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NUMERICAL TREATMENT OF CARDIAC DISEASES USING OPTIMAL CONTROL THEORY

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Abstract—We propose a mathematical modelization and optimization of the action of some drugs such as β-blockers—a particular drug (tertatolol) studied in Servier laboratories is specially examined. Linear compartmental models are first tried but they are not convenient for explaining the experimental data. Then a dose effect relation is directly seeked. One obtains a nonlinear relationship between the dose, the plasmatic concentration and the drug's effect. Using some optimal control methods allows one to define an optimal therapeutic giving the optimal doses and possibly the optimal times optimizing some given criteria.

1. INTRODUCTION

The β-blockers are used for the treatment of cardiac disorders[1] (hypertension, angina pectoris, cardiac arrhythmias). The medical effects are well proved[2]. Our study consists first to relate the blood concentration of such drugs and the medical effect. The main difficulty comes from the nonlinearity of the phenomenon. After obtaining a well-adapted mathematical model it becomes possible to solve optimal control problems involving optimal therapeutics (indeed we can find the optimal oral doses and the optimal times of injection). The experimental results are given by Servier laboratories (cardiologic division) and are relative to a drug called Tertatolol. A compartmental classical approach[3] was first used and allowed to prove the nonlinearity of the biological system. Then a "black box" study was proposed for obtaining a convenient mathematical relation between blood concentration of drug and pharmacodynamic effect. The associated optimal control problem may be solved numerically by using an original global optimization method[4] developed in Medimat laboratory.

2. CLASSICAL APPROACHES FOR MODELLING THE DRUG'S EFFECT

Classical literature[5] generally proposes simple linear relationships such as the following:

$$E = a \log C + b, \tag{2.1}$$

where C represents the concentration of drug in blood and E the effect. In the case of tertatolol, the effect is the product of the arterial pressure by the heart rate. The formula

(2.1) involves two constants a and b which have to be identified from experimental data. Table 1 gives experimental data performed with ten volunteers in good health. Table 1 gives the mean values. For each patient, the plasma concentration C and the effect E was measured at various times t_i:

$$t_i = 0, 0.5, 1, 2, 4, 6, 9, 12, 15, 24 \text{ h},$$

and for four doses,

$$D = 1, 2, 5, 10 \text{ mg}.$$

Unfortunately it was not possible to identify a and b [in (2.1)] satisfying the experimental data and the relationship (2.1). Therefore, the relationship between the effect E and the log C is not linear. Later we shall propose a nonlinear approximation generalizing (2.1). But before we must notice the drug's efficiency proved by the following results:

- The efficiency is an increasing function of the absorbed dose;
- the individual means of E are decreasing functions of the dose;
- the individual differences between the maximum and the minimum values of E are increasing functions of the dose.

Now coming back to the problem of finding a mathematical relation between the concentration and the effect, one can propose a natural generalisation of formula (2.1) such as the following:

$$E = b_0 + a_1 \log(1 + C) + a_2 \log^2(1 + C). \tag{2.2}$$

With the experimental data given by Table 1, we obtain (for $D = 2$ mg) $a_1 = -22.2017$, $a_2 = 0.756\,14\ldots$ and a good approximation of the effect[8]. In (2.2) b_0 is a constant depending on the individual. Of course this formula proves the nonlinearity of the relationship.

Another classical approach[6, 7] was also tried. It is based on the compartmental analysis[8] and consists to relate our variables by a three compartments model such as in Fig. 1.

Such a linear model leads to the following structural expression for the blood concentration of drug $C_1(t)$:

$$C_1 = a_0 e^{-\lambda_0 t} + a_1 e^{-\lambda_1 t} + a_2 e^{-\lambda_2 t} \qquad (\lambda_i \geq 0). \tag{2.3}$$

Table 1.

Doses Times (in hours)	1 mg		2 mg		5 mg		10 mg	
	C	E	C	E	C	E	C	E
0	0	28.5	0	26.1	0	24.5	0	25.4
1/2	7.7	25.5	28.9	21.3	58.5	19.0	150	17
1	15.6	22.6	32.3	18.7	88.9	15.9	190.4	14.2
2	20	20	32.5	17	111.4	14.5	197.9	13.8
4	11.1	21.2	22.1	17.3	71.6	14.7	116	14.4
6	5.7	23.9	11.7	20.5	38.2	16.1	66.5	16.4
9	1.4	24.6	5.2	21.3	20.7	17.7	33.5	16.3
12	0.3	25.5	2.6	22.6	10.9	18.1	20.5	17.9
15	0.15	25.9	0.8	24.8	5.2	20.3	11.7	19.4
24	0	26.4	0.3	23.2	2	20.8	5.2	20.1

