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Immune system–tumour efficiency ratio as a new oncological index for radiotherapy treatment optimization

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A dynamical system model for tumour–immune system interaction together with a method to mimic radiation therapy are proposed. A large population of virtual patients is simulated following an ideal radiation treatment. A characteristic parameter, the immune system–tumor efficiency ratio (ISTER) is introduced. ISTER dependence of treatment success and other features are studied. Radiotherapy treatment dose optimization, following ALARA (*As Low As Reasonably Achievable*) criterion, as well as a patient classification are drawn from the statistics results.

Keywords: modeling; optimization; radiotherapy; simulation.

1. Introduction

Some approaches to cancer growth and behaviour have been made in the past years. Dynamical system techniques use a population dynamics model (Kuznetsov *et al.*, 1994; Sachs *et al.*, 2001; Galach, 2003; Enderling *et al.*, 2006) to mathematically describe the tumour behaviour and its interaction with the immune system. Some of these works model tumour behaviour under clinical treatments like cytokines (Sotolongo-Costa *et al.*, 2003) or radiovirotherapy (Dingli *et al.*, 2006) and properly explain the qualitative behaviours of several tumours. Even though great efforts had been made to mathematically describe cancer radiotherapy treatments, they 'are vaguely tied to [clinical] observations' (Sachs *et al.*, 2001) and their large number of variables and coefficients make their results hardly transposable to a clinical context.

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Radiotherapy and surgery are the most effective treatments for cancer, and even while surgery has a longer tradition, radiotherapy treatments help to improve the control of many tumours (Steel, 1993). Even when tumour kind is taken into account to design the radiotherapy sessions, those treatments follow strict protocols that often apply a fixed physical radiation dose, hardly taking into account the patient immunological condition. Thus, a radiotherapy protocol might result in a very low success probability for some patients starting their treatments with a weakened immune system. In practice, such a treatment will be interrupted if the patient physical condition worsens, although the patient will have already received inappropriate doses of radiation.

Due to its importance, some works focus on the analysis of the different strategies of radiotherapy treatment (Enderling *et al.*, 2007) applied to a certain class of cancer tumour. Looking for an applicable although general method, we model a radiotherapy treatment making the simplest possible assumptions. Furthermore, we will introduce the immune system–tumor efficiency ratio (ISTER) parameter as a measure of the patient immune system strength to fight back cancer. This parameter allows to classify patients and find the success probability of each patient group following a radiotherapy treatment protocol. Finally, we will use these results to assess the optimized tissue effect (E) in terms of a given patient physical condition.

2. Model

We will use a Lotka–Volterra-like model to describe the tumour evolution based on some assumptions. Tumour cell growth $\dot{X}$ (as usual, a dot over a quantity represents its time derivative) depends on the current tumour population as aX and its mass–law interaction with lymphocytes, $-bXY$. Lymphocyte population grows due to tumour–immune system interaction, dXY, and falls in time exponentially, $-fY$, due to natural cell death. Tumour secretes interleukin, which produces an immune depression effect (Whiteside, 2002, 2006), and we will make the simplest assumption supposing it proportional to the tumour cell number,$-kX$. The tumour is localized and there is a constant flow, u, of lymphocytes from the immune system into this region.

So, we will model tumour–immune system interaction using the already known equations (Sotolongo-Costa *et al.*, 2003):

$$\begin{aligned} \dot{X} &= aX - bXY, \\ \dot{Y} &= dXY - fY - kX + u. \end{aligned} \tag{1}$$

To take into account the acute effects of radiotherapy, we introduce a radiotherapy characteristic time scale as well as the corresponding radiation effects. These effects of radiation on tissue are generally classified in three phases (Steel, 1993): physical phase, when radiation ionizes atoms; chemical phase, when ionized molecules interact with other biological components of the cell and, finally, biological phase, where the damage is fixed, and unrepairable cells are signalled to die by apoptosis.

