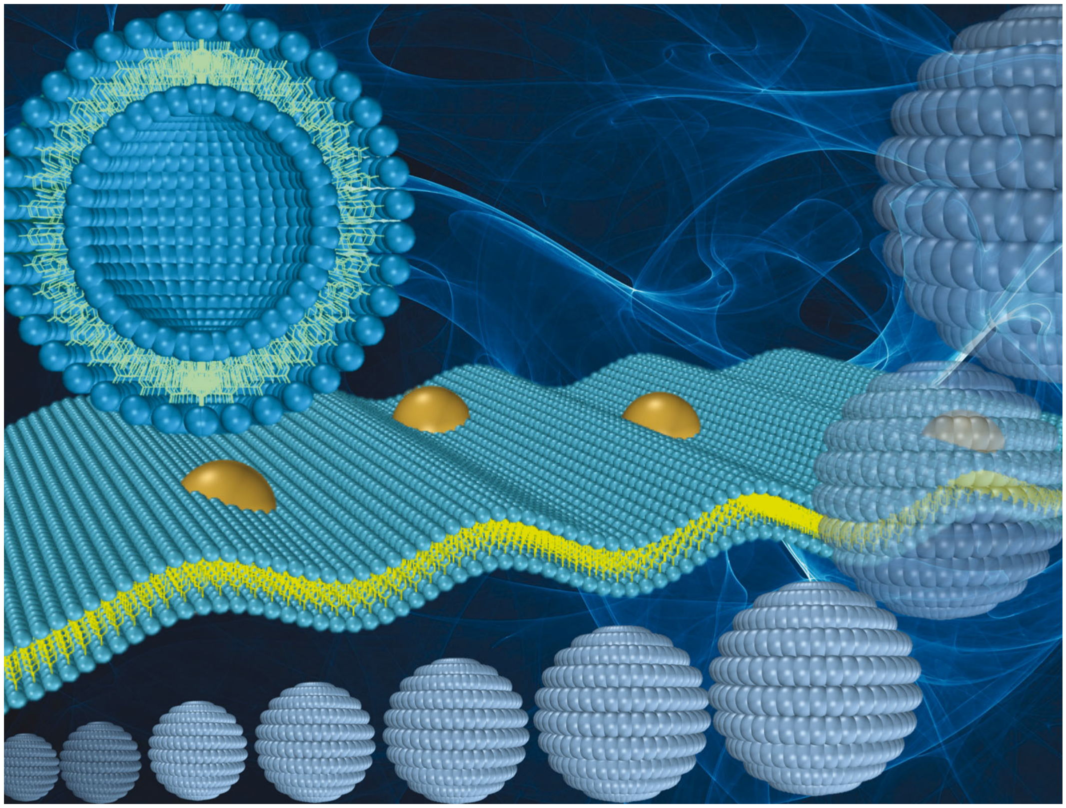
- Biological membranes are ubiquitous in life, and form the envelope through which cells interact with their surroundings.

- Lipid bilayers, which primarily consist of self-assembled phospholipid molecules, often form closed vesicles.

- Aside from fundamental biological studies, lipid-based can be created artificially in the laboratory for applications in drug design and delivery.



The thermodynamic fluctuations of the surface of quasi-spherical membranes is the topic of this talk.

