Evolution of the pulsatory liposome by analytical methods

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Abstract

This paper is a review for the analytical modelling of the biophysical engine represented by a liposome, filled with an osmotic solution, introduced into an aqueous medium. The processes leading to the appearance, evolution and disappearance of the liposome-pore are presented. Due to osmosis, the liposome grows to a maximum size that will lead to the appearance of a pore through which part of the internal solution flows. The liposome then shrinks and returns to its original size. This is the first cycle of the evolution of the pulsating liposome, after which a new cycle begins. Starting from certain values of the parameters and working in the analytical approach, we obtain the functions of the model as explicit solutions of the constitutive equations. These functions are liposome radius, pore radius and solute concentration. An analysis of the processes described by these functions is performed.

keywords: pulsatory liposome, biophysical engine, osmotic solution, phospholipid molecule, analytical methods.

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1 Introduction

The transport of molecules across the cell membrane is of interest in Biology [1, 2]. As an application, we encapsulate pharmaceuticals that need to be transported to a target tissue [3] where the vesicle should discharge its contents. A pulsatory liposome is such a vesicle filled with an aqueous solution having an impermeable membrane composed of a double layer of phospholipid molecules that are formed by a non-polar carbon chain having a hydrophobic tail and a hydrophilic head (Fig.1). The liposome is introduced into an aqueous environment, with water molecules entering the liposome due to osmosis (Fig.1). Thus, the liposome grows to a critical size and a pore suddenly appears. This leads to a decrease in the liposome radius while the pore radius increases to a maximum value, followed by the phase of decreasing to zero of the pore, and the liposome returns to its initial size [4-6]. A new cycle can begin.

In this paper, we analyse the results of analytical approaches working in linear approximation and also in the pore radius hypothesis [7-11]. The advantage of analytical approaches is to obtain explicit solutions. We validate the modelling by comparing it with the results of previous studies [3, 10].

The paper has the following structure:

In Section 2, the differential equations of the model, material constants and also the model parameters are presented. In Section 3, we present and analyse the pulsatory liposome model functions obtained by analytical methods, such as the linear approximation method and the pore radius assumption method, respectively. Finally, a summary and discussion of our results in relation to previous studies is provided. An appendix containing more computational details concludes the paper.

2 Pulsatory liposome modelling

Due to the pore occurring, liposome swelling stops, its evolution changes, and the liposome deflates (relaxes) [3, 12-14]. The pore radius increases to a maximum value r_M, then decreases until the pore disappears (Fig.2). The processes that contribute to the relaxation and return of the liposome to its initial size are described by a set of three differential equations [10, 11].

The functions that model our liposome are the following: R(t) - liposome radius, r(t) - pore radius, and C(t) - internal solute concentration.

Thus, we are talking about these three basic equations with the specification of several constants of material and model parameters.