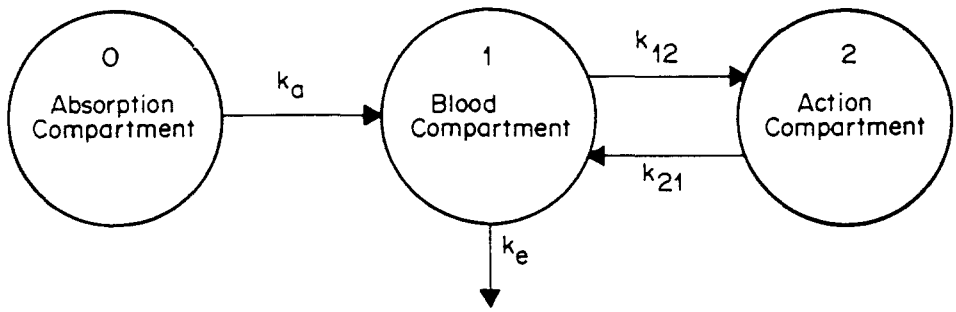

Fig. 1.

Identifying the a_i and λ_i ($i = 0, 1, 2$) involves characteristic values λ_i depending on the dose D (see Table 2). Furthermore, the parameters a_i are not proportional to the dose. All these facts involve the nonlinearity of the model[3, 8, 1]. The conclusions were the same when examining the 40 series of individual values.

Therefore, a linear compartmental model may not be adapted to our drug (tertatolol).

Formula (2.2) could be retained with some improvements. Indeed the coefficients a_1 and a_2 depend on D. Furthermore, (2.2) gives a poor approximation between 15 and 24 h. A delay has to be introduced in our model. Thus we prefered to build directly a relationship between the dose D, the plasmatic concentration C and the effect E. To do that a nonlinear generalization of (2.1) was imagined and the following relation was proposed:

$$E = b_0 + b_1 \log\{1 + C[\gamma_D(t)]\}, \tag{2.4}$$

where b_0 is a constant depending on individual; b_1 has to be identified as well as the function $\gamma_D(t)$ that plays the role of a delay function. Practically, C is taken as

$$C = a_1 e^{-\lambda_1 t} + a_2 e^{-\lambda_2 t} \qquad (\lambda_1, \lambda_2 \geqslant 0), \tag{2.5}$$

where a_1, a_2, λ_1, λ_2 are identified from the results corresponding to the dose $D = 2$ mg by minimizing the criterion

$$\min_{a_1, a_2, \lambda_1, \lambda_2} \sum_{j=1}^{10} \left[\sum_{i=1}^{2} a_i e^{-\lambda_i t_j} - C(t_j) \right], \tag{2.6}$$

where $C(t_j)$ represents the experimental data (concentrations) associated to $D = 2$ mg. The *global* optimum of this criterion was obtained by using a global optimization technique that will be described later. The main difficulty comes from the identification of $\gamma_D(t)$.

Table 2.

Doses	λ_0	λ_1	λ_2	a_0	a_1	a_2	δ% (standard deviation)
1 mg	1.633 39	1.383 01	0.427 67	193.492	−265.72	68.405	3.496%
2 mg	6.8834	0.4855	0.426 34	−20.733	−468.45	491.37	3.6018%
5 mg	0.730 083	0.574 84	0.139 29	−1079.47	1011.89	50.29	4.9063%
10 mg	1.331 95	0.717 82	0.220 11	−532.247	282.208	249.663	4.449%

We tried three possibilities for γ:

- a linear function according to t,
- a quadratic polynomial function,
- a cubic polynomial function.

The general structure used for $\gamma_D(t)$ was thus the following:

$$\gamma_D(t) = \sum_{k=1}^{m} a_k t^k \qquad \text{(where } m = 1, 2 \text{ or } 3\text{)}. \tag{2.7}$$

The parameter b_1 is determined independently of D. But the coefficients of $\gamma_D(t)$ in (2.7) are identified in function of the dose D (in fact polynomial functions of degree 3 were identified).

More precisely, the following optimization problem has to be solved:

$$\min_{b_1, a_1, \ldots, a_m} \sum_{j=1}^{10} (b_0 + b_1 \log\{1 + C[\gamma_D(t)]\} - E(t_j, D))^2 \tag{2.8}$$

for each dose D. Of course $\gamma_D(t)$ is replaced in (2.8) by its mathematical expression (2.7). Then the functions $a_k(D)$ in (2.7) are identified by using once more an optimization technique[9].

The mathematical relation (2.4) being completely identified, it becomes possible to consider the important problem of defining an optimal therapeutics relative to some optimal criterion.

