AN ANALYTICAL APPROACH FOR THE PULSATORY LIPOSOME IN THE PORE RADIUS HYPOTHESIS

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Communicated by Gabriela Marinoschi

One considers a unilamellar liposome filled with an aqueous solution of an osmotic solute. This liposome is introduced into an aqueous medium. Due to the osmosis process, the lipid vesicle swells up to a maximum size, when a transbilayer pore suddenly appears. Part of the internal solution leaks through this pore. The liposome deflates and returns to its initial size. The swelling begins again and the liposome begins a cyclical evolution. All the processes which contribute to the liposome relaxing and its coming back to the initial size are described by three differential equations. This system of differential equations used to model the liposome can be integrated using numerical methods. At the same time, in order to describe the behavior of the model functions, we propose an analytical method in which the variable is the radius of the pore. Thus, working under this hypothesis of the radius of the pore, we propose an analytical solution for this system of differential equations and give the analytical expressions of the model functions and their graphs.

AMS 2020 Subject Classification: 34N99, 35F05, 76D99.

Key words: pulsatory liposome, analytical method, biophysical engine.

1. **INTRODUCTION**

We consider a unilamellar liposome filled with an aqueous solution of an osmotic solute. A liposome is a small artificial spherical vesicle, whose membrane (lamella) is formed by a double layer of phospholipid molecules (see Figure 1) [10, 11, 17, 15]. If such a liposome is introduced into water, it has a cyclical dynamic evolution. The pulsatory liposome works as a three-stroke biomicroengine. For this reason, it is considered as an object of bionics. The osmotic solute is a solute for which the liposome membrane is impermeable. Due to the osmosis process, the liposome swells up to a critical size, when suddenly a transbilayer pore appears. The appearance of the pore changes the evolution of the liposome. The swelling of the liposome stops and its deflation begins. The evolution of the pore has two phases: first, the pore increases up to a maximum value of radius, then the radius decreases until the pore disappears, and the liposome reaches its initial size [13, 7, 8]. A new cycle can start.

REV. ROUMAINE MATH. PURES APPL. **69** (2024), *3-4*, 531–538
doi: 10.59277/RRMPA.2024.531.538

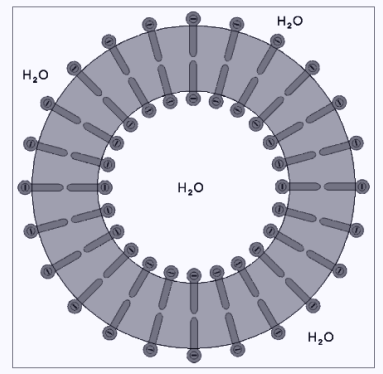

Figure 1 – The structure of a liposome.

The liposome is named in this paper LP-model. All the processes which contribute to the liposome relaxing and its coming back to the initial size are described by three differential equations [8, 18, 4, 2, 6]. The functions which are modeling our biological engine are as follows: $R(t)$ - the liposome radius, $r(t)$ - the pore radius, $C(t)$ - internal solute concentration. The three differential equations can be solved using numerical methods. An interesting observation is that in the system of differential equations that describe the functioning of the pulsatory liposome, the variable time, does not appear explicitly. In this paper, we propose an analytical approach working in the hypothesis of the radius of the pore [3]. In this approach the advantage of the analytical method lies in obtaining explicit solutions. They are validated by comparing with results from previous studies [3]. The structure of this paper is: in Section 2, we describe the LP model specifying the base equations and the material constants. In Section 3, we detail the LP-analysis method in the working hypothesis for the pore radius. Then, we obtain the explicit analytical expressions of the LP-model functions. We conclude by providing the graphical representations for two functions in the hypothesis for the evolution of the pore.

2. THE BASE EQUATIONS OF THE PULSATORY LIPOSOME

Due to the appearance of the pore, the swelling of the liposome stops, its evolution changes and the liposome deflates (relaxes) [13, 8, 18, 4, 12]. The relax stage of the pulsatory liposome is determined by the pore dynamics. The radius of the pore increases up to a maximum value, r_M, then decreases until the pore disappears (Figure 2).

