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A Mathematical Model for a New Kind of Drug Administration by using R.B.C.

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Abstract

A mathematical model for the drug delivery to tissues by using a preassigned cohort of red blood cells (RBC) loaded with a drug is presented. The model has a discrete time delay in the interaction between RBC and macrophage cells in the various tissues. A control problem to maintain the longest duration of the therapeutic effect is considered.

1 Drug Administration by Using RBC

Human and murine red blood cells (RBC) treated with $ZnCl_2$ and bis (sulfosuccinimidyl) suberate (BS^3) (a cross linking agent) undergo band 3 clustering and binding of hemoglobin to RBC membrane proteins. These clusters induce autologous IgG binding and complement fixation, thus favoring the phagocytosis of $ZnCl_2/BS^3$ treated cells by macrophages. The extension of RBC opsonization can be easily modulated by changing the $ZnCl_2$ concentration in the 0.l-1.0 mM range thus providing a way to affect RBC recognition by macrophages. Since the $ZnCl_2/BS^3$ treatment can also be performed on RBC loadeded with drugs or other substances, this procedure is an effective drug-targeting system to be used for the delivery of molecules to peritoneal, liver and spleen macrophages (L.Chiarantini et al : Modulated RBC survival by membrane protein clustering. Preprint.)

Macrophages phagocytate only RBC when they are recognized as senescent, i.e. with an age $a \geq \bar{a}$, $\bar{a} \simeq 120$ days, because the aging of RBC induce a progressive membrane clustering.

The RBC membrane clustering by $ZnCl_2/BS^3$ treatment enables to prepare a cohort of drug loaded RBC at time $t = 0$:

$$n(0,a) = \begin{cases} \varphi(a) > 0 & \forall a \in \Re_{+0} = [0, +\infty) \\ 0 & \forall a < 0 \end{cases} \tag{1}$$

such that RBC of age a at $t = 0$ will be recognized as senescent after a time $t = \bar{a} - a$. The shape of the initial age distribution φ of the drug loaded RBC is experimentally controlled, so as the total amount of loaded RBC is :

$$n_0 = \int_0^{+\infty} \varphi(a)da \ (ml\ RBC) \quad n_0 \in [n_1, n_2], \tag{2}$$

and the fraction of senescent RBC is

$$\alpha n_0 = \int_{\bar{a}}^{+\infty} \varphi(a)da \quad \alpha \in [0,1]. \tag{3}$$

The aim of the administration is to give a drug directly to the macrophages of various tissues : peritoneum, spleen, liver $\cdots$ by injecting at $t = 0$ in the blood circulation and to control the age distribution of RBC cohort, which is experimentally preassigned, in order to maintain the therapeutic effect for the longest time possible. Here only the RBC in the cohort with age $a \geq \bar{a}$ (i.e. senescent) are phagocytated by macrophages, releasing inside them the drug.

Other assumptions on the process are as follows :

1) The drug is not catabolized inside the RBC neither can diffuse through their membranes.

2) The drug is catabolized inside the macrophages.

3) The size of the macrophage population M_0 is constant on the time scale $\bar{a}$ of the drug administration.

4) Once phagocytated RBC a macrophage has an average digestion time $T(\simeq 4/5$ hours) during which it is inactive in the capture process of other RBC.

5) The average capture time is negligible with respect to the average digestion time T .

2 Formulation of The Model

At $t = 0$ we have a cohort of drug loaded RBC $n(0,a)$ given by (1) with an age distribution $\varphi(a)$. Let $\bar{a}$ be the age beyond which the RBC are recognized as senescent. The total number of loaded RBC is n_0 given by (2), of which αn_0 given by (3) is the senescent fraction at $t = 0$. If q_0 is the amount of drug (μ moli) loaded at $t = 0$ into the RBC cohort, the average amount of drug in each RBC is :

$$\beta = q_0/n_0. \tag{4}$$

2.1 RBC Equations

Let us consider for $t > 0$ the time evolution of the cohort of RBC $n(t,a)$.

If $a \leq \bar{a}$, then

$$\frac{\partial}{\partial t}n(t,a) + \frac{\partial}{\partial a}n(t,a) = 0 \tag{5}$$

with

$$\begin{aligned} i.c. \quad n(0,a) &= \varphi(a), \quad \forall a \in [0,\bar{a}] \\ b.c. \quad n(t,0) &= 0, \quad \forall t > 0 \end{aligned}$$

i.e. we have no newborns neither deaths. Then, the solution to (5) is expressed as

$$n(t,a) = \begin{cases} \varphi(a-t) & \text{if } t \leq a \\ 0 & \text{if } t > a, \forall a \in [0,\bar{a}]. \end{cases} \tag{6}$$

If $a > \bar{a}$, then

$$\frac{\partial}{\partial t}n(t,a) + \frac{\partial}{\partial a}n(t,a) = -K(a)n(t,a)x_3(t) \tag{7}$$

where $x_3(t)$ is the number of macrophages that at time t are free for the phagocytosis process. $K(a)$ is the average number of RBC with age a captured by a free macrophage per unit of time. We assume that $K(a) = K$ for $a > \bar{a}$.