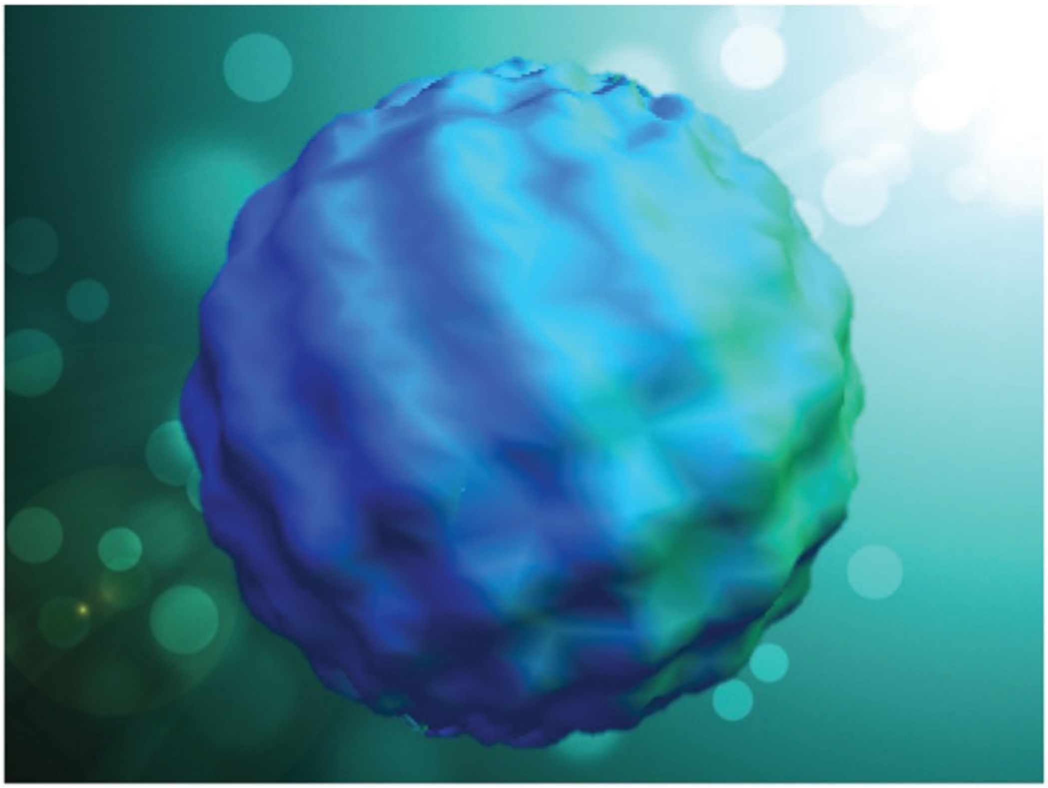
- **membrane's mechanical behavior is reasonably well-described by the phenomenological theory of elasticity (Canham (1970)–Helfrich(1973)'s framework) and just a few continuum parameters such as the bending moduli K_c and surface tension σ.**

- **To transform the basic concept of curvature energy as introduced more than forty years ago into a systematic quantitative theoretical description remained a challenge for quite some time.**