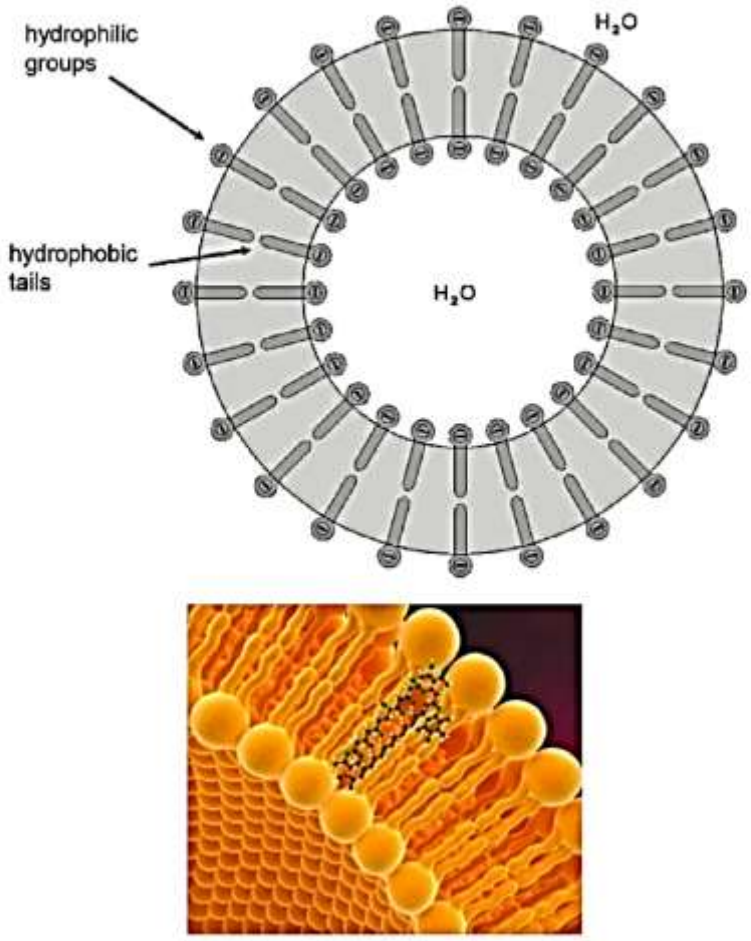

Figure 1: Liposome and phospholipid molecules - Image Credit https://upload.wikimedia.org/wikipedia/commons/e/e0/Liposom.png , https://www.news-medical.net/life-sciences/What-is-a-Liposome.aspx

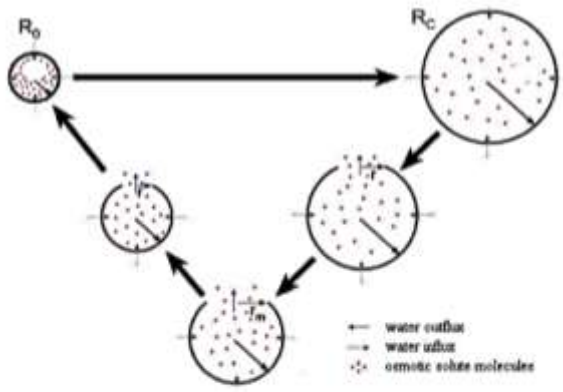

Figure 2: Phases of the liposome evolution

The porus radius equation is:

$$\frac{dr}{dt} = \frac{E_1 \cdot r}{4\eta_\ell R_0^2} \cdot S(R;R_0) - \frac{\gamma}{2\eta_m h}, S(R;R_0) = \left(\frac{R^2}{R_0^2} - \frac{r^2}{4R_0^2} - 1\right) \tag{1}$$

where γ is the line tension acting for pore closure, η_m is membrane viscosity,

$$\mathrm{E}_1 = E \cdot F, G = 2\gamma \cdot F, F = 4h \cdot \eta_m \tag{2}$$

$2h$ being thickness of the lipid bilayer and $E = 0.2Nm^{-1}$ the elastic modulus for surface stretching or compression.

The equation for the liposome radius is:

$$\frac{dR}{dt} = \frac{E \cdot r^2}{6\eta_\ell R_0^2} \cdot S(R;R_0) + P_W V_{\mu W}\left(1 - \frac{r^2}{4R_0^2}\right)\left(\Delta C - \frac{2\beta E}{R} \cdot S(R;R_0)\right) \tag{3}$$

where R_0 is the pulsatory liposome radius in the initial unscratched state and $r(t)$ is the pore radius; $\beta = 4.00914 \cdot 10^{-4} mol \cdot J^{-1}$; η_ℓ is the viscosity of aqueous solution; $\mu = P_W \cdot V_{\mu W} = 5.412 \cdot 10^{-10} \cdot m^4 \cdot mol^{-1} \cdot s^{-1}$, $V_{\mu W}$ being the water molar volume.

Finally, for the internal osmotic solute concentration $C(t)$ and also for the amount of solute, the equation is:

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

where $C(t)$ is the solute concentration inside the liposome, $V_{lip}(t)$ is the volume of the liposome and $Q(t) = C(t) \cdot V_{lip} = C(t) \cdot \frac{4\pi}{3} \cdot R^3(t)$ is the quantity of osmotic solute from internal solution.

3 Solving methods and results

By analytical modelling for the evolution of liposome in its three phases, namely the relaxation of liposome and its return to the initial size accompanied by the growth and decrease of the pore, we present some results regarding the solutions of the model in analytical forms. For the first life cycle of pulsatory liposome, some results for the functions of the model are presented as follows:

In panels-*a* of figures 3-4, we give the graphical representation for R and C as functions of the time variable t in the linear approximation in the growth and shrinking phases of the pore during first cycle. On the other hand, during first cycle of liposome lifetime, in panels-*b* of figures 3-4 , we give the graphical representations for R and C, but as functions of the porus radius variable r. We give in Appendix several calculus details for the expressions of functions in both approximations.

Comparing both of panels in figure 3, we observe the behaviour of R as a decreasing function. In addition, the graphical representations give with details of behaviour for R'- derivative of R-function in the neighbourhood of r_M at the transition between growth and shrinking phases of the pore. Furthermore, specifying the derivative C-function in the vicinity of transition moment between the growth and shrinking phases of the pore, figure 4 in both its panels confirms the decreasing behaviour for C-function. These results on the r,R,C functions of liposome modelling are in harmony with laboratory data from previous studies [3-8].