3. OPTIMAL THERAPEUTICS—A FIRST APPROACH USING A LINEAR MODEL

The main objective of a medical treatment consists in optimizing therapeutics. In other words we need to maintain the effect E approximately constant. According to the formulae (2.2) or (2.4) this problem is equivalent to the following:

Maintain the concentration C equal to a constant as far as possible. In other words the criterion

$$J = \int_0^T [C(t) - A]^2 \, dt, \qquad \text{where } A \text{ is a fixed constant,} \tag{3.1}$$

has to be minimized. In (3.1) the constant A is determined from medical considerations.

For each dose, the function C (noted C_1 in the following) may be considered in first (and rough) approximation as the solution of the three compartments model described in Fig. 1 and represented by the differential linear system

$$\begin{aligned}
\dot{C}_0 &= -k_a C_0, \\
\dot{C}_1 &= -(k_{12} + k_e) C_1 + k_{21} C_2 + k_a C_0(t), \\
\dot{C}_2 &= k_{12} C_1 - k_{21} C_2, \\
C_1(0) &= 0, \; C_2(0) = 0, \\
C_0(0) &= C^{te} \text{ related to } D (= D/V_1, \; V_1 \text{ volume of compartment 1}).
\end{aligned} \tag{3.2}$$

Of course, $C_1(t)$ is the solution of the following system:

$$\begin{aligned} \dot{C}_1 &= -(k_{12} + k_e)C_1 + k_{21}C_2 + u(t), \\ \dot{C}_2 &= k_{12}C_1 - k_{21}C_2, \\ C_1(0) &= C_2(0) = 0, \end{aligned} \tag{3.3}$$

where $u(t) = k_a C_0(t) = (Dk_a/V_1)\,\mathrm{e}^{-k_a t}$ is an input function coming in compartment 1. $u(t)$ may be considered as the control function and thus a first question arises: What is the optimal function $u(t)$ ensuring

$$\min_{u(t)} \left\{ J = \int [C_1(t) - A]^2 \, \mathrm{d}t \right\} ? \tag{3.4}$$

The answer is very easy. It suffices to consider first the case where the initial conditions in (3.3) are $C_1(0) = A$, $C_2(0) = 0$. Putting $C_1(t) \equiv A$ (for all $t \geqslant 0$) in (3.3) involves

$$\dot{C}_2 = k_{12}A - k_{21}C_2,$$

giving easily

$$C_2(t) = -(k_{12}/k_{21})\,[A\,\mathrm{e}^{-k_{21}t} - A]. \tag{3.5}$$

Then the first equation (3.3) leads to

$$u(t) = A[k_e + k_{12}\,\mathrm{e}^{-k_{21}t}]. \tag{3.6}$$

More generally, if we consider the general initial conditions

$$C_1(0) = C_2(0) = 0, \tag{3.7}$$

the Laplace transformation[10] allows to find a general solution which is a distribution function[10]. Indeed the optimal control given by (3.6) becomes

$$u(t) = A[\delta_{(0)} + k_e + k_{12}\,\mathrm{e}^{-k_{21}t}], \tag{3.8}$$

where $\delta_{(0)}$ is the Dirac function[10] corresponding practically to an instantaneous injection at time 0. The relationship (3.8) can be easily proved by transforming (3.3) with the Laplace transformation.

The optimal control problem (3.4) associated to the differential system (3.3) being solved (explicitly!) the general problem (3.2), (3.4) may be considered. The idea consists to find an optimal solution corresponding to oral doses D_i ($i = 0, \ldots, m$) given at times t_i and approximating the optimal controls (3.6) or (3.8). More precisely, the doses D_i and times t_i have to be determined for ensuring the minimization of the criterion

$$J_1 = \int_0^T \left[\sum_{j=0}^{m} D_j k_a\,\mathrm{e}^{-k_a(t-t_j)} Y(t - t_j) - Ak_e - Ak_{12}\,\mathrm{e}^{-k_{21}t} \right]^2 \mathrm{d}t, \tag{3.9}$$

where $D_j k_a\,\mathrm{e}^{-k_a(t-t_j)}$ corresponds to an input $u_j(t)$ in compartment 1 associated to an oral

dose D_i taken at time t_i. The function $Y(t - t_j)$ is the Heaviside function equals to 0 for $(t - t_j) < 0$ and equals to 1 for $(t - t_j) \geq 0$. The criterion (3.9) has to be minimized according to the parameters $D_0, \ldots, D_m, t_0, t_1, \ldots, t_m$. The sum in (3.9) takes into account the following hypothesis:

- when successive doses are absorbed the corresponding concentrations of drug must be added. The term

$$\sum_{j=0}^{m} D_j k_a \, e^{-k_a(t-t_j)} Y(t - t_j)$$

is thus the resulting concentration when $(m + 1)$ doses D_j are absorbed at time t_j. This hypothesis is in agreement with the classical parmacologic literature[11, 12]. This optimization problem (3.9) is equivalent to that of finding the "best" doses and times giving the best approximation of the exact optimal solution

$$Ak_e + Ak_{12} \, e^{-k_{21}t}.$$

Numerical results were performed with $A = 7.383\,426$ (biological constant determined by medical considerations) corresponding to an effect $E = 20$. The following optimal results were obtained for $T = 24$ hr:

$$t_0 = 0, \qquad D_0 = 1.013 \text{ mg}, \qquad D_1 = 3.168, \qquad t_1 = 16.74.$$

As we shall see later, these numerical results are not very different of those obtained by using nonlinear models.