We will classify all these heterogeneous effects, according to their time scale, in two groups: short- and long-term effects. Short-term effects occur at very small time scales compared with the time scales on which our model runs (those times for which changes in the X and Y variables of system (1) would become appreciable) and will be modelled as a single instantaneous change. On the other hand, long-term effects of radiation must be included as a new temporal evolution equation.

Then, we assume that those lymphocytes affected by the radiation die or loose their ability to attack tumour cells instantaneously after the radiation dose and that radiation dose is concentrated at an infinitesimal instant of time. At that very moment, long-term effects of radiation, like non-clonogenic

tumour cells appearance, start to take place, whereas short-term effects of radiation instantaneously modify the state of the system, grouped in δ functions in the equations.

We also assume that when a radiation dose is applied at a given instant T_n, it induces a fraction B_t of the tumour cells to lose their reproductive endowment and to die exponentially. The fraction S_t of tumour cells not affected by radiation follows the linear quadratic model (Enderling *et al.*, 2006; Düchting *et al.*, 1996),

$$S_t = 1 - B_t = \exp[-E] = \exp[-\alpha\Delta - \beta\Delta^2], \tag{2}$$

where E is known as the tissue effect, α and β are type A and type B damage coefficients (Steel, 1993) and Δ is the physical radiation dose expressed in Gy as usual in clinical contexts. Furthermore, a fraction B_l of lymphocytes is also killed by radiation in a manner similar to (2), although having different α and β coefficients. We must point out that tumour cells mostly die by unsuccessful mitosis, provoked by DNA damage (Steel, 1993), but lymphocytes die rapidly in what has been called 'interphase death' (Steel, 2002), decreasing rapidly in number.

To include long-term processes in (1), we write a new equation for non-clonogenic tumour cells Z (Dingli *et al.*, 2006), taking into account that lymphocyte population is also stimulated, as pZY, through its interaction with these cells. The number of non-clonogenic tumour cells decays exponentially as $-rZ$ due to the death of damaged cells and also as $-qZY$ due to the interaction with lymphocytes. Then, we arrive to the system

$$\begin{aligned}
\dot{X} &= aX - bXY - \dot{B}_t(T)X,\\
\dot{Y} &= dXY + pZY - fY - k(X+Z) + u - \dot{B}_l(T)Y,\\
\dot{Z} &= \dot{B}_t(T)X - rZ - qZY,
\end{aligned} \tag{3}$$

where $\dot{B}_t(T) = B_t \sum \delta(T - T_n)$ and $\dot{B}_l(T) = B_l \sum \delta(T - T_n)$ represent the amount of tumour cells and lymphocytes affected by radiation per unit time. T_n are the time instants when radiation doses are applied and $\delta(T - T_n)$ denotes Dirac's delta centred at T_n. We assume that lymphocytes interact in different ways with X and Z cells. As explained before, non-clonogenic tumour cells eventually die due to unsuccessful mitosis; however, we will assume they keep the same signalling protein production up to that time, causing the same depression over the immune system.

Equations (3) can be expressed in a dimensionless form taking the tumour duplication time $\tau_c = 1/a$ (in absence of external influences) as the characteristic time, so we introduce the dimensionless time $\tau = T/\tau_c$. Through the substitutions $X = ax/d$, $Y = ay/b$ and $Z = az/d$, we obtain the dimensionless system:

$$\begin{aligned}
\dot{x} &= x - xy - \gamma_t(\tau)x,\\
\dot{y} &= xy + \epsilon zy - \lambda y - \kappa(x+z) + \sigma - \gamma_l(\tau)y,\\
\dot{z} &= \gamma_t(\tau)x - \rho z - \eta zy,
\end{aligned} \tag{4}$$

with $\gamma_l(\tau) = \dot{B}_l(\tau)$, $\gamma_t(\tau) = \dot{B}_t(\tau)$, $\epsilon = p/d$, $\lambda = f/a$, $\kappa = kb/ad$, $\sigma = ub/a^2$, $\rho = ra/d$ and $\eta = qa^2/db$. All these parameters can be estimated by a similar procedure as in Rodríguez-Pérez *et al.* (2007).