4 Conclusions

We analysed the graphical representations for the analytical solutions in all three stages of the first cycle in the evolution of pulsatory liposome. From the model function diagrams, we can conclude that the results of analytical methods presented in this article are in harmony with previous studies. Since the osmotic solute can be a substance with pharmacological properties, the pulsatory liposome can be used in medical applications [11-15] and as a bionic object [16].

5 Appendix

In linear approximation (A1) [7], a linear behaviour for the pore evolution is used as follows:

$$r_a(t) = d(t - t_u) + r_0, d > 0, r_0 > 0, t_u \leq t < t_M. \tag{5}$$

$$r_b(t) = q(T_f - t), q > 0, t_M < t \leq T_f. \tag{6}$$

Based on the previous studies for the solute concentration function, we consider for the pore evolution a decreasing law in the 2nd and 3rd phases (Fig.2), as follows:

$$C_{ab}(t) = \kappa(t_u - t) + C_u, \kappa > 0, t_u \leq t \leq T_f. \tag{7}$$

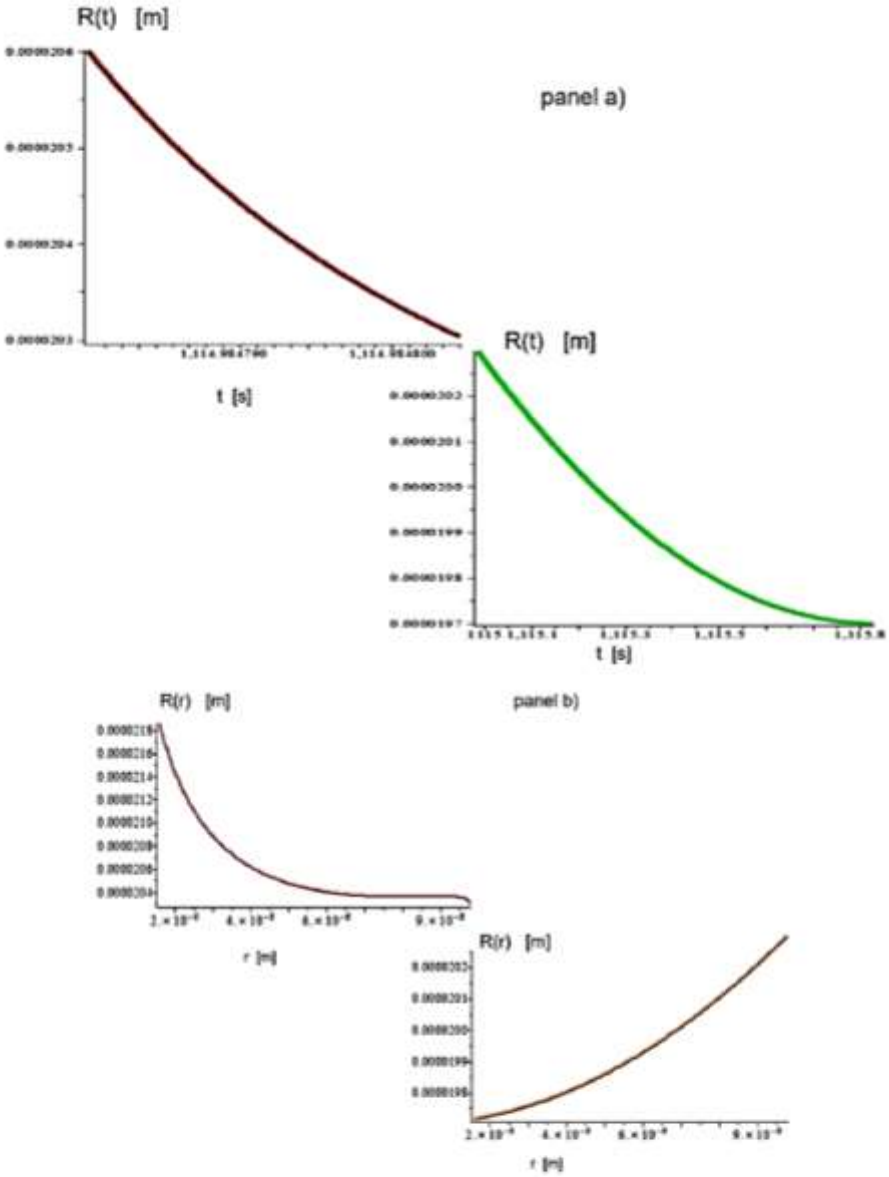

Figure 3: R-function in linear approximation (panel-a) and in r-hypothesis approximation (panel-b)[7] during the growth and shrinking phases of the pore

