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DETERMINISTIC AND STOCHASTIC MODELLING OF TUMOUR GROWTH AND OPTIMAL CHEMOTHERAPY

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One-dimensional mathematical models of tumour growth based on ordinary differential and stochastic differential equations are presented. Optimal cancer chemotherapy is compared in both models. The technique of dynamic programming and method of optimal switching among a finite number of Markov processes are used to obtain a sequence of optimal drug doses. A multidimensional stochastic model of tumour growth based on cell cycle is proposed. A hypothesis about interaction of two tumours is also presented.

1. Introduction

Many mathematical models have been used to describe the tumour growth and cancer treatment. A review of them can be found in works (Swan, 1990; Bertuzzi *et al.*, 1981). In this paper one-dimensional and compartment models of tumour growth and cancer treatment are discussed and one-dimensional stochastic and deterministic optimal chemotherapy models are compared. We undertake a task of calculating BL dosages and number of injections for each patient depending on tumour volume, its location and first recognizable symptoms of the disease in order to reduce tumour size. This enables us to make some forecasts for each patient regarding tumour response. The corresponding results were presented by Cicenas *et al.* (1992) and Eidukevičius (1992). Also a problem of interaction of two tumours (Characiejus and Eidukevičius, 1993) is mentioned. This investigation initiated by Dr. Characiejus from Lithuanian Oncology Centre will be continued and extended.

2. Deterministic One-Dimensional Model

A general tumour growth and cancer treatment can be formulated as a minimization problem as follows (Swan, 1990):

$$J(u) = \int_0^T [w(t,x) + g(t,u)]\,\mathrm{d}t + F(x(T)) \to \min \tag{1}$$

subject to

$$\dot{x} = x[f(x) - h(u)], \qquad x(0) = x_0 \tag{2}$$

where $x(t)$ is the volume of a tumour; t – time; x_0 – initial volume of a tumour; T – time when the treatment is finished; J – performance criterion; w, g, F –

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nonnegative functions, denoting the prices of tumour volume during the treatment, of drug toxicity and of the final tumour volume, respectively; u – drug concentration in the tumour (control parameter). Equation $\dot{x} = xf(x)$ gives a trajectory of tumour volume growth without treatment, $xh(u)$ is a loss term, i.e. a given dose of drug kills a constant fraction of tumour cell population. This general model was applied to lung cancer growth and chemotherapy. To describe tumour growth we use the following Cox – Woodbury – Meyers equation

$$\dot{x} = x\left(\frac{a}{1+bx} - m\right), \qquad x(0) = x_0, \quad a, b, m > 0 \tag{3}$$

which is based on a postulated inhibitory substance; moreover, we include drug saturation effect in our model. Other assumptions are based on lung cancer chemotherapy:

t_i – fixed time moments of medicine injections directly to the tumour, $t_i < T$;

n – number of injections;

$u(t) = u_i \exp(-p(t - t_i))$, $p > 0$, $t_i \le t < t_{i+1}$, $T = t_{n+1}$;

u_i – dose of medicine in the i–th injection from a finite set of doses U, $i = 1, 2, ..., n$.

Finally, we get the following tumour growth and treatment equation:

$$\begin{aligned} &\dot{x} = x\left(\frac{a}{1+bx} - m - \frac{cu}{1+du}\right), \qquad x(0) = x_0 \\ &a, b, m > 0, \qquad c = c(t) > 0, \qquad d = d(t) > 0 \end{aligned} \tag{4}$$

The mathematical model, the corresponding algorithm and computer program in FORTRAN 77 are intended for a general case, when tumour growth equation is taken into account. Hardly accessible clinical data and high amount of the required computational time compel us to simplify the general scheme formulated above, i.e. to give up modelling the tumour growth during the chemotherapy process. Fortunately, there are two reasons, which are, in our opinion, sufficient to make such simplification possible:

1. The treatment takes quite a short time — two or three weeks.
2. During the treatment the proliferation reduces and the amount of new cancer cells is not significally important (Baranco and Humphrey, 1971).

