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Original paper

A new optimization based approach to experimental combination chemotherapy*

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Abstract—A new approach towards the design of optimal multiple drug experimental cancer chemotherapy is presented. Once an adequate model is specified, an optimization procedure is used in order to achieve an optimal compromise between after treatment tumor size and toxic effects on healthy tissues. In our approach we consider a model including cancer cell population growth and pharmacokinetic dynamics. These elements of the model are essential in order to allow less empirical relationships between multiple drug delivery policies, and their effects on cancer and normal cells. The desired multiple drug dosage schedule is computed by minimizing a customizable cost function subject to dynamic constraints expressed by the model. However, this additional dynamic wealth increases the complexity of the problem which, in general, cannot be solved in a closed form. Therefore, we propose an iterative optimization algorithm of the projected gradient type where the Maximum Principle of Pontryagin is used to select the optimal control policy.

Key words: combination chemotherapy; optimization.

NOMENCLATURE

N total number of compartments.
N_W number of compartments assigned to phase W.
$x := \mathrm{col}\,(x_1, \ldots, x_N)$ being x_i the tumor cell population in the ith compartment.
p fraction of cells that after mitosis goes to phase G_1.
d_i cell death rate in the ith compartment.
r_i cell transition rate from the ith to the $i+1$th compartment.
ϕ matrix specifying the state dependence of the dynamics.

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M number of drugs considered.

$\hat{z} := \mathrm{col}(\hat{z}_1, \ldots, \hat{z}_M)$ being $\hat{z}_i$ the ith drug concentration at the tumor cells.

B_i effect of the ith drug concentration on the tumor growth model.

$\overline{D} := \mathrm{col}(0, D)$ effect of drugs administration rate in the pharmacokinetic model.

$y := \mathrm{col}(x, z)$ state variable satisfying $y(0) = y_0$ and where $z := \mathrm{col}(\bar{z}, c^s, v, w)$.

$\bar{z} := \mathrm{col}(\bar{z}_1, \ldots, \bar{z}_M)$ with $\bar{z}_j := \mathrm{col}(\bar{\bar{z}}_{j1}, \ldots, \bar{\bar{z}}_{jP})$ and $\bar{\bar{z}}_{ij}$ the ith drug concentration at the jth tissue.

$c^s := \mathrm{col}(c_1^s, \ldots, c_M^s)$ where $c_i^s(t)$ is the ith drug concentration at serum level.

$v := \mathrm{col}(v_1, \ldots, v_M)$ auxiliary variables in the drug concentration model at serum level.

$w := \mathrm{col}(w_1, \ldots, w_M)$ auxiliary variables in the drug concentration model at serum level.

K_{ai} absorption rate of the ith drug concentration at serum level.

K_{ei} elimination rate of the ith drug concentration at serum level.

α_{1i}, α_{2i} coefficients of the drug concentration model at serum level.

$u_i(t)$ ith drug administration rate at time t.

P number of tissues considered.

K_{ji}, I_{ji} coefficients of the generalized pharmacodynamic model.

$f(t, y)$ overall state variable dependence of the global model.

$\bar{f}_j(\bar{z}_j)$ non-linear effects (such as saturation and the interaction of other drugs) at the jth tissue in the pharmacokinetic model.

$\bar{\bar{f}}(z(t))$ state variable dependence of the pharmacokinetic model.

Ω_t instantaneous administration rate constraints of the given set of drugs.

T final treatment time.

$J(u)$ cost objective as a function of the control function u.

a weight penalizing the final tumor size.

b weight penalizing toxic effects accumulated in the selected tissues.

$p: [0, T] \to R^n$ adjoint variable defined in the statement of the Maximum Principle.

$C_{\mathrm{fd}}(u_i)$ cone of feasible control directions at u_i with negative polar $C_{\mathrm{fd}}^0(u_i)$.

$P_\Omega(z)$ projection of z on Ω.

1. INTRODUCTION

In this article, a new approach involving the application of optimal control to combination chemotherapy is proposed. By combination chemotherapy, we mean treatment protocols involving more than one drug. We introduce an optimization algorithm with the goal of defining a treatment protocol which minimizes an adequate cost function subject to some dynamic constraints representing the underlying biological system. Although we consider an instance where this is reasonably described by a multicompartmental model, our approach may easily be adapted to take into account more complex and possibly nonlinear, time varying models.