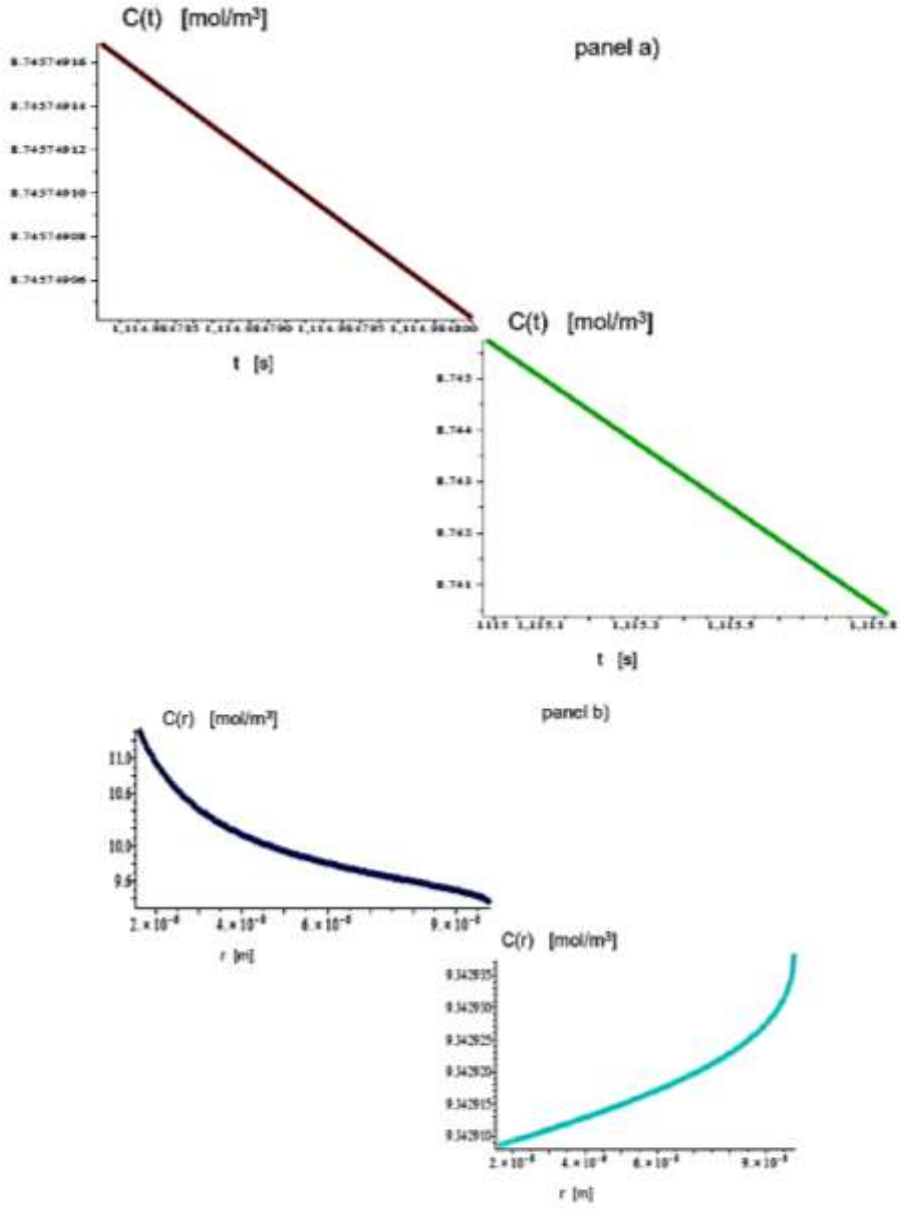

Figure 4: C-function in linear approximation (panel-a) and in r-hypothesis approximation (panel-b)[7] during the growth and shrinking phases of the pore

where d, q, κ and of course t_u, t_M, T_f remain to be determined into liposome-model.