For the simplified chemotherapy model

$$\begin{cases} \dot{x} = -\dfrac{cu}{1+du}x, \qquad x(0) = x_0 \\ c = c(t), \quad d = d(t) \text{ — nonnegative functions of time} \\ J(u) = \displaystyle\int_0^T [w(t,x) + g(t,u)]\,\mathrm{d}t + F(x(T)) \\ u(t) = u_i \exp(-p(t - t_i)),\ t_i \le t < t_{i+1},\ i = 1, 2..., n,\ T = t_{n+1} \end{cases} \tag{5}$$

a program in Turbo Pascal was written and the optimal doses can be obtained very quickly. The main problem is to calculate parameter p and to choose functions

c and d in equation (5) and w, g, F for the functional J. Estimation of p is based on blood concentration of Bleomycine after intravenous, intramuscular and intratumoural injections (Bleomycine description). Let $t_{0.5}$ denote the time period in which drug concentration decreases by a half after the injection. In our case $t_{0.5} = 6$ hours and $p = \ln 2/t_{0.5}$.

We obtain the functions c and d only if the hypothesis that they are constants during the treatment is accepted. Unfortunately, we cannot verify this hypothesis.

This problem of optimal control is solved by the method of dynamic programming because performance criterion includes the final state cost, functions w and g may depend on time t and the maximum principle does not help in finding a feadback optimal control.

3. Stochastic One-Dimensional Model

The results of treatment suggest that the drug effect is quite different even for similar tumours, i.e. the effect is random. It is natural to assume that some parameters in equation (5) are random, $x(t)$ is the solution of the Itô stochastic differential equation and the cost function is expectation:

$$a = a_0 + \sigma \dot{w}(t), \qquad \sigma,\ a_0 > 0 \tag{6}$$

i.e. parameter a is a function of time t and $a(t)$ is a normal random variable with mean a_0 and variance σ, where $\dot{w}(t)$ is white noise,

$$\mathrm{d}x(t) = -\frac{a_0 u_i \exp(-p(t-T_i))}{1 + bu_i \exp(-p(t-T_i))} x(t)\,\mathrm{d}t + \frac{\sigma u_i \exp(-p(t-T_i))}{1 + bu_i \exp(-p(t-T_i))} x(t)\,\mathrm{d}w(t) \tag{7}$$

where $T_i \le t < T_{i+1}$, $i = 1, 2, ..., n$, $w(t)$ – Wiener process,

$$J = E_{x_0}\left\{\int_0^{T_{n+1}} [w(t, x(t)) + g(t, u(t))]\,\mathrm{d}t + f(x(T_{n+1}))\right\} \tag{8}$$

and u_i are Borel functions from $[0, \infty)$ into U.

As a result we obtain a problem of optimal switching. In this model we have a set of Markov processes $X^u = (\Omega, F, F_t, x_t, P_x^u)$, where only P_x^u depends on $u \in U$.

In our model switching occurs at a finite number n of deterministic time moments $T_1, T_2, ..., T_n$ among a finite number of Markov processes. But our performance criterion is slightly different and the optimal treatment can be obtained using dynamic programming and it is a sequence of random doses $u_i = u_i(x(T_i))$, $i = 1, 2, ..., n$ which depend on the results of treatment at the moments of injections. The first optimal dose is a function of the initial tumour volume, the second one is unknown up to time moment T_1, because the treatment result is random and this dose is a function of x_{T_1}, etc.

4. Comparison of Stochastic and Deterministic Models

To compare stochastic and deterministic models assume $n = 1$ (treatment consists of one injection) and $w(x) = wx^k$, $g(x) = gx^k$, $f(x) = fx^k$, $w, g, f, \geq 0$, $k = 1, 2$. It is easy to see that

$$E_x(x(t))^k = x^k \exp\left\{k \int_0^t b(s)\,\mathrm{d}s + \frac{1}{2}k(k-1)\int_0^t \sigma(s)^2\,\mathrm{d}s\right\} \tag{9}$$

where

$$\mathrm{d}x(t) = b(t)x(t)\,\mathrm{d}t + \sigma(t)x(t)\,\mathrm{d}w(t), \quad x(0) = x \tag{10}$$

$b(t)$, $\sigma(t)$ are deterministic functions.