Unfortunately, due to the similarity of biochemical processes occurring in both normal and cancer cells, chemotherapeutic elimination of tumors is impossible without serious damage being caused to the normal cells. This difficulty has motivated several authors, e.g. [1–6], to investigate the use of engineering techniques in order to design optimal single drug chemotherapies. The main goal is to find the best (in the sense of maximizing the patient's life expectancy) post-treatment compromise between tumor size and damage caused to healthy tissues. A good review appears in Swan [7]. Although some of the simulated results seem to agree fairly well with what one expects from the clinical point of view, empirical considerations (see, e.g. [8]) suggest that differences of behavior between normal and cancer cells may be better exploited by combining the action of several cycle- and phase-specific drugs.

When dealing with the optimal design of multiple drug chemotherapy [9], we observed that the added complexity with respect to the single drug case makes it too cumbersome, if not impossible, to obtain a closed form solution as in Pereira *et al.* [10], or deduce it via mathematical analysis like in Swan [3] and Sundareshan and Fundakowski [5]. Therefore, in order to solve the above problem, we propose an iterative optimization algorithm developed in Pereira *et al.* [10]. Here, a projected gradient search direction technique permits us to update the current optimal control estimate and the necessary conditions of optimality in the form of a Maximum Principle of Pontryagin [11] are used as a stopping condition. We extend some of our previous work [9] in the sense that the model now incorporates pharmacokinetic considerations. This additional model wealth allows a more realistic description of the drug concentration profiles at the various tissues as a response to a given combination chemotherapeutic protocol. Therefore, better treatment strategies may be obtained as solutions to the optimal control problem with these dynamic constraints.

2. THE MODEL

The computation of a combination chemotherapy that, for a given patient, achieves the best compromise between after treatment tumor size and damage to healthy tissues requires an adequate mathematical formulation. The model should be able to describe not only the growth of the relevant cell populations subjected to certain concentrations of a given set of drugs, but also the dynamic response of their serum and tissue concentrations to any given administration policy. A list of symbols used in the definition of the model and in the statement of the optimal control problem is presented in the Nomenclature.

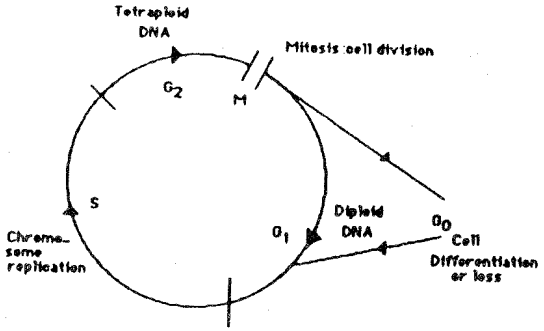

Figure 1. The cell cycle.

We start by dealing with the model component concerning the tumor growth. In order to make this paper self contained, we present next some classical material on cell kinetics. One of the main advantages of using cell kinetics to model tumor growth is to avoid difficulties inherent to the complexity and incompleteness of biochemical equations underlying the cell maturation process [5]. Furthermore, by taking advantage of differences in behavior between cancer and normal cells and of the phase and cycle specificity of a wide range of drugs, they allow the choice of a set of drugs and the respective dosage schedule [12].

The classic diagram presented in Fig. 1 illustrates the cell cycle phenomena. This periodic process consists in a number of transformations giving, in general, the origin to two daughter cells with a diploid amount of DNA in phase M (mitosis). Then, they either enter G_0, a usually long resting phase, or G_1 during which RNA and protein are synthesized. DNA is produced during the S (synthesis) phase in such a way that at the beginning of G_2 phase the cell has a tetraploid amount of DNA. During this stage, RNA and protein are synthesized in preparation for cell division.

