AN OPTIMAL CONTROL PROBLEM FOR THE ADMINISTRATION OF A DRUG BY USING RED BLOOD CELLS AS BIOREACTORS

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INTRODUCTION

Mathematical models are often used to solve decision problems. A typical decision problem in clinical practice is that of optimal dosage of drugs, i.e. the choice of a dosage regimen in order to maintain a therapeutic level for a long time without producing serious side effects (see e.g.[1]). If a drug is encapsulated within a given volume of erythrocytes for treatment, the values of two parameters must be determined in order to obtain a desired result: the volume of erythrocytes prepared and the amount of the drug which is loaded inside them. In this paper an optimal control problem is formulated on the basis of a mathematical model which has been recently proposed in[2] and[3] to describe the administration of a drug after having encapsulated it inside erythrocytes as a non-diffusible prodrug. This model allows us to obtain an estimate of the maximum concentration of the drug in the plasma, and from this information we can recognize the set of allowable decisions (or admissible controls) which is the set of values of the control parameters which lead to therapeutic and non-toxic drug concentration in plasma. The solution of the optimal control problem indicates that in the set of admissible control parameters a unique point exists which gives the maximum time of therapeutic effect without reaching a toxic concentration. This point represents the optimal dosage strategy.

THE MATHEMATICAL MODEL

The model proposed in[2] and[3] is based on the compartmental representation shown in Fig.1 . If the concentrations of material in the compartments are taken as state variables, i.e. $x_1(t)$:=prodrug concentration in the injected erythrocytes at time t, $x_2(t)$:=drug

The Use of Resealed Erythrocytes as Carriers and Bioreactors
Edited by M. Magnani and J.R. DeLoach, Plenum Press, New York, 1992

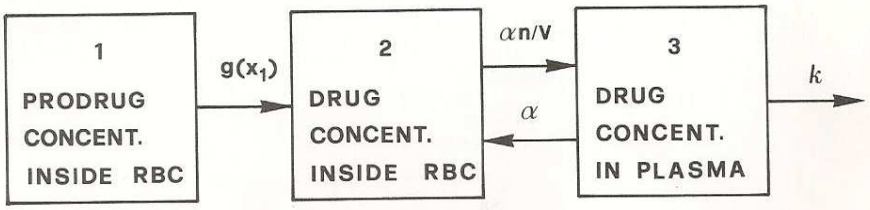

Figure 1. The three - compartment model corresponding to equations (1)

concentration inside the injected erythrocytes at time t, $x_3(t)$:=drug concentration in the plasma at time t, the evolution of the system is described by the following differential equations:

$$\begin{aligned} \dot{x}_1 &= -g(x_1) \\ \dot{x}_2 &= g(x_1) - \alpha(x_2 - x_3) \\ \dot{x}_3 &= \alpha \frac{n}{V}(x_2 - x_3) - kx_3 \end{aligned} \tag{1}$$

where $\dot{}$ denotes the time derivative , i.e. the rate of change of the concentrations with time, α is linear diffusion coefficient through the RBC membrane [h^{-1}], V is the plasma's volume [ml], k is the cumulative loss rate of the drug from the plasma [h^{-1}], n is the volume of RBC loaded with the prodrug [ml] . The function $g(x_1)$ represents the reaction rate with which the prodrug is converted to the diffusible active drug by the erythrocyte resident enzymes. Usually it is assumed :

$$g(x_1) = \frac{V_{max}\, x_1}{K_m + x_1} \tag{2}$$

where V_{max} is the maximum reaction rate [mM/h] and K_m the Michaelis-Menten constant [mM].

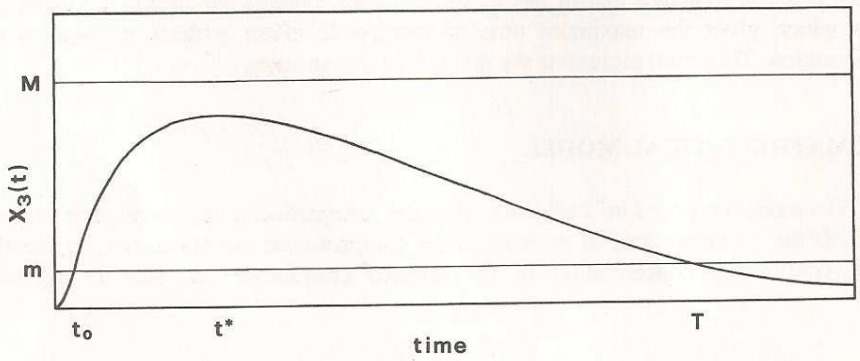

Figure 2. A typical curve of drug concentration in plasma obtained by solving equations (1).

