Analytical and numerical results for the pulsatory liposome

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Abstract: *In this work, we consider a special and interesting bionic object - the pulsatory liposome, which are an unilamellar liposome (lipid vesicle) filled with aqueous solution of osmotic solute. This liposome is introduced in a hypotonic aqueous medium of large dimensions and, due to osmosis process, it has a dynamic and cyclic evolution. The swelling of the liposome during a cycle is described by a differential equation. The liposome relaxing and all the processes which contribute to the liposome relaxing and its coming back to the initial size (pore evolution and internal solution delivery) are described by three differential equations. For each cycle this set of differential equations may be integrated using analytical and numerical methods. The pulsatory liposome can be likened to a biophysical engine. We discuss the results obtained by both methods that we can apply in domains such as astrobiology.*

Key Words: *Pulsatory liposome, astrobiology, biophysical engine, liposome activity life*

1. INTRODUCTION

The liposome is a lipid vesicle formed by one bilayer of phospholipids that separates the external aqueous environment from the internal aqueous medium. Sometimes the lipid bilayer of the liposome is also called the lamella. Liposomes are used as artificial model for cell membrane in biophysical membrane studies [1-5]. The pulsatory liposome is a very interesting bionic object that comes into being due to the process of osmosis [6-8].

Due to the osmosis process the liposome has a cyclic evolution. The lipid vesicle swells to a critical size, when suddenly a transbilayer pore appears. The appearance of the pore

changes the direction of the liposome's evolution. The internal solution drains through this pore, and the liposome deflates until it returns to its initial size. The swelling starts again and a new cycle begins. The liposome goes through a periodic process [1, 3, 9-11]. The evolution of the pore has two phases: first, the radius of the pore increases to its maximum value, then the radius decreases until it disappears when the liposome reaches its initial size. We can easily see that the pulsatory liposome works like a three-stroke engine (liposome swelling, pore radius increase, and pore radius decrease until the pore disappears).

The pulsatory liposome will release an amount (a pulse) of its internal solution during each cycle. If the osmotic solute is a pharmacological substance, the pulsatile liposome can be used in medical applications [9-17]. It is possible that the mechanism of transmembrane pore formation or the working of pulsatory liposomes may have applications in astrobiology [16, 18]

All the processes that contribute to the relaxation of the liposome and its return to the initial size (decrease of the liposome radius, evolution of the pore radius, and reduction of the internal solvent quantity) are described by three differential equations [1-3, 7, 8]. This system of differential equations can be integrated using numerical methods. Based on several analytical methods, we solve these equations and their explicit solutions are validated by comparing them with previous studies results [1, 2].

2. MATHEMATICAL DESCRIPTION OF THE DYNAMIC EVOLUTION OF THE PULSATORY LIPOSOME

The pulsatory liposome has a cyclical evolution determined by the process of osmosis and the appearance of the transbilayer pore.

The dynamic functioning of the pulsatory liposome is determined by the osmosis process and the appearance of the transmembrane pore [1, 2, 4-6].

The evolution of the pulsatory liposome during a cycle is described by the following quantities: the liposome radius, $R(t)$, the pore radius, $r(t)$ and the solute concentration inside the liposome, $C(t)$. Sometimes, instead of the solute concentration, the amount of solute inside the liposome is used, $Q(t)$.

A cycle is characterized by the cycle duration, T, and the amount of solute released ΔQ during the cycle.

Figure 1 shows the evolution of the pulsatory liposome during a cycle.

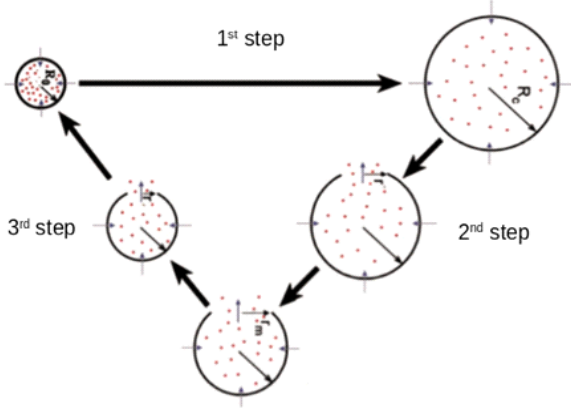

Fig. 1 Stages of pulsatory liposome evolution during a cycle: liposome swelling (1st step), pore radius increase (2st step), decreasing of the pore radius (3st step)