By organizing the cell population in various compartments defined by the amount of DNA and/or RNA, Takahashi [13, 14] and Sundareshan and Fundakowski [5], among others (see Eisen [15] for a review), described the maturation process of a cell population as solution of

$$x_i(0) = x_i^0, \qquad \text{for} \quad 1 \leqslant i \leqslant N,$$

$$\dot{x}_i(t) = -(r_i + d_i)x_i(t) + r_{i-1}x_{i-1}(t), \qquad \text{for} \quad 1 \leqslant i \leqslant N_{G_0} \text{ or } N_{G_0+1} < i \leqslant N,$$

$$\dot{x}_1(t) = -(r_1 + d_1)x_1(t) + 2(1-p)r_N x_N(t),$$

and

$$\dot{x}_{N_{G_0+1}}(t) = -(r_{N_{G_0+1}} + d_{N_{G_0+1}})x_{N_{G_0+1}}(t) + 2pr_N x_N(t)$$

where $\dot{x}$ is the time derivative of x, N is the total number of compartments, N_W is the number of compartments assigned to phase W, $x := (x_1, \ldots, x_N)$ is the population

distribution, p is the fraction of cells that after mitosis goes to phase G_1, and d_i a
r_i are, respectively, the death rate in the ith compartment and the transition rate fro
the ith to the $i+1$th compartment. A more compact form is $\dot{x}(t) = \phi x(t)$, $x(0) = x$
where x_0 is the initial population distribution and ϕ is the following matrix

$$\begin{bmatrix}
-(r_1+d_1) & 0 & 0 & \cdots & 0 & \cdots & 0 & 2r_N(1-p) \\
r_1 & -(r_2+d_2) & 0 & \cdots & 0 & \cdots & 0 & 0 \\
0 & r_2 & -(r_3+d_3) & \cdots & 0 & \cdots & 0 & 0 \\
\cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\
0 & 0 & 0 & \cdots & -(r_{N_{G_0+1}} + d_{N_{G_0+1}}) & \cdots & 0 & 2r_N p \\
\cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\
0 & 0 & 0 & \cdots & 0 & \cdots & -(r_{N-1}+d_{N-1}) & 0 \\
0 & 0 & 0 & \cdots & 0 & \cdots & r_{N-1} & -(r_N+d_N)
\end{bmatrix}$$

Details concerning the estimation of the above parameters values via an algorithm o
Narendra and Kudva [16] based on the second method of Lyapunov are described in
Sundaraeshan and Fundakowski [5].

In principle, it is possible to design an adequate drug dosage schedule that, by modifying transition and death rates in some compartments, allows tumor growth control. Previous investigations [8, 12, 17] based on experimental data permitted the incorporation of significant simplifying assumptions. They concluded that it may be quite reasonable to assume that the fractional rate of killed cells in a given compartment varies linearly with the drug concentration. This hypothesis was used by Sundareshan and Fundakowski [5] and Bahrami and Kim [1] for a single drug case. If independence of effects of a given set of M drugs is also assumed, then,

$$\dot{x}(t) = \left[\phi - \sum_{i=1}^{M} B_i \hat{z}_i(t)\right] x(t), \qquad x(0) = x_0 \tag{1}$$

where $\hat{z}_i(t)$ is the concentration at time t of the ith drug, $i = 1, \ldots, M$, at the tissue where the tumor is located and B_i reflects the effect of the ith drug on the transition and death rates of each compartment. We would like to note that, in any given particular case, other (possibly non-linear) relationships between drug concentrations and tissue growth may be incorporated into the model if suggested by the underlying experimental evidence.

Now, we turn to the model component describing tissue and serum pharmacokinetics. Since these vary considerably from drug to drug and, possibly, from patient to patient, e.g. with renal deficiencies, they play an important role in the definition of a patient-tailored and drug-tailored combination chemotherapy. A review of general pharmacokinetic models is presented in Cherruault [18] and Eisen [15] where the convenience of compartmental models is emphasized and specific identification methods are proposed.

In Pedreira and Muniz [19], it is shown that a second-order linear system provides a good model for the serum concentration of each drug. Let us consider the following

model for the serum concentration, $c_i^s(t)$, of the ith drug:

$$\dot{c}_i^s(t) = \alpha_{1i} v_i(t) + \alpha_{2i} w_i(t) \tag{2}$$

where v_i and w_i are auxiliary variables satisfying

$$\dot{v}_i(t) = -K_{ei} v_i(t) + u_i(t)$$

and

$$\dot{w}_i(t) = -K_{ai} w_i(t) + u_i(t)$$

where the absorption rate, K_{ai}, the elimination rate, K_{ei}, $\alpha_{1i} < 0$ and $\alpha_{2i} > 0$ are parameters associated with the ith drug that may be estimated by optimization techniques, e.g. Hooke and Jeeves (see Polak [20]), based on *in vivo* measurements (see Pereira *et al.* [9]), and $u_i(t)$ is the ith drug administration rate at time t.