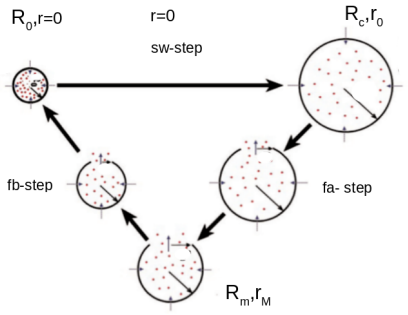

Figure 2 – The evolution of a pulsatory liposome during a cycle.

The following differential equation describes the radius of the pore $r(t)$ evolution:

$$\frac{dr}{dt} = r \cdot \tilde{E}\left(\frac{R^2}{R_0^2} - 1 - \frac{r^2}{4R_0^2}\right) - G, \tag{1}$$

where γ is the line tension acting for pore closure, η_m is the membrane viscosity, $\tilde{E} = \frac{E}{F}, G = \frac{2\gamma}{F}, F = 4h\eta_m$; $2h$ is the thickness of the lipid bilayer.

The radius of the pulsatory liposome and the concentration of the osmotic solute decrease. The decrease of the liposome radius R(t) is described by the following differential equation:

$$\begin{aligned}\frac{dR}{dt} =& \frac{-r^3}{6 \cdot \eta_\ell \cdot R^3} \cdot E\left(\frac{R^2}{R_0^2} - 1 - \frac{r^2}{4R_0^2}\right) \\ &+ P_w V_{\mu w} \cdot \left(1 - \frac{r^2}{4R^2}\right) \cdot \left[C - \frac{2\beta E}{R}\left(\frac{R^2}{R_0^2} - 1 - \frac{r^2}{4R_0^2}\right)\right]^c\end{aligned} \tag{2}$$

where R_0 is the pulsatory liposome radius in the initial unscretched state and $r(t)$ is the pore radius; $\beta = 4.00914 \cdot 10^{-4}\,\mathrm{mol \cdot J^{-1}}$; η_ℓ is the viscosity of aqueous solution; $\mu = P_w \cdot V_{\mu w} = 5.412 \cdot 10^{-10}\mathrm{m^4 \cdot mol^{-1} \cdot s^{-1}}$, $V_{\mu w}$ – being the water molar volume and $E = 0.2\mathrm{N \cdot m^{-1}}$ is the elastic modulus for surface stretching or compression.

The change of the internal concentration of the osmotic solute C(t) is given by the equation:

$$\frac{d[ln(C \cdot V_{lip})]}{dt} = \frac{-r^3}{2 \cdot \eta_\ell \cdot R^4} \cdot E \cdot \left[\frac{R^2}{R_0^2} - \left(1 + \frac{r^2}{4R_0^2}\right)\right] \tag{3}$$

where $C(t)$ is the solute concentration inside the liposome, $V_{lip}(t)$ is the volume of the liposome and $C \cdot V_{lip} = Q$ is the quantity of osmotic solute from internal solution.

The internal solute quantity is $Q(t) = C(t)V_{lip} = C_(t) \cdot R(t)^3 \cdot \frac{4\pi}{3}$.

3. THE PORE RADIUS HYPOTHESIS METHOD AND ITS RESULTS

As a method to analyze the pore dynamics in the phase-fa (growth of pores) and phase-fb (reduction of pores) of the LP-model, we present in the following the working hypothesis derived from the search for solutions of the model in a predefined form, as follows. In r-hypothesis, we consider the function of pore radius with its derivatives relative to time having the below forms where T_1 is the duration of the pore growth phase, T_2 is the duration of the pore decrease phase. Stating that $r(t)$ is continuous for its value r_M, we determine below T_1 and T_2 in formulae (9).