4. OPTIMAL THERAPEUTICS ASSOCIATED TO NONLINEAR MODELS

Recall the formula relating the dose, the concentration and the effect of the drug (tertatolol):

$$E = b_0 + b_1 \log[1 + C(\gamma_D(t))]. \tag{4.1}$$

We are now working with identified parameter b_1 and function $\gamma_D(t)$. Optimal therapeutics may be determined by setting the following optimal control problem: Find the inputs (doses) $D_0, \ldots, D_j$ and the times of absorption $t_0, \ldots, t_j$ such that the criterion

$$\int_0^T [E(t) - 20]^2 \, dt \tag{4.2}$$

be minimum. The constant 20 (and later 19) is an effect value defined by biological considerations and corresponding to a satisfactory value of the effect. The time T is fixed and may be great. Of course, it will be necessary to precise the function $E(t)$ in presence of successive doses D_i absorbed at times t_i.

Using the additivity of the concentrations when successive doses are given and fixing first the times t_i and the number of doses $j + 1$, we obtain the simplified optimization problem:

$$\min_{D_0,\ldots,D_j} \int_0^T [E(t) - 20]^2 \, dt = \min_{D_0,\ldots,D_j} \sum_{i=0}^{j} \int_{t_i}^{t_{i+1}} [E_i(t) - 20]^2 \, dt, \tag{4.3}$$

where the function $E_i(t)$ introduced in (4.3) is defined by

$$E_i(t) = b_0 + b_1 \log\left(1 + \sum_{k=i-1}^{i} C[\gamma_{D_k}(t - 24k)]Y(t - 24k)\right), \tag{4.4}$$

with $t \in (t_i, t_{i+1})$, and where we use *only* the two last terms of concentrations corresponding to the doses D_i and D_{i-1}. This approximation is justified by the experimental data: The concentrations are weak after 24 h following the absorption. If we want to consider all the concentrations, the formula (4.4) becomes

$$E_i(t) = b_0 + b_1 \log\left(1 + \sum_{k=0}^{i} C[\gamma_{D_k}(t - 24k)]Y(t - 24k)\right). \tag{4.5}$$

Of course it is easy to generalize to an arbitrary time interval $\beta \neq 24$. Instead of supposing the concentrations additivity it is possible to introduce the additivity of effects which involves a new formula for $E_i(t)$, effect on (t_i, t_{i+1}):

$$E_i(t) = b_0 + \sum_{k=0}^{i} b_1 \log\{1 + C[\gamma_{D_k}(t - \beta k)]\}, \tag{4.6}$$

where β is the interval between two successive times t_i, t_{i-1}. Decompositions similar to those used in dynamic programming[13] can be developed. We obtain

$$\min_{D_0,\ldots,D_j} \sum_{i=0}^{j} \int_{t_i}^{t_{i+1}} (E_i - 20)^2 \, dt$$

$$= \min_{D_0,\ldots,D_{j-1}} \left[\int_0^{t_1} (E_0 - 20)^2 \, dt + \cdots + \min_{D_j} \int_{t_j}^{t_{j+1}} (E_j - 20)^2 \, dt \right], \tag{4.7}$$

because in the first sum all terms but the last are independent of D_j. In the same way we deduce

$$\min_{D_0,\ldots,D_{j-1}} \left[\int_0^{t_1} (E_0 - 20)^2 \, dt + \cdots + \min_{D_j} \int_{t_j}^{t_{j+1}} (E_j - 20)^2 \, dt \right]$$

$$= \min_{D_0,\ldots,D_{j-2}} \left[\int_0^{t_1} (E_0 - 20)^2 \, dt + \cdots + \min_{D_{j-1}} \left(\int_{t_{j-1}}^{t_j} (E_{j-1} - 20)^2 \, dt \right.\right.$$

$$\left.\left. + \min_{D_j} \int_{t_j}^{t_{j+1}} (E_j - 20)^2 \, dt \right) \right]. \tag{4.8}$$

This relation is obtained because only the two last terms on the right-hand side are dependent of D_{j-1}. The process is continued until

$$\min_{D_0,\ldots,D_j} \sum_{i=0}^{j} \int_{t_i}^{t_{i+1}} (E_i - 20)^2 \, dt = \min_{D_0} \left\{ \int_0^{t_1} (E_0 - 20)^2 \, dt + \min_{D_1} \left[\int_{t_1}^{t_2} (E_1 - 20)^2 \, dt \right.\right.$$

$$\left.\left. + \cdots + \min \left(\int_{t_j}^{t_{j+1}} (E_j - 20)^2 \, dt \right) \cdots \right] \right\}. \tag{4.9}$$