- Liposome swelling

The liposome swelling stage is described by the following equations [1, 2, 7, 9, 18]:

$$\frac{dR}{dt} = P_w V_{\mu w}\left[\Delta C_m + \frac{2\beta E}{R}\left(1 - \frac{R^2}{R_0^2}\right)\right] \quad (1)$$

where, R_0 is the pulsatory liposome radius in the initial unstreched state.

$$\Delta C_m = C_{int} - C_{out} \quad (2)$$

is the transmembrane gradient of the osmotic solute concentration and $C_{int} = C_0$ is the internal solute concentration; $C_{out} = 0$ is the external solute concentration.

$\beta = 1/(N_A k_B T)$; N_A – Avogadro number; k_B – the Boltzmann constant; T – the absolute temperature.

P_w is the water permeability through the liposome membrane; $V_{\mu w}$ – the water molar volume; E is the elastic modulus for surface stretching or compression.

This differential equation has an analytical solution:

- Liposome relaxation

Due to the appearance of the pore, the swelling of the liposome stops and its evolution changes, the liposome deflates.

The liposome relaxation is described by a set of three differential equations [1, 2, 7, 10]:

$$\frac{dR}{dt} = \frac{-Er^3}{6\eta_l R^3}\left(\frac{R^2}{R_0^2} - \frac{r^2}{4R_0^2} - 1\right) + P_w V_{\mu w}\left(1 - \frac{r^2}{4R_0^2}\right)\left[\Delta C + \frac{2\beta E}{R}\left(\frac{R^2}{R_0^2} - \frac{r^2}{4R_0^2} - 1\right)\right] \quad (3)$$

The pore evolution

$$\frac{dr}{dt} = \frac{-Er}{4\eta_l}\left(\frac{R^2}{R_0^2} - \frac{r^2}{4R_0^2} - 1\right) - \frac{\gamma}{2\eta_m h} \quad (4)$$

The osmotic solute concentration

$$\frac{d\left[\ln\left(CV_{lip}\right)\right]}{dt} = \frac{Er^2}{2\eta_l R^4}\left(1 - \frac{R^2}{R_0^2} + \frac{r^2}{4R_0^2}\right) \quad (5)$$

We solved this system of three differential equations numerically using Euler's method and presented the results in Table 1 in Section 3

- Analytical method for the operation of the pulsatory liposome

Figure 2 shows the behavior of the pulsating liposome over the course of an activity cycle [18–25].

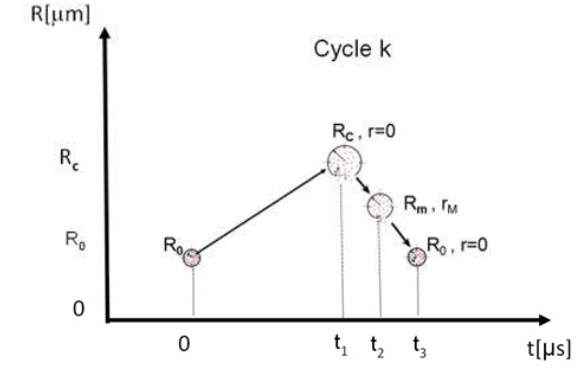

Fig. 2 Evolution of the pulsatory liposome radius during a cycle of its activity

A cycle of the pulsatory liposome's activity has three phases:

- swelling of liposome, f_1;
- increase of pore radius, f_2;
- decreasing of the pore radius until it disappears, f_3.

The transition moments between these phases f_1-f_2-f_3 are:

- moment t_1 is at the boundary between phase f_1 (which consists of the growth of the liposome) and phase f_2, triggered by the appearance of the pore;
- moment t_2 is when the pore is at its maximum radius;
- moment t_3 is at the disappearance of the pore.