We recall that due to the osmosis process the liposome swells up to a critical size, when suddenly a pore appears of r_0 radius. In fa-phase (see Figure 2), the porus radius is increasing from r_0 to r_M, where r_0 is an input parameter for the model which indicates the start of the porus growth phase:

$$\dot{r} = \frac{\pi}{2T_1}\sqrt{r_M^2 - r^2} > 0, \ddot{r} = -\Big(\frac{\pi}{2T_1}\Big)^2 r < 0. \tag{4}$$

In fb-phase (Figure 2), the pore radius is decreasing from r_M to 0 which closes the liposome cycle:

$$\dot{r} = \frac{-\pi}{2T_2}\sqrt{r_M^2 - r^2} < 0, \ddot{r} = -\Big(\frac{\pi}{2T_2}\Big)^2 r < 0. \tag{5}$$

Using the r-hypothesis in equation (1) and understanding that T denotes a parameter which means the time period of the proper phase, we obtain:

$$R(r;T) = R_0\sqrt{1 + \frac{r^2}{4R_0^2} + \frac{G + \dot{r}}{\tilde{E}r}} \tag{6}$$

where $\tilde{E}, G$ are defined in equation (1) with γ, η_m as constants of material.

Also, as a consequence of r-hypothesis, we calculate the derivative of function R relative to time in phases fa and fb:

$$\dot{R}(r;T) = \frac{R_0^2}{2R}\Big(\frac{r\dot{r}}{2R_0^2} + \frac{G}{\tilde{E}}\frac{\ddot{r}}{r} - \frac{(G + \dot{r})\dot{r}}{\tilde{E}r^2}\Big). \tag{7}$$

Then, from equation (2), we calculate the solute concentration in phases fa and fb:

$$C(r;T) = \left(\frac{\frac{\tilde{E}}{6\eta_1}\cdot\frac{r^3}{R(r;T)^2}}{Be\cdot\mu\big(1 - \frac{r^2}{4R(r;T)^2}\big)} + 1\right)\cdot\sigma(r;T) + \frac{\dot{R}(r;T)}{\mu\cdot\big(1 - \frac{r^2}{4R(r;T)^2}\big)} \tag{8}$$

where $\sigma(r;T) = \frac{Be}{R(r;T)}\cdot\big(\frac{R(r;T)^2}{R_0^2} - \frac{r^2}{4R_0^2} - 1\big)$ and $Be = 2\beta E$.

Working in r-hypothesis, we ask that the conditions of continuity be met for the functions $R(r;T)$ and $C(r;T)$ in r_0 in the start of fa-phase and also in $r=0$ at the end of fb-phase.

So, we obtain the parameters of LP-model such as T_1 – the duration of the pore growth phase and T_2 – the duration of the pore decrease phase:

$$T_1 = \frac{\pi}{2}\frac{\sqrt{r_M^2 - r_0^2}}{\tilde{E}r\left(\frac{R_c^2}{R_0^2} - \frac{r_0^2}{4R_0^2} - 1\right) - G}, \; T_2 = \frac{\pi \cdot r_M}{2G}. \tag{9}$$

Applying formulae (9) in equation (6), we obtain the radius of the pulsating liposome both in phases fa and fb:

$$R(r;T_1) = R_0\sqrt{1 + \frac{r^2}{4R_0^2} + \frac{G + \frac{\pi}{2T_1}\sqrt{r_M^2 - r^2}}{\tilde{E}r}}, \; r_0 \le r \le r_M. \tag{10}$$

$$R(r;T_2) = R_0\sqrt{1 + \frac{r^2}{4R_0^2} + \frac{G - \frac{\pi}{2T_2}\sqrt{r_M^2 - r^2}}{\tilde{E}r}}, \; r_M \ge r > 0. \tag{11}$$

Because the function $r(t)$ is continuous for the value r_M, we derive that $R(r;T)$ is also continuous in r_M and obtain:

$$R(r_M;T_1) = R(r_M;T_2) = R_M = R_0\sqrt{1 + \frac{r_M^2}{4R_0} + \frac{G}{\tilde{E}r_M}}. \tag{12}$$