It is quite reasonable to assume [21] that the drug concentration variation in the tissue is proportional to the difference between the serum and tissue concentrations. This assumption and the influence of other drugs may be taken into account in the following general equation describing the dynamics of the ith drug at the jth tissue:

$$\dot{\bar{z}}_{ji}(t) = K_{ji} c_i^s(t) + I_{ji} \bar{z}_{ji}(t) + \bar{f}_j\left(\bar{z}_j(t)\right) \tag{3}$$

where $\bar{f}_j$ takes into account non-linear effects such as saturation and the interaction of other drugs and $\bar{z}_j = \mathrm{col}\,(\bar{z}_{j1}, \ldots, \bar{z}_{jM})$ with $\bar{z}_{ji}$ denoting the ith drug concentration at the jth tissue. This function together with the coefficients K_{ji} and I_{ji}, $i = 1, \ldots, M$, $j = 1, \ldots, P$, will have to be estimated. Here, M is the total number of drugs and P is the number of tissues considered. We would like to note that the tumor itself is one of the above mentioned P tissues, i.e. $\hat{z}_i = \bar{z}_{ik}$, for a given k between 1 and P.

The dynamics relating cell and tissue drug concentrations are not very well understood from the biological point of view. However, since the delay between a given drug concentration value at cell and corresponding tissue level is quite small, it seems reasonable to neglect the respective dynamics. However, as soon as a model of this dynamic process is known and proved relevant, it may be easily accommodated by adding new components to the pharmacokinetic model.

By putting together (2) and (3) one gets

$$\dot{z}(t) = \bar{f}(z(t)) + Du(t), \qquad z(0) = z_0$$

where $\bar{f}$ is the resulting non-linear function and D is a matrix describing how $u(t)$, a M-vector whose components are administration rates for each drug at time t, affects the state vector z, and z_0 is the initial value of z.

The components of z are $\bar{z}$, c^s, v and w, where $\bar{z}$ and $c^s = \mathrm{col}\,(c_1^s, \ldots, c_M^s)$ are drug concentrations considered at, respectively, the tissue and serum levels and

$v = \mathrm{col}\,(v_1, \ldots, v_M)$ and $w = \mathrm{col}\,(w_1, \ldots, w_M)$ are the auxiliary variables require to define the dynamics of the various drugs concentration at serum level.

Let us define $\overline{D} := \mathrm{col}\,(0, D)$, $y := \mathrm{col}\,(x, z)$ and

$$f(t, y) := \mathrm{col}\left(\left[\phi - \sum_{i=1}^{M} B_i \hat{z}_i(t)\right] x,\ \bar{f}(z)\right).$$

Then, model equations may be written as

$$\dot{y}(t) = f\left(t, y(t)\right) + \overline{D}u(t), \quad y(0) = y_0, \quad u(t) \in \Omega_t, \quad \text{for all } t \in [0, T] \tag{4}$$

where $\Omega_t \subset R^M$ is the subset of instantaneous constraints of the given set of drugs, T is the final treatment time and y_0 is the initial state.

A final note concerning the model is in order. Knowledge in this important field is evolving very fast and, in the near future, better models dispensing with some of the simplifying assumptions we adopted may replace the one in (3). However, the general framework provided by the set of differential equations, boundary conditions and static control constraints in the form of an inclusion will still permit the use of the solution method we describe in the next section.

3. THE SOLUTION METHOD

In order to evaluate a given treatment strategy, one must define an objective function based on clinical considerations. This cost function should reflect two different conflicting elements: after treatment tumor size and toxicity effects. The optimal drug delivery strategy is the one that is feasible and minimizes the cost function. Therefore, it may be seen as the solution to an optimal control problem whose dynamical and control constraints realistically describe the particular situation at hand. The statement of this problem is as follows:

$$\begin{aligned} \textbf{(P)} \quad \text{Minimize} \quad & a'x(T) + \int_0^T b'\bar{z}(t)\,dt \\ \text{subject to} \quad & \dot{y}(t) = f\left(t, y(t)\right) + \overline{D}u(t), \\ & y(0) = y_0, \\ & u(t) \in \Omega_t \subset R^M. \end{aligned}$$

Here, a' denotes the transpose of vector a, y, y_0, x, $\bar{z}$, u, Ω_t, f and $\overline{D}$ maintain the meaning of the previous section, and a and b are positive vector valued weights penalizing, respectively, the final tumor size and toxic effects accumulated in serum and selected tissues. Terms $a'x(T)$ and $\int_0^T b'\bar{z}(t)\,dt$ deserve some comments. By choosing a given component of a to be greater than others, we are forcing the optimization

procedure to eliminate a larger percentage of the population in the compartment corresponding to the selected component. On the other hand, the components of b which should be chosen larger are those that correspond to the healthier and more sensitive tissues where the presence of drugs should be most avoided. The values of coefficients a and b should be chosen on a case by case basis and the relative value of their components should reflect the clinical goals to be attained.