If an amount of q_o μmoles of prodrug is loaded at t=0 into n ml of erythrocytes the initial condition for the equations (1) is:

$$x_1(0)=qo/n; \quad x_2(0)=0; \quad x_3(o)=0 \qquad (3)$$

The first differential equation in (1) is nonlinear and decoupled from the others. Thus the second and the third equations can be solved as a system of linear differential equations with forcing term $g(x_1)$, and the explicit expression of $x_3(t)$ can be obtained. A typical curve of the concentration $x_3(t)$ of the drug in the plasma is shown in Fig. 2. The solution represented in this figure is obtained with the condition $\alpha > k$. The same condition will be assumed in the following.

STATEMENT OF THE OPTIMAL CONTROL PROBLEM

The solution $x_3(t)$, which gives the drug concentration in the plasma (see Fig. 2), depends on the two controllable parameters n and q_o which represent the volume of erythrocytes injected and the amount of prodrug loaded inside them respectively. Accordingly we can write $x_3=x_3(t,n,q_o)$. The control parameters n and q_o must satisfy some constraints:

i) the volume of injected erythrocytes must lie within a finite range, i.e. $n_1<n<n_2$

ii)the initial concentration qo/n of prodrug inside the erythrocytes cannot overcome a given threshold, i.e. $0<q_o/n<\bar{c}$.

These two conditions define a region Ω in the plane (n,q_o) shown in Fig.3a. Let m be the minimum concentration of the drug in the plasma having a therapeutic effect and M be the toxic concentration (see Fig. 2). Let t_o be the instant at which the drug concentration in plasma begins to be therapeutic and $T>t_o$ the instant at which it ceases to be therapeutic (see Fig.2). These quantities depend on the control parameters n and q_o, hence we can write: $t_o=t_o(n,q_o)$ and $T=T(n,q_o)$. Let us now define the time of pharmacologic activity:

$$J(n,q_o)=T(n,q_o) - t_o(n,q_O) \qquad (4)$$

The problem of optimal control is that of finding the values (n^*, q_o^*) of the control parameters such that the time of pharmacologic activity J defined in (4) is maximum without reaching the toxic threshold. In other words we require :

A) $m < x_3(t, n^*, q_o^*) < M$ for each $to(n^*, q_o^*) < t < T(n^*, q_o^*)$

B) $J(n^*,q_o^*) = T(n^*, q_o^*) - to(n^*, q_o^*)$ is maximum.

An admissible control (n,q_o) is one which satisfies the conditions i) and ii), and is such that the request A is satisfied. If, as in Fig. 2, we call t* the instant at which the drug concentration in plasma x_3 attains its maximum value, then (n,q_o) is an admissible control if and only if $m<x_3(t^*,n,q_o)<M$, i.e. the maximum concentration of the drug in plasma is therapeutic but non toxic. The set of admissible controls is included in and depends on the values of m and M. Two typical examples are shown in Fig. 3b,c. In fig. 3c the value of M is lower than in Fig. 3b. The set $\tilde{\Omega}$ is represented by the shaded area whereas the regions (I) and (II) in Ω represent the control parameters for which $x_3(t^*)>M$ (toxic concentrations occur) and for which $x_3(t^*)<m$ (non therapeutic concentration) respectively.

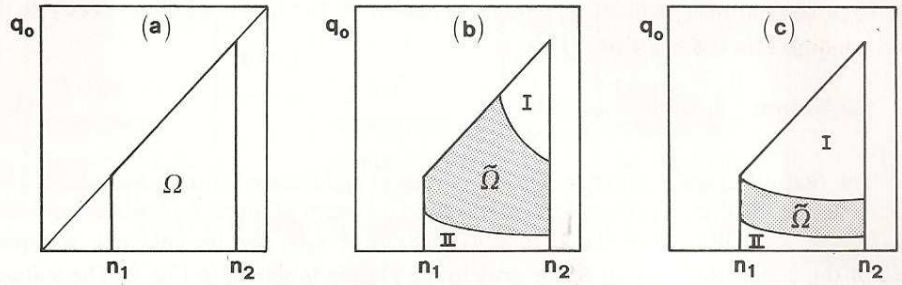

Figure 3. Examples of regions of admissible controls (n,q_o) as explained in "statement of the optimal control problem".

THE SOLUTION OF THE PROBLEM

The problem of optimal drug administration strategy stated above has a unique solution. The point (n^*, q_o^*), in the region $\tilde{\Omega}$ of admissible controls, giving the longest pharmacologic activity can be found on the basis of the following result given in [4] :

(R1) $\frac{\partial J}{\partial(q_o/n)} > 0$, i.e. the time of pharmacologic activity

increases for increasing initial concentration q_o/n. This can be achieved by:

(R1.1) keeping q_o constant and decreasing n;

(R1.2) keeping n constant and increasing q_o;

(R1.3) increasing the initial concentration q_o/n by varying both n and q_o.