Let us define by

$$x_1(t) = \int_{\bar{a}}^{+\infty} n(t,a)da \tag{8}$$

the number of senescent loaded RBC at time t . By integration of (7) between $\bar{a}$ and $+\infty$ we obtain :

$$\frac{d}{dt}x_1(t) = -Kx_1(t)x_3(t) + n(t,\bar{a}) \tag{9}$$

with i.c.

$$x_1(0) = \int_{\bar{a}}^{+\infty} \varphi(a)da = \alpha n_0, \tag{10}$$

and

$$n(t,\bar{a}) = \begin{cases} \varphi(\bar{a}-t) & \text{if } 0 \leq t \leq \bar{a} \\ 0 & \text{if } t > \bar{a}. \end{cases} \tag{11}$$

2.2 Macrophage Equations

Let M_0 be the total number of macrophage cells. For $\forall t > 0$ the macrophages belong to one of the two classes :

$x_2(t)$: macrophages which are digesting senescent RBC (either from the loaded cohort of RBC and from normal blood circulation),

$x_3(t)$: macrophages which are free for phagocytosis of senescent RBC.

Therefore

$$M_0 = x_2(t) + x_3(t), \quad \forall t \geq 0. \tag{12}$$

Furthermore we assume that

a) If $x_2(t-T)$ are the macrophages which are digesting at $t-T$, the number of macrophages becoming free at t will be $\gamma x_2(t-T)$, where $[\gamma]=[day^{-1}]$ and $\gamma < 1$. This takes account of the fact that among $x_2(t-T)$ there are macrophages that phagocytated RBC at previous times before $t-T$.

b) The number of non-loaded senescent RBC is assumed to be constant and will be denoted by $\bar{E}$.

Hence

$$\frac{dx_3}{dt} = -Kx_1(t)x_3(t) - K\bar{E}x_3(t) + \gamma x_2(t-T), \quad \forall t \geq 0. \tag{13}$$

We must specify the i.c. on $x_3(t)$ for $t \in [-T, 0]$. For $t \in [-T, 0), x_1(t) = 0$ (no senescent loaded RBC are present before $t = 0$). Therefore

$$\begin{aligned} &\frac{dx_3}{dt} = -K\bar{E}x_3(t) + \gamma x_2(t-T) \\ &x_2(t) + x_3(t) = M_0, \quad t \in [-T, 0). \end{aligned} \tag{14}$$

We assume that

c) Without loaded RBC the system composed of macrophages and senescent RBC is at a positive equilibrium state which is stable.

Accordingly, the equilibrium of (14) is

$$\bar{x}_3 = \frac{\gamma M_0}{K\bar{E}+\gamma}, \qquad \bar{x}_2 = \frac{K\bar{E}M_0}{K\bar{E}+\gamma} \tag{15}$$

and its stability is ensured provided that

$$K\bar{E} > \gamma. \tag{16}$$

At $t = 0$ the amount of senescent loaded RBC injected is $x_1(0) = \alpha n_0$, and therefore at $t = 0$, x_3 is shifted from its equilibrium $\bar{x}_3$ to the value :

$$x_3^0 = \frac{\gamma M_0}{K(\bar{E} + x_1(0)) + \gamma}. \tag{17}$$

In conclusion, for the free macrophages we have

$$\frac{dx_3}{dt} = -Kx_1(t)x_3(t) - K\bar{E}x_3(t) + \gamma(M_0 - x_3(t-T)), \quad t > 0 \tag{18}$$

with i.c.

$$x_3(s) = \bar{x}_3, \quad s \in [-T, 0), \quad x_3(0) = x_3^0. \tag{19}$$

2.3 Drug Equation

We denote the average drug concentration in the macrophages by $x_4(t)$. If V is the total volume of macrophage population and $\beta = q_0/n_0$ is the average drug amount for each loaded RBC , then the input for $x_4(t)$ is $\beta K x_1(t) x_3(t)/V$.