In general, it is very difficult to obtain a closed form solution to this problem. Therefore, we propose a search direction of the projected gradient type (see Pereira *et al.* [10]) in order to find an optimal patient-tailored drug dosage schedule. The satisfaction of necessary conditions of optimality in the form of a Maximum Principle of Pontryagin (see Pontryagin *et al.* [11]) is used to detect the convergence of the iterative improvement of control estimates. The statement of the necessary conditions of optimality may be particularized for this problem as follows:

Let (y, u) be a minimizing process for (**P**). Then, there is an adjoint function, p: $[0, T] \to R^n$, satisfying the adjoint differential equation

$$-\dot{p}'(t) = p'(t) f_y(t, y(t)) - (0, b'),$$
$$-p'(T) = (a', 0)$$

(f_y denotes the Jacobian of f with respect to y) and such that, for almost all t in $[0, T]$, $u(t)$ maximizes the map

$$u \longrightarrow p'(t)\overline{D}u \quad \text{in } \Omega_t.$$

The algorithm described below will produce, after a number of iterations, a control policy close to a local minimizer of the cost function [10]:

1. *Initialization.* Set $i := 0$ and choose a feasible control policy u_i.
2. *Estimates update.* Integrate the state and adjoint variable differential equations in order to get y_i and p_i; compute $\overline{D}'p(t)$.
3. *Test of optimality.* Compute $C_{fd}(u_i)$, the cone of feasible control directions at u_i; if $\overline{D}'p(t) \in C^0_{fd}(u_i)$, the negative polar of $C_{fd}(u_i)$, then stop since the optimal policy has been found. Otherwise:
4. *Control update.* Define s_i and set $u_{i+1}(t) = P_{\Omega_t}(u_i(t) - s_i \overline{D}'p(t))$ (in particular, we may choose s_i as a minimizer of $s \to J(P_{\Omega_t}(u_i - s\overline{D}'p))$; set $i = i + 1$ and go to step 2).

Here $J(u)$ is the cost function in its dependence on u and $P_{\Omega_t}(z)$ is the projection of z on Ω_t. Usually this operation is computationally quite expensive. However, in practice, very efficient algorithms may be constructed by taking advantage of the fact that control constraint sets are well approximated by polytopes. Reasonably low computational cost is achieved by approximately computing the step size which solves, at each iteration, the one-dimensional minimization problem.

By using relatively standard arguments, it is concluded in Pereira *et al.* [10] that, under some fairly usual hypotheses on the data of this problem and adequate choice of stepsize in each iteration, this algorithm produces a strictly decreasing sequence of controls converging to another satisfying the necessary conditions of optimality. Since the cost function is not convex, several local minima may exist and the one that will be given as the solution of the problem depends on the chosen initial control strategy estimate. Therefore, in order to select the one yielding the lowest cost, solutions obtained when starting the algorithm from any element of a given set of estimates should be compared. For a given situation, this set of initial control estimates may be based on a chemotherapic treatment protocol selected after clinical analysis.

In order to provide an idea of the use of the above algorithm in the definition of an optimal combination dosage schedule, we present the following scenario.

Let us consider a hypothetical tumor whose growth dynamics, based on that of a test tube collection of cells, is modelled by a seven compartmental model, with two compartments assigned to phase G_0–G_1, two to G_2–M and three to phase S. These compartments were suggested by relative phase duration and transition rate considerations obtained via analysis of several DNA histograms of the cell population. The estimation procedure mentioned in the previous section yielded $p = 0.9$ and the values for the remaining parameters of matrix ϕ in equation (1) are given in Table 1. Our hypothetical tumor whose initial size estimate is 9.85 units (1 unit = 10^8 cells) corresponding to a state age vector $X_0 = \text{col}\,(0.95,\ 2.6,\ 1.3,\ 1.1,\ 1.1,\ 1.4,\ 1.4)$ is to be controlled by a combination chemotherapy based on two drugs, an S phase specific and a cycle specific one, applied during 60 h.