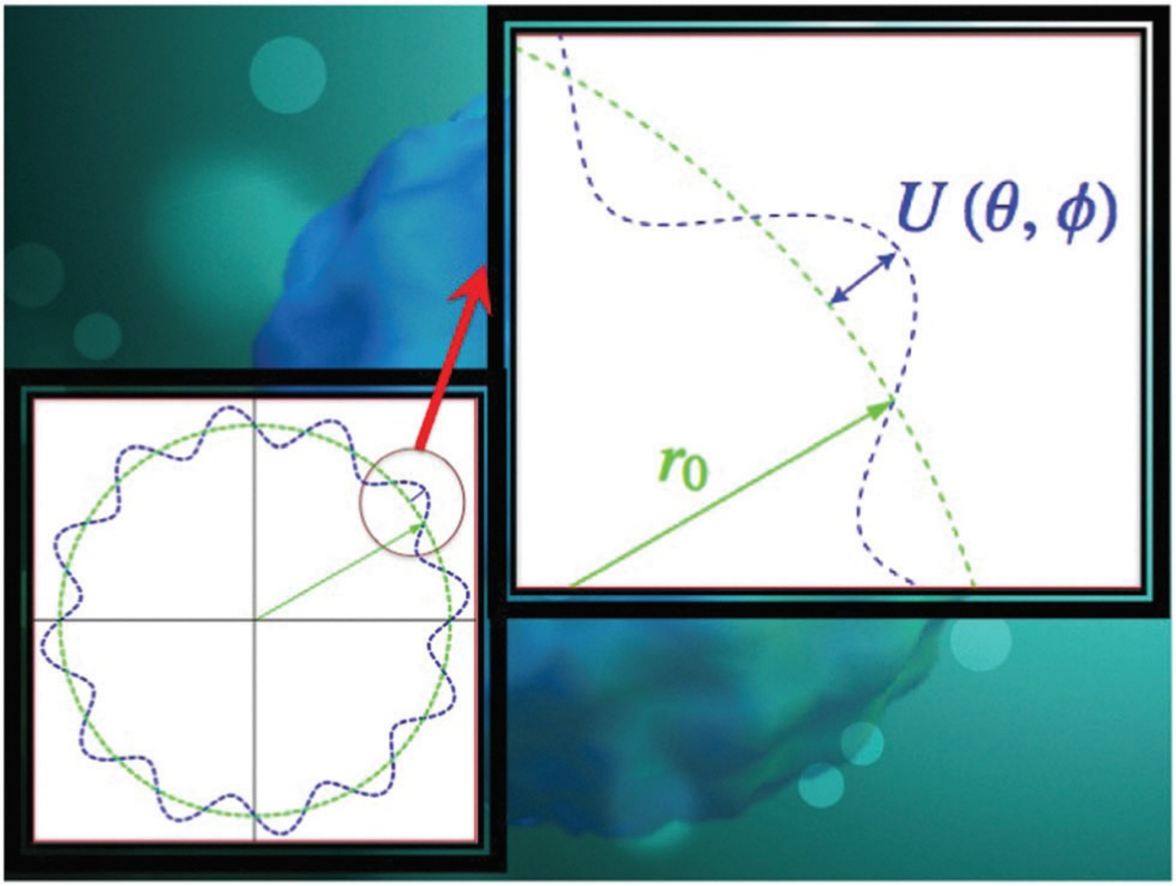
The vesicle shapes obtained by minimizing the appropriate curvature energy subject to the geometric constraints formally correspond to solving a zero temperature problem. Video microscopy reveals that these shapes typically exhibit visible thermal fluctuations.

- Thermal fluctuations one of the cornerstones of biophysical research on membranes.

- How can these fluctuations be described?



Due to the small bending stiffness compared with the thermal energy scale the vesicles undergo considerable undulations at physiological temperatures.



- The displacement field $U(\theta, \phi)$ measures the local deviation from a spherical reference surface.

- In practice, the differential geometry involved is tricky, and taking care of the geometrical constraints is not entirely trivial.

- In phase contrast light microscopy of an ondulating vesicles it is only its cross-section with the focal plane we observe. How do we establish the connection between the 3-d statistical model and the measured 2-d observed contours? This problem was solved and studied by the Bulgarian - French collaboration: Faucon, Mitov, Meleard, Bivas, Bothorel in a series of papers.

- **Let have a** *nearly spherical* **lipid vesicle with** *fixed volume* V **and fixed area !** A**.**

- **Let** r_0 **be the radius of a** *reference sphere* **with the same volume** $V = \frac{4}{3}\pi r_0^3$**.**

- **Let the shape of the membrane fluctuated around the sphere with area** $4\pi r_0^2$**.**

- **Let** $U(\theta, \phi, t)$ **be the modulus of the radius-vector of a point on the surface of the vesicle, with polar coordinates** (θ, ϕ)**, at time** t **in a laboratory reference frame, with origin** O **placed inside the vesicle.**

• **Let us define the dimensionless quantity:**

$$\frac{U(\theta,\phi,t)-r_0}{r_0}=u(\theta,\phi,t), \tag{1}$$

• **The function $u(\theta,\varphi,t)$ is decomposed in a series of spherical harmonics:**

$$u(\theta,\varphi,t)=\sum_{n=0}^{n_{max}}\sum_{m=-n}^{n} u_n^m(t) Y_n^m(\theta,\phi), \tag{2}$$

$Y_n^m(\theta,\phi)$ is the orthonormal basis of the spherical harmonics functions.

The amplitudes $u_n^m(t)$ = ?