If the drug inside the macrophages is catabolized by an enzyme reaction we can assume the average concentration of the drug sufficiently small s.t. $V_m x_4/(K_m + x_4) \simeq \eta x_4$ $(i.e. x_4 << K_m)$ where V_m, K_m respectively are the averages of maximum catabolic rate and affinity constant on the macrophage population, and $\eta = V_m/K_m, [\eta] = [day^{-1}]$. Therefore

$$\frac{dx_4}{dt} = \frac{\beta}{V} K x_1(t) x_3(t) - \eta x_4(t), \quad \forall t > 0 \tag{20}$$

with $x_4(0) = 0$.

2.4 Total Model Equations

In conclusion, the model equations are given (for $t > 0$) by

$$\begin{aligned}
&\frac{dx_1}{dt} = -K x_1(t) x_3(t) + n(t, \bar{a}), \quad x_1(0) = \alpha n_0 \\
&x_2(t) = M_0 - x_3(t), \quad x_2(s) = \bar{x}_2, \quad s \in [-T, 0), \quad x_2(0) = x_2^0 \\
&\frac{dx_3}{dt} = -K x_1(t) x_3(t) - K \bar{E} x_3(t) + \gamma x_2(t - T), \\
&\qquad\qquad x_3(s) = \bar{x}_3, \ s \in [-T, 0), \ x_3(0) = x_3^0 \\
&\frac{dx_4}{dt} = \frac{\beta}{V} K x_1(t) x_3(t) - \eta x_4(t), \quad x_4(0) = 0
\end{aligned} \tag{21}$$

where

$$n(t,\bar{a}) = \begin{cases} \varphi(\bar{a}-t), & t \in [0,\bar{a}] \\ 0, & t > \bar{a}, \end{cases}$$

and the constraints on the parameters are

$$K\bar{E} > \gamma, \qquad \gamma T = 1. \tag{22}$$

3 Problems

We can prove easily the following basic properties of the solutions :

a) positivity ;

b) boundedness ;

c) asymptotic stability of $(x_1 = 0,\ x_2 = \bar{x}_2,\ x_3 = \bar{x}_3,\ x_4 = 0)$.

Let m be the average drug concentration in the macrophages beyond which the drug has therapeutic effect, and let M be the average drug concentration in the macrophages beyond which the drug has cytotoxic effect, where

$$0 < m < M. \tag{23}$$

The control problem (C.P.) can be formulated as follows :

C.P. How to choose $\varphi : [0,\bar{a}] \to \Re_+, \varphi \in C^1([0,\bar{a}])$, and $\alpha \in [0,1]$ s.t.

i) $\exists t_1, t_2 \in \Re_+ (t_1 < t_2)$ satisfying $m < x_4(t) < M$ for $\forall t \in (t_1, t_2)$ and $x_4(t_1) = x_4(t_2) = m$;

ii) $\Delta t = t_2 - t_1$ be maximum ;

iii) $n_0 = \int_0^{\bar{a}} \varphi(a)da/(1-\alpha)$, $n_0 \in [n_1, n_2]$ be minimum .

4 Control Problem

Here we will consider the C.P. and give an estimate for the time duration Δt where drug administration is effective.

Let us consider (21) for $t \in [0, \bar{a}]$. Then

$$n(t, \bar{a}) = \varphi(\bar{a} - t), \quad \forall t \in [0, \bar{a}]. \tag{24}$$

Let σ be the average value of φ over $[0, \bar{a}]$:

$$\sigma = \frac{1}{\bar{a}} \int_0^{\bar{a}} \varphi(a) da. \tag{25}$$

Since $\int_0^{\bar{a}} \varphi(a) da = n_0(1 - \alpha)$, we have

$$\sigma = \frac{n_0(1 - \alpha)}{\bar{a}}. \tag{26}$$

Furthermore, we denote by

$$\rho = \max_{a \in [0, \bar{a}]} \varphi(a), \quad \mu = \min_{a \in [0, \bar{a}]} \varphi(a). \tag{27}$$

Denoted by $u_3(t) = x_3(t) - \bar{x}_3$, $\bar{u}_3 = x_3^0 - \bar{x}_3$, it is easy to show that

$$\bar{x}_3 - \delta < x_3(t) < \bar{x}_3 + \delta, \quad \forall t \geq 0 \tag{28}$$

where

$$\delta^2 = \max\{\bar{u}_3^2, \frac{KL}{2(K\bar{E} - \gamma)} \bar{x}_3^2\} \tag{29}$$

and L is a bound for x_1 , that is,

$$0 < x_1(t) < L, \quad \forall t > 0. \tag{30}$$

Of course $L_0 = n_0$ is a bound for $x_1(t)$. Therefore

$$c_0^- = \bar{x}_3 - \delta_0 < x_3(t) < \bar{x}_3 + \delta_0 = c_0^+ \tag{31}$$

where δ_0 is defined according to (29) with $L = L_0$. Provided that $c_0^- > 0$, by using the 1^{st} equation in (21) with (31), for x_1 we have the better estimate as

$$0 < x_1(t) < L_1 = \alpha n_0 + \frac{\rho}{Kc_0^-}, \quad \forall t > 0. \tag{32}$$