Then a numerical algorithm may be proposed:

- At step 0 $\int_{t_j}^{t_{j+1}} (E_j - 20)^2 \, dt$ is minimized according to D_j for different values of D_{j-1} (practically 1, 2, 5, 10 mg). The function D_j is thus identified using a fixed mathematical structure such as the following:

$$D_j = \phi_0(D_{j-1}) = A_1 \, e^{\lambda_1 D_{j-1}} + A_2 \, e^{\lambda_2 D_{j-1}}. \tag{4.10}$$

- At step j, the following sum is minimized according to the single variable D_0:

$$\min_{D_0} \left[\int_0^{t_1} (E_0 - 20)^2 \, dt + \int_{t_1}^{t_2} \{E_1[D_0, \phi_{j-1}(D_0)] - 20\}^2 \, dt \right.$$
$$\left. + \cdots + \int_{t_j}^{t_{j+1}} \{E_j[\phi_1(D_{j-2}), \phi_0(D_{j-1})] - 20\}^2 \, dt \right]. \tag{4.11}$$

D_0 being determined, we can define successively $D_1, \ldots, D_j$ by using the following relations:

$$D_1 = \phi_{j-1}(D_0), \qquad D_2 = \phi_{j-2}(D_1), \ldots, \qquad D_j = \phi_0(D_{j-1}). \tag{4.12}$$

Numerical results based on this technique will be detailed in the next paragraph.

The previous method was well adapted to the particular optimal problem where the times of absorption were fixed. Now we will treat the *general* problem consisting in finding the doses D_i *and* the times t_i. More precisely we want to solve

$$\min_{\substack{D_0,\ldots,D_m \\ t_0,\ldots,t_m}} \int_0^T [E(t) - 19]^2 \, dt = \min_{\substack{D_0,\ldots,D_m \\ t_0,\ldots,t_m}} \sum_{i=0}^{m} \int_{t_i}^{t_{i+1}} [E_i(t) - 19]^2 \, dt, \tag{4.13}$$

where the biological constant is chosen equal to 19 and where the effect $E_i(t)$ on $[t_i, t_{i+1}]$ is defined by the formula

$$E_i(t) = b_0 + b_1 \log \left\{ 1 + \sum_{k=0}^{i} C[\gamma_{D_k}(t - \beta k)] \right\}, \tag{4.14}$$

using the additivity of concentrations. A numerical algorithm giving only a *suboptimum* may be performed as follows:

- At step 0 the following optimization problem is solved:

$$\min_{D_0, t_0} \int_{t_0}^{t_1} (E_0 - 19)^2 \, dt, \tag{4.15}$$

where t_0' and t_1' are fixed (for instance $t_0' = t_0 = 0$, $t_1' = 24$ h). Let D_0 and t_0 the optimal calculated solutions.

- At step k we need to solve the optimization problem

$$\min_{D_{k-1}} \int_{t_{k-1}}^{t_k'} (E_{k-1} - 19)^2 \, dt, \tag{4.16}$$

with t_k' fixed (for instance $t_k' = 24\,k$).

Solving this problem for several values t_{k-1} allows to find the relation $D_{k-1} = \phi(t_{k-1})$. In fact we may look for a fixed formula such as

$$D_{k-1} = a_1 e^{\lambda_1 t_{k-1}} + a_2 e^{\lambda_2 t_{k-1}} = \phi(t_{k-1}), \tag{4.17}$$

where a_1, a_2, λ_1, λ_2 are identified with an optimization technique[14, 15].

• Then at step k_{bis} we consider the optimization problem

$$\min_{t_{k-1}} \left[\int_{t'_{k-1}}^{t_{k-1}} (E_{k-2} - 19)^2 \, dt + \int_{t_{k-1}}^{t'_k} (E_{k-1} - 19)^2 \, dt \right], \tag{4.18}$$

where t'_{k-1}, t'_k are fixed (for instance we chose $t'_k = 24$ k). Using a numerical optimization algorithm[19] gives t_{k-1}. Indeed the function in (4.18) depends only on t_{k-1} by putting the expression (4.17) $[D_{k-1} = \phi(t_{k-1})]$ in the formula (4.14) giving $E_i(t)$ in function of D_i. Numerical experiences will be given later. Before we shall describe a new global minimization technique which will be applied to our optimal therapeutics problems.