Furthermore if q_0/n is constant, on each line $q_0/n=c$ we have:

(R2) $\frac{\partial J}{\partial(q_o/n)} > 0$, i.e. the time of pharmacologic activity increases for increasing n. These two results allow us to state the following:

Proposition. The optimal control (n^*, q_o^*) in the set of admissible controls is the one for which the initial concentration inside the erythrocytes q_o/n is maximum and on the line on which q_o/n is maximum the volume of erythrocytes, n*, must assume its maximum.

Proof. Consider a generic control $u=(n,q_o)$ inside . The optimal control (n^*,q_o^*) can always be reached following one of the two following pathways:

i) starting from $u= (n,q_o)$ we keep q_o constant and we decrease n up to n_1. Therefore $J(n,q_o)$ increases along this path as stated in (R1). Then, with $n=n_1$ fixed, we increase q_o up to $q_o=cn_1$. As shown by (R1) $J(n,q_o)$ is still increasing. Finally on the straight line of constant concentration $q_o/n=c$ $J(n,q_o)$ increases for increasing n according to (R2) until it reaches its maximum at (n^*, q_o^*) (Fig. 4a);

(ii) Starting from $u=(n,q_o)$ we keep n constant and q_o is increased. From (R1) $J(n,q_o)$ is increasing. Then, on the line $q_o/n=\bar{c}$, $J(n,q_o)$ increased for increasing n because of (R2) and again J will reach its maximum at (n^*, q_o^*) (Fig.4b).

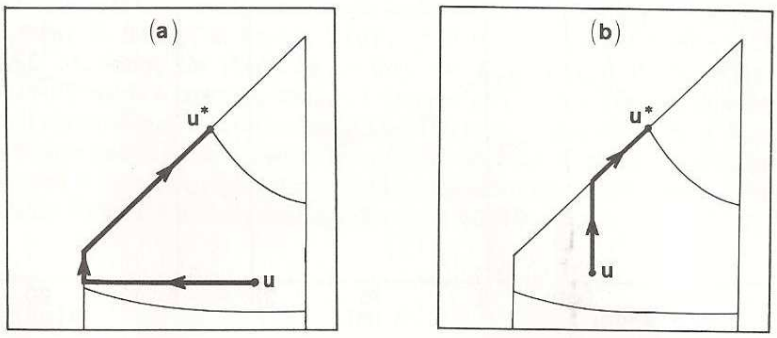

Figure 4. The paths (a) and (b) reaching the optimal control, as described in "The solution of the problem".

THE CASE OF ddCyd ADMINISTRATION FOR HIV TREATMENT

The results of section 4 have been applied to the case of the administration of 2',3'-dideoxycytidine (ddCyd) by using 2',3'-dideoxycytidine-5'-phosphate (ddCMP) as non-diffusible prodrug. The values of the parameters, V_{max} and K_m are given in[5] and[6]: $\alpha=4.8h^{-1}$; $K_m = 6$ mM ; $V_{max} = 1.5$ mM/h . The value of the elimination rate k, estimated on the basis of the data given in[7], is $k = 0.58\ h^{-1}$. A reasonable estimate of plasma volume is V= 5000 ml. According to[8] we take m = 0.5 μM and M = 10 μM. The constraints on the control parameters are: 5 ml $\leq n \leq$ 30 ml; qo/n 10 mM. In this case the region $\tilde{\Omega}$ of admissible control parameters (n,q_o) has been numerically estimated on the basis of "over" and "under" estimates of the maximum concentration $x_3(t)$ and is shown in Fig.5a. The optimal control (n^*, q_o^*) is the vertex of coordinates $u^*=(n^*=30$ ml, $q_o^* = 300$ μmoles) shown in Fig. 5a. With these optimal values of n and q_o the curve $x_3(t)$ of the drug concentration in the plasma is that shown in Fig. 5b and in this case the time of pharmacologic activity is $J = T - t_o = 24$ h.

With the values of the parameters listed above the variations of $J(n,q_o)$ have beeen numerically computed when the control parameters move along the paths described in section 4. In Fig. 6a the amount q_o of loaded prodrug is increased with a fixed value of

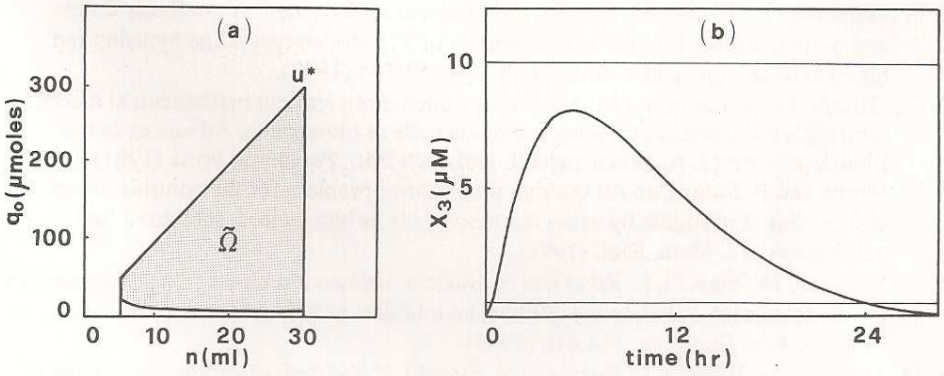

Figure 5. The region of admissible control (a) and the optimal solution (b) for ddCyd.