By using this estimate in (28) we obtain

$$c_1^- = \bar{x}_3 - \delta_1 < x_3(t) < \bar{x}_3 + \delta_1 = c_1^+ \tag{33}$$

where δ_1 is obtained from (29) with $L = L_1$. From the 1^{st} and 4^{th} equation in (21) we get

$$\frac{dx_4}{dt} = \frac{\beta}{V}\varphi(\bar{a} - t) - \eta x_4 - \frac{\beta}{V}\frac{dx_1}{dt}, \quad \forall t \in [0, \bar{a}] \tag{34}$$

$$-Kc_1^+ x_1 + \mu < \frac{dx_1}{dt} < -Kc_1^- x_1 + \rho, \quad \forall t \in [0, \bar{a}]. \tag{35}$$

Thanks to (34),(35) and provided that

$$\frac{\mu}{Kc_1^+} < x_1(0) = \alpha n_0 < \frac{\rho}{Kc_1^-} \tag{36}$$

we finally obtain

$$-\eta x_4 + \frac{\beta}{V}\sigma^- < \frac{dx_4}{dt} < -\eta x_4 + \frac{\beta}{V}\sigma^+, \quad x_4(0) = 0 \tag{37}$$

where

$$\sigma^- = (\frac{c_1^-}{c_1^+})\mu - (\rho - \mu), \quad \sigma^+ = (\frac{c_1^+}{c_1^-})\rho + (\rho - \mu). \tag{38}$$

Of course, we must choose $\varphi(a)$ with $\rho = \max\varphi, \mu = \min\varphi$ in order that $\sigma^- > 0$. Then

$$x_4^-(t) = \frac{\beta}{V}\frac{\sigma^-}{\eta}(1 - e^{-\eta t}) < x_4(t) < x_4^+(t) = \frac{\beta}{V}\frac{\sigma^+}{\eta}(1 - e^{-\eta t}), \quad t \in [0, \bar{a}] \tag{39}$$

and for $t > \bar{a}$

$$x_4^-(t) = \frac{\beta}{V}\frac{\sigma^-}{\eta}e^{-\eta(t-\bar{a})} < x_4(t). \tag{40}$$

The C.P. has a solution if

$$m < \frac{\beta}{V}\frac{\sigma^-}{\eta}, \quad \frac{\beta}{V}\frac{\sigma^+}{\eta} < M. \tag{41}$$

If we denote the time $\bar{t}_i$ $(i = 1, 2)$ satisfying $x_4^-(t_i) = m, \bar{t}_1 > t_1$ and $\bar{t}_2 < t_2$, then duration of therapeutic effect is s.t.

$$\Delta t = t_2 - t_1 > \bar{t}_2 - \bar{t}_1 = \bar{a} + \frac{1}{\eta}\log(\frac{\beta}{V}\frac{\sigma^-}{\eta}\frac{1}{m} - 1). \tag{42}$$

In order to have $\Delta t > \bar{a}$ it is sufficient that

$$\sigma^- > 2m\eta\frac{V}{\beta}, \text{ where } \sigma^- = (\frac{c_1^-}{c_1^+})\mu - (\rho - \mu). \tag{43}$$

Therefore

$$\sigma = \frac{n_0(1-\alpha)}{\bar{a}} > \mu = \min\varphi(a) > (\frac{c_1^+}{c_1^-})[2m\eta\frac{V}{\beta} + (\rho - \mu)].$$

If we assume a constant age distribution, i.e.

$$n(t, \bar{a}) = \begin{cases} \varphi(\bar{a} - t) = \sigma & t \in [0, \bar{a}] \\ 0 & t > \bar{a}, \end{cases} \tag{44}$$

then we have $\rho = \mu$. Hence in order to have $\Delta t > \bar{a}$, it is sufficient

$$\sigma = \frac{n_0(1-\alpha)}{\bar{a}} > (\frac{c_1^+}{c_1^-})2m\eta\frac{V}{\beta}.$$

Therefore the above two inequalities suggest that a constant age distribution of the drug loaded RBC may be the best choice for the C.P. since, in agreement with the requirement iii) of C.P., the constant age distribution (44) requires a lower amount n_0 of drug loaded RBC. A detailed analysis of the model and of the related C.P. will be presented in a future paper by the same authors.

REFERENCE

L.Chiarantini, L.Rossi, A.Fraternale and M.Magnani: Modulated Red Blood Cell Survival By Membrane Protein Clustering. Submitted, 1993.