5. A GLOBAL OPTIMIZATION METHOD FOR SOLVING OPTIMAL THERAPEUTICS PROBLEMS

Let us consider the general optimization problem introduced in the previous paragraph:

$$\min_{\substack{D_0,\ldots,D_m \\ t_1,\ldots,t_m}} \int_0^T [E(t) - L]^2 \, dt, \tag{5.1}$$

with the contraints $0 \leqslant D_j \leqslant 10$, $24j \leqslant t_j \leqslant 24(j+1)$, $j = 1, \ldots, m$. In (5.1) the constant L may be arbitrary (for instance equal to 19 or 20 or to any "optimal" value defined by the physician). The formula associated to $E(t)$ on $[0, T]$ with successive doses at time t_i may be defined as follows:

$$E_i(t) = b_0 + b_1 \log \left(1 + \sum_{k=0}^{i} C(\gamma_{D_k}, t - t_k) Y(t - t_k) \right) \tag{5.2}$$

on (t_i, t_{i+1}).

This relation uses the additivity of the plasmatic concentrations. In practical problems coming for instance from pharmacodynamics and needing minimization or maximization methods, only the absolute extremum can supply the best result, i.e. the best solution of our optimal control problem. Thus a method giving this value would be very important and interesting. Unfortunately, the classical literature does not supply many techniques in this area outside of the case involving one-variable functions. Our idea[16] consists to transform the n-variables functions into a one variable function. To do that we use a simple transformation called Alienor[4] and based on the property of the Archimedian spiral ($r = a\theta$). The curve representing the spiral lies at a maximum distance ($2\pi a$) from any point M in the space R^2.

Then let us consider an optimization problem:

$$\min_{x,y} f(x, y). \tag{5.3}$$

Setting $x = a\theta \cos \theta$, $y = a\theta \sin \theta$, $\theta \geq 0$, involves

$$\min f(x, y) \not\equiv \min_{\theta} f(a\theta \cos \theta, a\theta \sin \theta) = \min_{\theta} G(\theta), \tag{5.4}$$

leading to a one-variable minimization problem.

This transformation can easily be generalized to n variables giving a tree structure[17]. From an optimal point θ the coordinates x, y may be calculated by using $x = a\theta \cos \theta$, $y = a\theta \sin \theta$ and conversely if we want to obtain θ in function of x, y we have

$$\theta = (1/a) \sqrt{x^2 + y^2}. \tag{5.5}$$

Generalization to n variables does not present any difficulty.

Let us now apply the Alienor transformation to the problem (5.1) with, for instance, five variables t_1, t_2, D_0, D_1, D_2. The following transformations have to be performed:

$$t_1 = (\theta_2 \cos \theta_2)/2\pi, \qquad t_2 = (\theta_2 \sin \theta_2)/2\pi, \qquad D_0 = (\theta_3 \cos \theta_3)/2\pi,$$
$$D_1 = (\theta_3 \sin \theta_3)/2\pi, \qquad D_2 = (\theta_4 \cos \theta_4)/2\pi,$$

where a is chosen equal to $1/2\pi$[17]. Then

$$\theta_0 = (\theta \cos \theta)/2\pi, \qquad \theta_1 = (\theta \sin \theta)/2\pi, \qquad \theta_2 = (\theta_0 \cos \theta_0)/2\pi,$$
$$\theta_3 = (\theta_0 \sin \theta_0)/2\pi, \qquad \theta_4 = (\theta_1 \cos \theta_1)/2\pi.$$

We note that one obtains a unique variable θ involving a new optimization problem according to the single variable θ. It suffices to explicit the functional

$$\int_0^T [E(t) - L]^2 \, dt$$

in function of θ.

For obtaining this dependence the parameters $t_1, t_2, \ldots, D_2$ have to be expressed in function of θ by using the previous transformation. Numerical experiences will be described in the following. Some crafts are necessary for accelerating the numerical process[17]. For complementary informations one can consult [17].

Remark. Some other classical optimization techniques were also tested[18]. For instance, we used the Vignes's method[19, 20] which is a variant of the Hooke and Jeeves method[9]. The main inconvenience of these techniques is that they give a *local* optimum and we are never sure to obtain a global optimum. Furthermore, they need the derivability of the function to optimize. On the contrary our global method needs only the continuity. And even the continuity is not necessary! Of course this global method can be used for many biological problems involving some criterion optimization[21, 22] and even for solving functional equations.

6. A LAST METHOD BASED ON A NON LINEAR RELATION

In the previous parts we detailed some methods using optimization or dynamic programming techniques. These methods allow to determine optimal therapeutics when oral multiple doses are considered. In the present approach we propose to use directly the concentration in the blood compartment and to generalize the third paragraph where a

linear compartmental model was considered. Indeed concentrations in blood compartment 1 (Fig. 1) may be used in place of E because we built a functional relation between E and C, that is to say

$$E = b_0 + b_1 \log\{1 + C[\gamma_D(t)]\}, \tag{6.1}$$

where the constant b_1 and the function $\gamma_D(t)$ was identified from experimental data (Table 1).