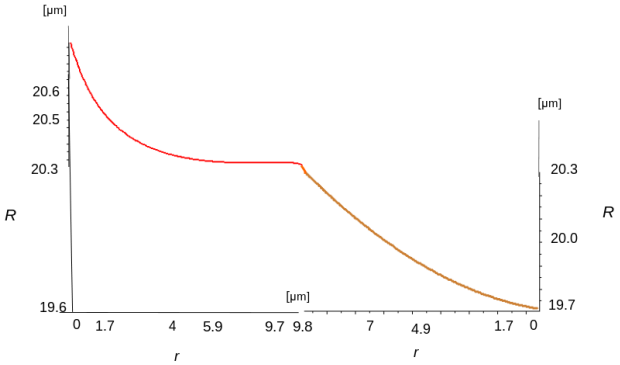

Figure 3 – The evolution of the liposome radius during the relax stage.

The second important function of the dynamics of a pulsatory liposome during its evolution is the concentration of the osmotic solute.

Using formulae (9) in equation (8), we obtain the concentration of the solute in phases fa and fb:

(13)
$$C(r;T_1)=\frac{Be}{R(r;T_1)}\left(\frac{G+\frac{\pi}{2T_1}\sqrt{r_M^2-r^2}}{\tilde{E}r}\right)+C_c-\frac{Be}{R_c}\left(\frac{R_c^2}{R_0^2}-\frac{r_0^2}{4R_0^2}-1\right).$$

(14)
$$C(r;T_2)=\frac{Be}{R(r;T_2)}\left(\frac{G-\frac{\pi}{2T_2}\sqrt{r_M^2-r^2}}{\tilde{E}r}\right)+C_M-\frac{Be}{R_M}\left(\frac{R_M^2}{R_0^2}-\frac{r_M^2}{4R_0^2}-1\right).$$

where $C_c=C(r_0;T_1)$ and $C_M=C(r_M;T_1)$.

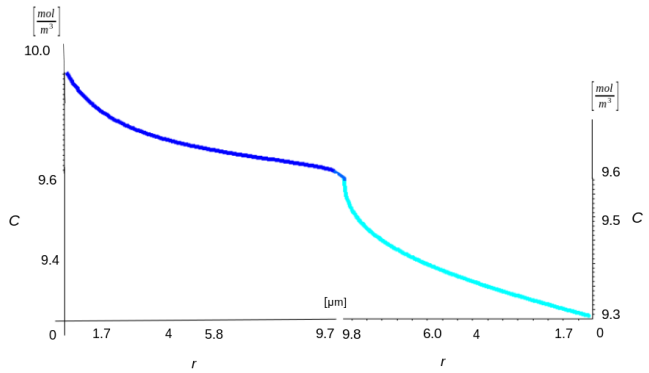

Figure 4 – The evolution of the liposome solute-concentration during the relax stage.

In Figures 3 and 4, via equations (10)–(14), we represent the liposome radius $R(r;T)$ and the solute concentration $C(r;T)$ as the functions of the pore radius for both phases increase, respectively decrease. The graphs of these functions are continuous in r_M due to the condition imposed for the function $r(t)$ to be continuous for the value r_M. These aspects are in harmony with the previous studies [3].

4. CONCLUSIONS

Starting from the hypothesis that the radius of the pore determines the evolution of the pulsatory liposome in its relaxation phase, we obtained the functions of liposome radius and also the ones of the concentration of the osmotic solute during both pore evolution phases. It is very interesting and useful that we were able to calculate important parameters of the evolution of the pulsatory liposome: the duration of the pore growth phase, the duration of

the pore decrease phase, the radius of the liposome when the pore is maxim and finally the concentration of the solute at the end of the cycle. From plots of LP-model functions, we can conclude that their analytical expressions obtained in this article are in harmony with the previous studies. Since the osmotic solute can be a substance with pharmacological properties, the pulsating liposome can be used in medical applications [19, 16, 14, 20] and as a bionic object [9].

Acknowledgments. The authors would like to thank physicist Valentin Ioan Remus Niculescu and dr. Sorin Stefan Radnef from INCAS.

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