What call about them theory and experiment ?

Theory(Milner and Safran (1987),Seifert (1995)): The area constraint restricts fluctuations. This effect can be attributed somewhat phenomenologically to an "effective" or "entropic" surface tension $\overline{\Sigma}_{MS}$:

$$\langle [u_n^m(t)]^2 \rangle = \frac{kT}{K_c} \frac{1}{(n-1)(n+2)[n(n+1)+\overline{\Sigma}_{MS}]}, \quad (3)$$

- K_c is the bending elasticity modulus

- In $\overline{\Sigma}_{MS} = \frac{r_0^2}{K_c}\sigma$ (dimensionless) σ is a Lagrange multiplier which ensures the mean area of the vesicle membrane to be equal to some prescribed value.

Experiment :

- **flicker spectroscopy method**

- **micromechanical manipulation method**

Bivas and co-authors: (1989),(1992), ..., Bulgarian - French laboratory (1997 -2004)... up to now!

Theory and experiment: bending rigidity K_c and "surface tension" constant" $\overline{\Sigma}_{MS}$ are inferred from fitting the experimental data on $u_n^m(t)$ onto the functional given by upper Eq. (3) !

The surface tension

The area functional of the membrane $S(\mathcal{V})$:

$$S(\mathcal{V}) := 4\pi r_0^2 + \Delta S(\mathcal{V}), \tag{4}$$

- $\Delta S(\mathcal{V})$ **is the excess area of the membrane .**

- $\mathcal{V}$ **is used as a shorthand for the real value functions** $(u_2^{-2}, u_2^{-1}, \ldots, u_{n_{max}}^{n_{max}})$**,**

$$\Delta S(\mathcal{V}) = \frac{R^2}{2}\Big[\sum_{n=2}^{n_{max}} \sum_{m=-n}^{n} (n-1)(n+2)(u_n^m)^2\Big]. \tag{5}$$

When the area functional $S(\mathcal{V})$ deviates (after stretching or compression) from the optimal area S_0 the membrane experiences a surface tension

$$\sigma(\mathcal{V}) = K_s \frac{S(\mathcal{V}) - S_0}{S_0}, \qquad (6)$$

where K_s is the area compressibility modulus.

The Hamiltonian:

$$H(\mathcal{V}) = H_c(\mathcal{V}) + H_s(\mathcal{V}), \tag{7}$$

where

$$H_c(\mathcal{V}) = \frac{1}{2} K_c \sum_{n=2}^{n_{max}} \sum_{m=-n}^{n} (n-1)n(n+1)(n+2)(u_n^m)^2 \tag{8}$$

and

$$H_s(\mathcal{V}) = \frac{S_0}{2K_s}[\sigma(\mathcal{V})]^2. \tag{9}$$

Note:

$$\sigma(\mathcal{V}) := L\left(\Big[\sum_{n=2}^{n_{max}} \sum_{m=-n}^{n} (n-1)(n+2)(u_n^m)^2\Big]\right)$$

The Bogoliubov inequalities:

In the case

$$0 \leq f[H] - f[H_{app}(\Sigma)] \leq \langle H - H_{app}(\Sigma)\rangle_{H_{app}(\Sigma)}, \quad (10)$$

where $f[H]$ is the free energy of the Hamiltonian H and $f[H_{app}(\Sigma_{app})]$ is the free energy of a presumably simpler Hamiltonian $H_{app}(\Sigma_{app})$, depending on a variational parameter Σ:

The self-consistent equation:

$$\overline{\overline{\Sigma}} = \overline{\sigma}_0 + \overline{C} \sum_{n=2}^{n_{max}} \frac{2n+1}{n(n+1) + \overline{\overline{\Sigma}}}, \tag{11}$$

$$\overline{\sigma}_0 = \frac{r_0^2}{K_c} K_s \frac{4\pi R^2 - S_0}{S_0}, \tag{12}$$

$$\overline{C} = \gamma K_s \frac{r_0^2}{K_c}, \qquad \gamma \equiv \frac{1}{8\pi} \frac{kT}{K_c}. \tag{13}$$