Since data concerning the pharmacokinetic model are not available, we also introduce an additional simplification by neglecting its dynamics. This is simply achieved by replacing $\bar{z}$ by the drug administration rates described by a two component vector u which was normalized to take values on the set $\Omega(k) = [0, 1] \times [0, 1]$ for all k. Observe that this means that the toxicity effects of the two drugs are assumed to be independent of each other.

Let us assume that our goal is to find a compromise between the minimization of the total amount of the administered drugs and that of the tumor size, with no particular emphasis on any subpopulation. Also assume that the S phase specific drug is considered one and a half times more toxic than the cycle specific one and that life expectancy is maximized if the ratio between tumor size and the total weighted amount of drug is equal to 7/5. A set of values reflecting the described criteria include all components of a are equal to 1 and $b = \text{col}\,(3/7, 2/7)$.

Table 1.
Compartmental model parameter values

	Compartment						
	1	2	3	4	5	6	7
r_i	0.016	0.083	0.150	0.160	0.140	0.100	0.090
d_i	0.0013	0.0012	0.005	0.005	0.003	0.001	0.001

Table 2.
Optimal control policy with a cycle- and a S-specific drugs

Time	Cycle	S phase
1	1	1
2	1	0
3	1	0
4	1	0
5	0	0
6	0	0
7	0	0
8	0	0
9	0	0
10	0	0
11	0	0
12	0	0
13	0	0
14	0	0
15	0	0
16	0	0
17	0	0
18	0	0
19	0	1
20	1	1

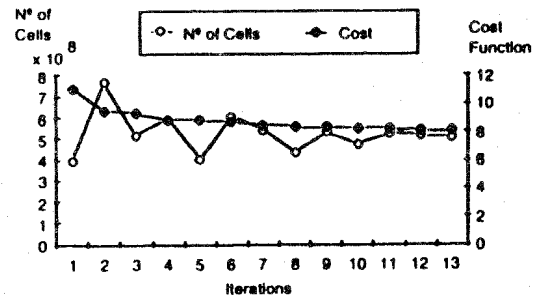

Figure 2. Cell population and cost function evolution as the iterative procedure converges.

Given the smaller computational burden and the relatively small error observed in simulation trials, we will consider a discretized version of the above optimal control problem with a time unit of three hours where the state transition matrix was approximated to first order. When we assign a certain value to a drug at a time k, what we mean is that between times k and $k+1$ that amount of drug is kept constant at tumor cells.

Starting with an initial policy of half of full amount of either drug, the algorithm converged in 13 iterations producing the optimal control policy listed in Table 2 yielding a final tumor size of 5.079×10^8 cells and a value for the cost function of 8.079.

The behaviour of the algorithm can be assessed by inspecting Fig. 2.

4. FINAL REMARKS

We present a new approach concerning the optimal cancer combination chemotherapy problem. Although in the above hypothetical example only population growth dynamics were considered, the algorithm is independent of the specific nature of these equations and may be applied to the case where cell population growth and pharmacokinetics are associated in the same model. Since the more precise the mathematical description of the underlying biological system, the more meaningful is the outcome of the employed optimization procedure, we believe that the proposed approach represents a promising tool towards the definition of at least suboptimal cancer chemotherapies. We also point out that, by permitting multiple drug therapies, more realistic situations may be considered if realistic mathematical models are available.

We accounted for the toxicity effects by penalizing the drug concentration, instead of using directly the total amount of the administered drug. One should notice that, by using the drug delivery rate in the penalty function, one is, in fact, assuming that the drug is directly applied to the cell. We avoided this undesirable simplification by considering the dynamic relationship between the drug administration policy and its corresponding concentration profile at the cell level. Unfortunately, these advantages increase the complexity of the problem which is dealt with by using an iterative algorithm. Since the optimization technique we propose is quite flexible, a wide range of dynamical models may be considered as physical constraints. Therefore, we hope that this approach will allow the incorporation of some of the future advances in the medical and biochemical fields, specially those related to the cell maturation and pharmacokinetics. The success of application will always depend on proper medical support in each step of the process, and also, on the incorporation of future scientific developments, specially those coming from the biochemical field.

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