From (6.1), $E = 19$ involves the concentration $A = 11.8264$. Then our optimal therapeutic problem may be set as follows: Find the doses D_i and the times of absorption t_i such that

$$\int_0^T [C(t) - A]^2 \, dt \tag{6.2}$$

be minimized ($i = 1, \ldots, m$). The main difficulty consists to precise $C(t)$ on $[0, T]$.

It is possible by introducing a *nonlinear* compartmental model in which $C(t)$ is described by the formula:

$$C(t, D) = \sum_{i=1}^{3} a_i(D) \exp[\lambda_i(D)t]. \tag{6.3}$$

Unlike the linear compartmental models, the mathematical expression (6.3) involves parameters λ_i depending on the dose D. A nonlinear model with three compartments may be associated to (6.3). It involves exchange parameters k_{ij} depending on D. In (6.3) the coefficients a_i and λ_i are unknown and must be identified as functions of D by using optimization techniques[23]. Then we can precise the function $C(t)$ appearing in (6.2). Let us set

$$C(t) = \sum_{i=1}^{m} Y(t - t_i)C(D_i, t - t_i), \tag{6.4}$$

where $Y(t)$ is the Heaviside function previously defined and where $C(D, t)$ is expressed by (6.3).

The definition (6.4) results from the additivity of plasmatic concentrations. Setting

$$u(t) = \sum_{i=1}^{m} D_i \delta_{(t_i)}, \tag{6.5}$$

where $\delta_{(t_i)}$ is the Dirac mass at time t_i, the optimal control problem (6.2) becomes

$$\min_{u(t)} \int_0^T [C(t) - A]^2 \, dt, \tag{6.6}$$

with $C(t)$ given by (6.4). More precisely we must solve

$$\begin{aligned} &\min_{D_1, t_1, \ldots, D_m, t_m} \int_0^T \left(\sum_{i=1}^{m} Y(t - t_i)C(D_i, t - t_i) - A \right)^2 dt, \\ &\min_{D_1, t_1, \ldots, D_m, t_m} \int_0^T \left(\sum_{i=1}^{m} \sum_{j=1}^{3} a_j(D_j) \exp[\lambda_j(D_i)(t - t_i)] Y(t - t_i) - A \right)^2 dt. \end{aligned} \tag{6.7}$$

Direct optimization techniques may be used for solving (6.7). Of course, the global method may be performed without any difficulty because the unknowns appears in an explicit manner.

Remark. A variant of this technique consists to propose a model described by a non linear differential system. Then for minimizing

$$\int_0^T [C(t) - A]^2 \, dt,$$

we decompose the interval $[0, T]$ into subintervals $[t_i, t_{i-1}]$ in which the differential system is linearized. On each interval (t_i, t_{i+1}) the following criterion:

$$\int_{t_i}^{t_{i+1}} [C(t) - A]^2 \, dt$$

is minimized according to the a control $u(t)$, input function in the blood compartment. The using of the explicit method valid for linear compartmental models allows (Sec. 2) to find an exact, explicit, optimal solution $u(t)$ on each interval (t_i, t_{i-1}). Recall that the optimal solution is obtained with the Laplace transformation.

7. NUMERICAL RESULTS

Alienor or Vignes techniques were used for the parameters identification of models. When integrals appear, they are approximated with the midpoint or Gaussian formulae[24].

(a) The dose effect relation

$$E = b_0 + b_1 \log\{1 + C[\gamma_D(t)]\}$$

was identified. First we chose

$$C = a_1 e^{\lambda_1 t} + a_2 e^{\lambda_2 t},$$

where the parameters $a_1, a_2, \lambda_1, \lambda_2$ were calculated by the Vignes's method. One obtained

$$a_1 = -a_2 = -54.437, \qquad \lambda_1 = -1.918, \qquad \lambda_2 = -0.246.$$

After several attempts we chose a cubic polynomial approximation for $\gamma_D(t)$. Setting

$$\gamma_D(t) = \sum_{i=1}^{3} \left(\sum_{j=1}^{4} C_{ij} D^{4-j} \right) t^i, \qquad E = (e_{ij}), \tag{7.1}$$

an optimization technique gives the following identified parameters e_{ij}:

$$E = \begin{pmatrix} 9.982\,17E-04 & -0.019\,291\,9 & 0.148\,249 & 0.189\,783 \\ 4.752\,32E-04 & -4.088\,83E-03 & -0.024\,962\,1 & 0.236\,936 \\ -2.551\,01E-05 & 2.549\,12E-04 & 5.418\,93E-04 & -0.008\,267 \end{pmatrix}, \tag{7.2}$$

with $b_0 = 25$. b_1 was equal to $-2.687\,578\,62$

Table 3 allows to compare the calculated effects E_c to the experimental measured effects E_{exp}.