The fitting functional:

$$\langle (u_n^m)^2 \rangle_{H_{app}(\overline{\Sigma}_{app})} = \frac{kT}{K_c} \frac{1}{(n-1)(n+2)[n(n+1)+\overline{\Sigma}_{app}]}. \qquad (14)$$

- **Here, the MS effective surface tension $\overline{\Sigma}_{MS} = \frac{r_0^2}{K_c}\sigma$ is replaced by $\overline{\Sigma}_{app}$**

- **In MS theory σ was a Lagrange multiplier**

The physical meaning of $\overline{\Sigma}_{app}$:

$$\overline{\Sigma}_{app} \equiv \frac{r_0^2}{K_c} \langle \sigma(\mathcal{V}) \rangle_{H_{app}(\overline{\Sigma}_{app})} , \tag{15}$$

where $\sigma(\mathcal{V})$ is the true (not normalized) tension of the membrane !

Recall:

$$\sigma(\mathcal{V}) = K_s \frac{S(\mathcal{V}) - S_0}{S_0}, \tag{16}$$

The solution of the self-consistent equation

The problem:

$$\sum_{n=2}^{n_{max}} \frac{2n+1}{(n+1/2)^2+\Sigma-1/4} \approx \ln\frac{N}{\Sigma}+\frac{\Sigma}{N}$$
$$+O\left(\frac{1}{N^{1/2}}\right)+O\left(\frac{1}{\Sigma}\right)+O\left(\left[\frac{\Sigma}{N}\right]^2\right), \quad N \approx n_{max}^2 \tag{17}$$

The self-consistent equation may be presented (up to the used approximations) in the form:

$$xe^x = \left(\frac{1}{\overline{\overline{C}}} - \frac{1}{N}\right) N e^{\overline{\sigma}_0/\overline{C}}, \tag{18}$$

where

$$x = \left(\frac{1}{\overline{\overline{C}}} - \frac{1}{N}\right) \overline{\overline{\Sigma}}_{app}. \tag{19}$$

Eq. (18) can be solved in terms of the Lambert function $\mathrm{W}(x)$. Recall that by definition $\mathrm{W}(xe^x) = x$

$$\overline{\overline{\Sigma}}_{app} = \left(\frac{1}{\overline{\overline{C}}} - \frac{1}{N}\right)^{-1} \mathbf{W}\left[\left(\frac{1}{\overline{\overline{C}}} - \frac{1}{N}\right) \overline{\overline{\Sigma}}_{MS} \mathbf{exp}\left(-\frac{\overline{\overline{\Sigma}}_{MS}}{N}\right)\right]. \tag{20}$$

Two limiting cases:

i)

$$\overline{\Sigma}_{app} = \overline{C}\mathbf{ln}\left(\frac{\overline{\Sigma}_{MS}}{\overline{C}}\right), \qquad \frac{\overline{\Sigma}_{MS}}{\overline{C}} >> 1, \tag{21}$$

or

ii)

$$\overline{\Sigma}_{app} = \overline{\Sigma}_{MS}, \qquad \frac{\overline{\Sigma}_{MS}}{\overline{C}} << 1, \tag{22}$$

The fitting functional:

$$\langle (u_n^m)^2 \rangle = \frac{8\pi\gamma}{(n-1)(n+2)\left\{ n(n+1) + \gamma \overline{K}_s \ln \frac{\overline{\Sigma}_{MS}}{\gamma \overline{K}_s} \right\}}, \tag{23}$$

where $\overline{K}_s = \frac{R^2}{K_c} K_s$ is the dimensionless area compressibility modulus. Let us recall that the above equation becomes valid provided that the condition

$$\frac{\overline{\Sigma}_{MS}}{\gamma \overline{K}_s} >> 1, \qquad \gamma \equiv \frac{1}{8\pi} \frac{kT}{K_c}. \tag{24}$$

is fulfilled.

Thank you for the attention !