For the stochastic model the price for initial tumour volume x is

$$J(x) = \inf_{u_1} E_x\left\{\int_0^c \left[wx(t)^k + gu(t)^k\right]\mathrm{d}t + fx(c)^k\right\} \tag{11}$$

and the prices for the tumour volume during treatment and final volume in stochastic and deterministic models are equal for $k = 1$, because in (9) we have $k(k-1) = 0$, and for $k = 2$ in the stochastic case this price increases, i.e. the doses to achieve on the average the same result as in the deterministic model must be bigger.

5. Multidimensional Model

We used one-dimensional stochastic differential equation in the cancer chemotherapy model. Now we are going to study a stochastic cell cycle compartment model. The following deterministic system of ordinary differential equations

$$\begin{cases} \dot{x}_1 = 2d_N x_N - d_1 x_1 \\ \dot{x}_i = d_{i-1}x_{i-1} - d_i x_i, \qquad i = 2, \ldots, N \end{cases} \tag{12}$$

where N is the number of phases of the cell cycle, describes a well-known model of cell cycle. The time spent by cells in phases is stochastic and it is natural to use multidimensional Itô stochastic differential equation as in the previous one-dimensional model. Deterministic coefficients d_i can be changed by stochastic ones:

$$d_i(t) = a_i + c_i\dot{w}_i(t) \tag{13}$$

where $\dot{w}_i$ is white noise, a_i, c_i – positive constants, w_i, $i = 1, \ldots, N$ – independent Wiener processes. Thus, we get the following cell cycle model:

$$\begin{cases} \mathrm{d}x_1 = (2a_N x_N - a_1 x_1)\,\mathrm{d}t - c_1 x_1\,\mathrm{d}w_1 + 2c_N x_N\,\mathrm{d}w_N \\ \mathrm{d}x_i = (a_{i-1}x_{i-1} - a_i x_i)\,\mathrm{d}t - c_i x_i\,\mathrm{d}w_i + c_{i-1}x_{i-1}\,\mathrm{d}w_{i-1}, \ i = 2, \ldots, N \end{cases} \tag{14}$$

The process of chemotherapy can be modelled by the following system of linear stochastic differential equations, where u is a control parameter:

$$\begin{cases} \mathrm{d}x_1 = (2a_N x_N - a_1 x_1)\,\mathrm{d}t + b_1 u\,\mathrm{d}t - c_1 x_1\,\mathrm{d}w_1 + 2c_N x_N\,\mathrm{d}w_N \\ \mathrm{d}x_i = (a_{i-1}x_{i-1} - a_i x_i)\,\mathrm{d}t + b_i u\,\mathrm{d}t - c_i x_i\,\mathrm{d}w_i + c_{i-1}x_{i-1}\,\mathrm{d}w_i, \ i = 2, \ldots, N \end{cases} \tag{15}$$

$$J(u) = E^u \left\{ \int_0^T \left[w(t, x(t)) + g(t, u(t)) \right] \mathrm{d}t + f(x(T)) \right\} \tag{16}$$

The multidrug case can be treated similarly. Furthermore, a special form of optimal control, switching as in the case of one-dimensional model with one drug, can be studied.

The problem of parameter estimation in the deterministic and stochastic models is very important and difficult. There are methods to calculate parameter estimates, but we have insufficient data. Now together with specialists from the Lithuanian Centre we are going to get more information during the treatment and to carry Oncology out some new experiments. We have to estimate not only drift parameters, but also diffusion coefficients. Experiments to determine cell kinetic parameters before and during the treatment are also very important.

6. Interaction of Two Tumours

Some facts suggest the existence of mutual interaction (mediated by serum factors?) between two tumours or between tumour and distant normal tissue. We studied the mutual interaction between two solid SL2 tumours implanted in the same DBA/2 mouse, the first tumour being implanted two days before implantation of the second tumour. In this model, the growth of the first tumour is stimulated by the presence of the other tumour, while the growth of the other tumour is inhibited by the first one. We suggest that dynamics of the first and the other tumour volumes may be described by a system of non-linear ordinary differential equations which include saturation effect (Gompertz, logistic, etc.) and proliferation and saturation parameters are functions of the volumes of interacting tumours.

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