SUPPORTING INFORMATION

Cyclic Activity of an Osmotically-Stressed Liposome in a Finite Hypotonic Environment

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CONTENT:

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1. Determination of the final state of the first cycle of a pulsatory liposome.

For the first cycle, the law of mass conservation applies during the first cycle of the swelling process, as follows:

$$C_{01}V_0 = C_1V \qquad \textbf{(S1)}$$

where, C_{01} and C_1 are the initial solute concentration and the solute concentration when the liposomal volume, V, is reached during the swelling process. The corresponding time-dependent radius of the liposome is $R(t)$. The initial liposomal volume before the swelling process is V_0, and the corresponding vesicle radius is R_0. During the first cycle of the swelling process $C_{out} = 0$; thereby, $\Delta C_m = C_1$. Using **eqns.** (**8**) and (**S1**), one can determine the final form of the differential equation that describes the swelling process of the first cycle.

$$\frac{dR}{dt} = P_w V_{\mu w}\left[\frac{C_{01}R_0^3}{R^3} - \frac{2\beta E}{R}\left(\frac{R^2}{R_0^2} - 1\right)\right] \qquad \textbf{(S2)}$$

Differential **eqn. (1)** can be solved replacing the variable $R(t)$ in **eqn. (S2)** with $x\ (t)$, where

$$x(t) = \frac{R(t)}{R_0} \qquad \textbf{(S3)}$$

Then, the differential equation (A2) becomes:

$$\frac{dx}{dt} = -\frac{2\beta E P_w V_{\mu w}}{R_0^2 x^3}\left(x^4 - x^2 - \frac{C_{01}R_0}{2\beta E}\right) \qquad \textbf{(S4)}$$

The initial time condition is $x(0) = 1$.

Eqn. (S4) can be solved analytically and its solution is the following:

$$\frac{8\alpha\beta E P_w V_{\mu w}}{R_0^2}t = (\alpha + 1)ln\left|\frac{\alpha-1}{2x^2-\alpha-1}\right| + (\alpha - 1)ln\left|\frac{\alpha+1}{2x^2+\alpha-1}\right| \qquad \textbf{(S5)}$$

where

$$\alpha = \sqrt{1 + \frac{2C_{01}R_0}{\beta E}} \qquad \textbf{(S6)}$$

Differential **eqn. (S5)** has a solution that is a bijective function:

$t = t(x)$, with $x \in \left[1, \frac{R_c}{R_0}\right]$ and $t \geq 0$ **(S7)**

where R_c is the critical radius of the liposome. Here, we define R_c/R_0 as the critical swelling ratio.

2. Determination of the swelling phase of the n-th cycle of a pulsatory liposome.

Let us assign that the solute concentration at the end of the swelling stage of the (n-1)-th cycle is $C_{c(n-1)}$. During the relaxation regime, a finite amount of internal solute is ousted within the external hypotonic bath. Yet, the internal solute concentration remains unchanged, because this relaxation process is very short-lived.[1] Therefore, the solute concentration at the start of the n-th cycle of the liposome is C_{0n}, which is equal to $C_{c(n-1)}$. Since the mass is conserved for each cycle during the swelling process, one can obtain the following relationship:

$$C_{on} = C_{0(n-1)} \frac{R_0^3}{R_c^3} = f^{n-1} C_{01} \quad \textbf{(S8)}$$

where

$$f = \frac{R_0^3}{R_c^3} \quad \textbf{(S9)}$$

is the reciprocal of the swelling critical ratio to the cube power. The swelling ratio is the ratio between the liposomal radius in the stretched state, just before the pore nucleation, and the liposomal radius in the fully relaxed state (when $\sigma = 0$). Therefore, the total amount of extruded solute from all previous cycles into the external hypotonic bath is the following:

$$\Delta Q_{n-1} = C_{01} V_0 - C_{0n} V_0 = C_{01} V_0 (1 - f^{n-1}) \quad \textbf{(S10)}$$

The solute concentration within the external bath will change starting with the second cycle. For example, for the n-th cycle, the initial solute concentration outside the pulsatory liposome is equal to:

$$C_{e0n} = \frac{\Delta Q_{n-1}}{V_b - V_0} \quad \textbf{(S11)}$$

If we consider the ratio of the bath volume, V_b, to the initial liposomal volume, V_0, then

$$F = \frac{R_b^3}{R_0^3} \quad \textbf{(S12)}$$

$$C_{e0n} = C_{01} \frac{1-f^{n-1}}{F-1} \quad \textbf{(S13)}$$

where R_b is the radius of the spherical external bath. During the liposome swelling in the n-th cycle, the external solute concentration, C_{en}, is amplified to the following value:

$$C_{en} = \frac{\Delta Q_{n-1}}{V_b - V} = C_{01} \frac{1-f^{n-1}}{F-x^3} \quad \textbf{(S14)}$$

where x is the expansion coefficient of the pulsatory liposome ($x = V/V_0$) during the swelling process. $x(t)$ shows the relative expanded liposomal volume with respect to its initial volume. One can calculate the transmembrane gradient of solute concentration during the liposomal swelling regime in the n-th cycle:

$$\Delta C_n = C_n - C_{en} = C_{01}\left(\frac{f^{n-1}}{x^3} - \frac{1-f^{n-1}}{F-x^3}\right) \quad \textbf{(S15)}$$

Therefore, the differential equation of the swelling process of the pulsatory liposome in the n-th cycle can be obtained substituting ΔC_n from **eqn. (S15)** in **eqn. (8)**, the main text.

$$\frac{dx}{dt} = \frac{P_w V_{\mu w} C_{01}}{R_0}\left[\frac{f^{n-1}}{x^3} - \frac{2\beta E}{R_0 C_{01}}\left(x - \frac{1}{x}\right) - \frac{1-f^{n-1}}{F-x^3}\right] \quad \textbf{(S16)}$$

REFERENCES

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