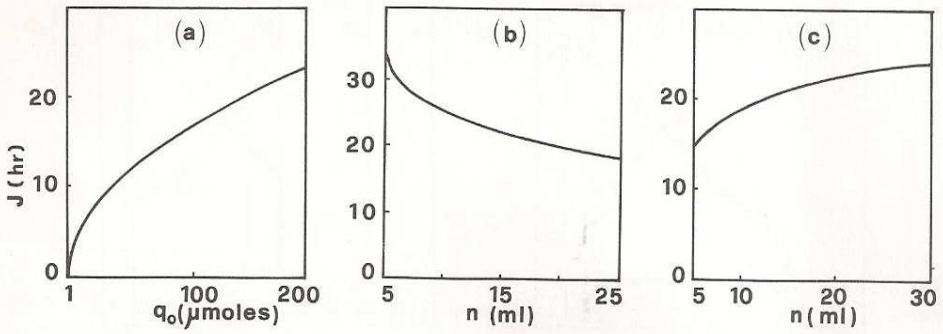

Figure 6. The time of pharmacological activity with fixed n, q_O and q_o/n respectively.

n=20 ml (path R1.2). In Fig. 6b q_o=45 μmoles is fixed and n is allowed to vary (path R1.1). Finally in Fig. 6c the initial concentration q_o/n=10 mM is fixed and by increasing the volume of erythrocytes n we are moving along a line of constant concentration (path R2). The graphs confirm the conclusions of section 4.

CONCLUSIONS

In the present paper the problem of optimal dosage is considered for the administration of a drug by using erythrocytes as circulating bioreactors. The study has been carried out on the basis of a mathematical model which describes the release of the drug in plasma after having entrapped it inside erythrocytes as a non-diffusible prodrug. The target of the optimization problem is to prolong the pharmacologic activity without causing side effects. The control parameters, which have been uniquely determined in order to reach the target, are the amount of prodrug loaded and the volume of erythrocytes injected. Their optimal values are such that the initial concentration of prodrug inside the red blood cells must be maximum and the volume of the erythrocytes prepared must be maximum observing the given constraints.

REFERENCES

1. R. Bellman, Mathematical methods in Medicine, World Scientific (1974).
2. F. Solimano, G.I. Bischi, M. Bianchi, L. Rossi and M. Magnani, A nonlinear three-compartment model for the administration of 2',3'-di-deoxycytidine by using red blood cells as bioreactors, Bull. Math. Biol. 52:785 (1990).
3. G.I. Bischi, F. Solimano and M. Magnani, A three-compartment mathematical model for drug administration by using red blood cells as bioreactors, Advances in the Biosciences 81:17, R. Green and J.R. DeLoach Eds., Pergamon Press (1981).
4. E. Beretta and F. Solimano, An optimal time control problem for the administration of 2',3'-dideoxycytidine by using red blood cells as bioreactors, submitted for publication in J. Math. Biol. (1991).
5. M. Magnani, M. Bianchi, L. Rossi and V. Stocchi, Human red blood cells as bioreactors for the release of 2',3'-dideoxycytidine, an inhibitor of HIV infectivity, Biochem. Biophys. Res. Commun. 164:446 (1989).
6. M. Magnani, M. Bianchi, L. Rossi and V. Stocchi, 2',3'-dideoxycytidine permeation of the human erythrocyte membrane, Biochem. Int. 19:227 (1989).

7. R. Yarchoan, R.V. Thomas, J.P. Allain, N. McAtee, R. Dubinsky, H. Mitsuja, T.J. Lawley, B. Safai, C.E. Myres, C.F. Perno, R.W. Klecker, R.J. Willis, M.A. Fischl, M.C. McNeely, J.M. Pluda, M. Leuther, J.M. Collins and S. Broder, Phase I of 2',3'-dideoxycytidine in severe human immunodeficiecy virus infection as a single agent and alternating with zidovudine (AZT), The Lancet 76 (1988).
8. M. Mitsuya and S. Broder, Inhibition of the in vitro infectivity and cytopathic effect of human T - lymphotrophic virus type III/lynphadenopathy-associated virus (HTLV-III/LAV) by 2',3'-dideoxynucleosides, Proc. Natl. Acad. Sci. USA 83:1911 (1986).