Note that a linear approximation for $\gamma_D(t)$ as function of t is still convenient. This approximation will be retained for the next calculus.

(b) The dynamic programming technique[6] was applied for finding the optimum of

$$\min_{D_0,\ldots,D_j} \sum_{i=1}^{j} \int_{t_i}^{T_{i+1}} (E_i - 20)^2 \, dt, \tag{7.3}$$

with $t_{i+1} - t_i = 24$ h, $t_0 = 0$. The calculated optimal doses were the following:

$$D_0 = 4.69, \quad D_1 = 4.53, \quad D_2 = 4.52, \quad D_3 = 4.67, \tag{7.4}$$

with

$$t_0 = 0, \quad t_1 = 24 \text{ h}, \quad t_2 = 48 \text{ h}, \quad t_3 = 72 \text{ h}.$$

(c) The general problem was treated with the algorithm giving a suboptimum. The optimal doses and times are

$$D_0 = 5.895, \quad t_0 = 0, \quad D_1 = 5.69, \quad t_1 = 28 \text{ h}.$$

(d) The global optimization technique (Alienor) was performed for the problem:

$$\min_{\substack{D_0,\ldots,D_j \\ t_1,\ldots,t_j \\ t_0 = 0}} \int_0^T [E(t) - L]^2 \, dt. \tag{7.5}$$

- $j = 2$, $T = 72$ h, $L = 19$ involve

$$D_0 = 8.07, \quad t_0 = 0, \quad D_1 = 1, \quad t_1 = 38.69 \text{ h}, \quad D_2 = 5.3, \quad t_2 = 51.84 \text{ h}.$$

- For $j = 2$, $T = 72$, $L = 20$ in (7.5) one obtains

$$D_0 = 6.895, \quad t_0 = 0, \quad D_1 = 1, \quad t_1 = 43.56, \quad D_2 = 1, \quad t_2 = 58.89,$$

Table 3.

Doses	1 mg		2 mg		5 mg		10 mg	
Time (in hours)	E_{exp}	E_c	E_{exp}	E_c	E_{exp}	E_c	E_{exp}	E_c
0	28.5	28.5	26.1	26.1	24.5	24.5	25.4	25.4
0.5	25.5	25.64	21.3	21.18	19	18.26	17	18.05
1	22.6	21.81	18.7	18.64	15.9	16.58	14.2	16.69
2	20	19.2	17	16.71	14.5	15.21	13.8	15.84
4	21.2	19.43	17.3	16.98	14.7	14.97	14.4	16.05
6	23.9	21.22	20.5	18.58	16.1	15.75	16.4	16.85
9	24.6	24.31	21.3	21.35	17.7	17.29	16.3	18.13
12	25.5	26.66	22.6	23.62	18.1	18.84	17.9	19.1
15	25.9	27.72	24.8	24.84	20.3	20.12	19.4	19.53
24	26.4	26.18	23.2	23.12	20.8	20.77	20.1	20.05

other numerical results are available in technical reports of Medimat and Servier laboratories.

8. CONCLUSIONS

Some mathematical and numerical techniques were presented for studying the obtention of optimal therapeutics when a dose effect model can be previously established. The classical literature gives some attempts in this direction but generally only in the *linear* case.

In [15] Sheiner proposed functional forms for structural biological models. He suggested polynomial, exponential or Hill functions. The logarithmic form was forgotten in spite of its good adaptation to biological systems.

Furthermore, [12], [25] and [26] give simple *linear* pharmacokinetic models used for identifying the pharmacokinetic parameters or for determining input doses. Our present work is devoted to the modelling of non linear kinetics (non linear dose-effect relations) and to the resolution of the associated optimal control problems involving optimal therapeutics. By this way we showed that the drug's action can be optimized. In [27] Swan described optimal control problems related to the optimal administration of drugs. He obtained some explicit solutions for linear compartmental models involving two or three compartments. The using of dynamic programming and conjugate gradient methods are also considered. But no nonlinear problem was considered. On the contrary our work proposes a theory for optimizing the drugs' effect when the relationships are nonlinear (coming in particular from nonlinear compartmental models). Furthermore, we used classical optimization techniques[28] for solving optimal control problems associated to our nonlinear models. But an original global optimization method was also tested. One can see that the numerical results are quite identical. Moreover, they are in agreement with the physicians' experience. The practical consequences of the mathematical study of tertatolol are the following:

- A dose of about 5 mg per day (24 h) is quite optimal;
- if the absorption is early (or late) around optimal times, there are few consequences on the effect.

Introducing optimal control methods in pharmacokinetics and pharmacodynamics lead to an improvement of therapeutics and can bring a theoritical justification to clinical investigations.

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