In r-hypothesis approximation (A2) [9], we recall that due to the osmosis process liposome swells up to a critical size, when suddenly a pore appears of r_0 radius. In fa-phase (Fig.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 porus growth phase:

$$\dot{r} = \frac{\pi}{2T_1}\sqrt{r_M^2 - r^2} > 0, \ddot{r} = -\left(\frac{\pi}{2T_1}\right)^2 r < 0 \tag{8}$$

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

$$\dot{r} = \frac{-\pi}{2T_2}\sqrt{r_M^2 - r^2} < 0, \ddot{r} = -\left(\frac{\pi}{2T_2}\right)^2 r < 0 \tag{9}$$

Understanding that T denotes a parameter which means the time period of the proper phase, we obtain:

$$R(r;T) = R_0\sqrt{1 + \frac{r^2}{4R_0^2} + \frac{G + \dot{r}}{\tilde{E}r}} \tag{10}$$

where $\tilde{E}, G, \gamma, \eta_m$ as constants of material.

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

$$\dot{R}(r;T) = \frac{R_0^2}{2R}\left(\frac{r\dot{r}}{2R_0^2} + \frac{G}{\tilde{E}}\frac{\ddot{r}}{r} - \frac{(G + \dot{r})\dot{r}}{\tilde{E}r^2}\right) \tag{11}$$

Then, the solute concentration in phases fa and fb has the expression:

$$C(r;T) = \left(\frac{\frac{\tilde{E}}{6\eta_1}\cdot\frac{r^3}{R(r;T)^4}}{Be\cdot\mu\left(1 - \frac{r^2}{4R(r;T)^2}\right)} + 1\right)\cdot\sigma(r;T) + \frac{\dot{R}(r;T)}{\mu\cdot\left(1 - \frac{r^2}{4R(r;T)^2}\right)} \tag{12}$$

where $\sigma(r;T) = \frac{Be}{R(r;T)}\cdot\left(\frac{R(r;T)^2}{R_0^2} - \frac{r^2}{4R_0^2} - 1\right)$ 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.

Thus, we obtain the parameters of liposome-model such as T_1 - the duration of pore growth phase and T_2 - the duration of pore decrease phase:

$$T_1 = \frac{\pi}{2}\frac{\sqrt{r_M^2 - r_0^2}}{\tilde{E}r\left(\frac{R_0^2}{R_0^2} - \frac{r_0^2}{4R_0^2} - 1\right) - G}, T_2 = \frac{\pi\cdot r_M}{2G} \tag{13}$$

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R E F E R E N C E S

[1] Dumitru Popescu, *The Pulsatory Lipid Vesicle Dynamics under Osmotic Stress*, (Lambert Academic Publishing and AV Academikerverlag, Saarbruecken, Germany, 2012).

[2] Dumitru Popescu, Alin Gabriel Popescu, In Liposomes - Recent Advances, New Perspectives and Applications, IntechOpen Ed. Rajeev K. Tyagi, cap.6, **85,** (2023).

[3] D. Popescu, A. G. Popescu, B. Amuzescu, Romanian J.Biophys. **20**, 37, (2010).

[4] F. Brochard-Wyart, P. G. de Gennes, O. Sander, Physica A **278**, 32, (2000).

[5] L. Movileanu, D. Popescu, In: Recent Research Developments in Biophysics (chapter 4) vol 3 Part I, Transworld Research Network, Kerala, **61,** (2004).

[6] F. Brochard, P. G. DE Gennes, O. Sandre, Physica A **278**, 32, (2000).

[7] D. R. Constantin, D. Popescu, Romanian Journal of Physics **69,** 701, (2024).

[8] D. Popescu, Diana R. Constantin, V. I. Niculescu, INCAS BULLETIN **16**, 1, 89, (2024).

[9] Diana Radnef-Constantin, D. Popescu, A. A. Mocanu, Rev. Roumaine Math. Pures Appl. **69,** (3-4), (2024).

[10] D. Popescu, Proceedings of the Romanian Academy, Series A **11**, 108, (2010).

[11] D. Popescu, Diana R. Radnef-Constantin, Ro. Phys. J. (2025, in press).

[12] J.A. Zasadziski, Curr. Opin. Solid State Mat. Sci. **2**, 345, (1997).

[13] D. Popescu, Biochim. Biophys. Acta **1152**, 35, (1993).

[14] D. Popescu, S. Ion, A. I. Popescu, L. Movileanu, Planar Lipid Bilayers (BLMs) and Their Applications, H. Ti Tien and A. Ottova (editors), Elsevier Science Publishers, Amsterdam **3**, 173, (2003).

[15] D. Popescu, C. N. Zaharia, I. Stelian, M. L.Flonta, Romanian J. Biophys. **16**, 189, (2006).

[16] A. Popescu, *Tratat de Bionica (A Compendium of Bionic),* (Bucharest University Publishing House, Bucharest, 2022).