We present the working hypothesis in the trigonometric approximation for the pore radius functions in f_2 and f_3 phases, respectively.
The pore function for f_2 phase is:

$$r_1(T_1, t) = r_2 \sin\left(\frac{\pi}{2T_1}(t - t_1)\right), \quad T_1 = t_2 - t_1 \tag{6}$$

and for f_3 phase

$$r_2(T_2, t) = r_2 \sin\left(\frac{\pi}{2T_2}(T_2 - t)\right), \quad T_2 = t_3 - t_2 \tag{7}$$

where the durations T_1, T_2 has the flowing formulae

$$T_1 = \frac{\pi}{2}\frac{\sqrt{r_2^2 - r_1^2}}{EEr_1\left(\frac{R_1^2}{R_0^2} - \frac{r_1^2}{4R_0^2} - 1\right) - G}, T_2 = \frac{\pi r_2}{2G} \text{ where } EE = \frac{E}{4\eta_l} \text{ and } G = \frac{\gamma}{2\eta_m h} \tag{8}$$

Using trigonometric approximation, namely equations (6-7), in the pore radius equation (4), we compute the liposome radius in the f_2 and f_3 phases.

$$R(r, T) = R_0\sqrt{1 + \frac{r^2}{4R_0^2} + \frac{G + \dot{r}}{EEr}}$$

On the other hand, from the process equations for the functions *R(t)* and *C(t)*, the analytical expression for the function *Q(t)* is:

$$Q = Q_0 \cdot e^{-I}$$

$$I = \frac{EE}{2\eta_t} \cdot \int_0^T \left(\frac{r}{R^2}\right)^2 \cdot \left(1 - \frac{R^2}{R_0^2} + \frac{r^2}{4R_0^2}\right) dt$$

where *T* is the duration of that phase and the formula

$$Q = C \cdot V_{lip}$$

which is necessary to compute the solute concentration function *C(t)*.
The results obtained using the trigonometric approximation are presented in Table 2 in Section 3.

3. RESULTS AND DISCUTIONS

Further, we compare the set results for C_0=10 [mol/m^3] both in numerical and analytical approaches for the first cycle of pulsatory liposome [19-21, 26-33].

Tabel 1. The results obtained by Euler method

Cycle 1	f_1	f_2	f_3
t[s]	0..t_1 0..190	0..t_1…….t_2 0..0,125..0,250	t_2…….t_3 0,250..1,800
r[μm]	0..0	r_1..r_2 7..9,8	r_2…0 9,8..0
R[μm]	R_0…..R_1 19,7..20,6	R_1……R_2 20,55..20,38	R_2……R_0 20,38..19,99
C[mol/m^3]	C_0..C_1 10..8,75	C_1…….C_2 8,7458..8,744	C_2…..C_3 8,744..8,734
Durata[s]	τ = 190	T_1=0,125	T_2=1,800

Table 2. The results in the trigonometric approximation

Cycle 1	f_1	f_2	f_3
t[s]	0..t_1 0..185,7	0..t_1……...t_2 0..0,000044..0,000088	t_2……t_3 0,000088..1,330042
r[μm]	0..0	r_1…...r_2 6,95..9,8	r_1…0 9,8..0
R[μm]	R_0…..R_1 19,7..20,55	R_1…..R_2 20,6..20,3	R_2….R_0 20,3..19,7
C[mol/m^3]	C_0..C_1 10..8,75	C_1…….C_2 8,7458..8,4715	C_2……C_3 8,4715..8,3088
Durata[s]	τ=185,778	T_1=0,000088	T_2=1,330033

In Tables 1 and 2, we present the key moments t_1, t_2, t_3 of the transition between phases f_1, f_2, f_3, the evolution of the pore radius *r(t)* and the liposome radius *R(t)*, the concentration function *C(t)*, as well as the durations of the three phases: τ, T_1, T_2. We also use in these tables the corresponding notations *r1, r2, R1, R2* for *rc, rM, Rc, Rm* (see Fig. 2), respectively.

By analyzing and comparing the results obtained through the application of the two analytical and numerical methods, which are specified in Table 1 and Table 2, we find that the values are extremely close for most of the variables in the process content e. g. the key moments and the values of pore and liposome radii between the three stages, but there are also some differences such as the duration of the phase f_2 and the rate of concentration decrease in phases f_2 and f_3.

We note that the analytical method gives a more detailed description than the numerical one, the advantage of the numerical method being, however, that it can circumvent the problematic aspects that arise in the analytical solution of the equations [23-25, 33].

Also, the differences noted in the results obtained analytically and numerically suggest the continuation of studying the processes that occur in the evolution of the liposome in a subsequent study such as astrobiology [16, 18].

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