2.1 *Clinical interest region and stochastic tumour model cutoff*

A linear stability analysis of the system (4) shows that tumour will vanish to $L_0 = (0; \sigma/\lambda; 0)$ if $\sigma/\lambda > 1$ and will remain controlled around $L_1 = ((\lambda - \sigma)/(1 - \kappa); 1; 0)$ if $\kappa < \sigma/\lambda < 1$ or $\kappa > 1$ (Sotolongo-Costa *et al.*, 2003). If the system is L_0 stable and initial tumour size is small enough, then the radiation treatment is unnecessary, whereas if tumour size is large enough, then the treatment will take it closer to L_0.

The L_1-controlled growth state will be reached only if both parameters fulfill the same condition, in other words, if σ/λ and κ are both greater or smaller than unity at the same time. Any other condition makes $L_1 < 0$, and even when the stable point mathematically exists, it cannot be approximated from realistic initial conditions (that should remain positive along the simulation time). For those patients with $\kappa > 1$ and $\sigma/\lambda < 1$, the main effects of the tumour will be the depression of immune system, they will perform badly according to Karnofsky performance scale (Sundstrom *et al.*, 2004) and will not fulfill physical requirements to be subject to treatment.

However, for $\sigma/\lambda < \kappa < 1$, tumour will grow exponentially and tumour eradication will be achieved only by bringing the system close enough to L_0 so that the immune system can get rid of the tumour. Figure 1 shows stable and unstable regions of (4) and highlights Region III on which this work will focus.

The chosen characteristic time and the dimensionless parameters allow us to give a very intuitive interpretation of the critical parameters of (4). We can see σ/λ as the efficiency of immune system over tumour growth and κ as the 'deficiency' of the immune system due to tumour growth.

It is also easy to see that radiation treatments do not change the stability conditions of system (3), given that radiotherapy does not change tumour or lymphocytes growth rate but can drive the number of both kind of cells to very small values. This means that, for the chosen region in the parameter space, any remaining tumour cells will eventually reproduce and grow exponentially after the end of the treatment. Although (4) allow for infinitesimal x values, in real systems when the number of tumour cells becomes small enough immune system may kill them (Steel, 1993). However, in other cases when a few tumour

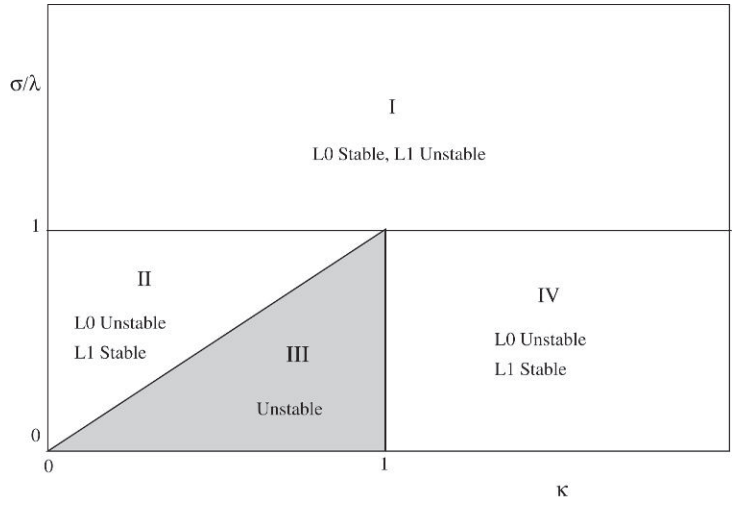

FIG. 1. Phase diagram of (4). This work focuses inside shadowed region ($\sigma/\lambda < \kappa < 1$) where tumour growth is exponential and radiotherapy plays an important role.

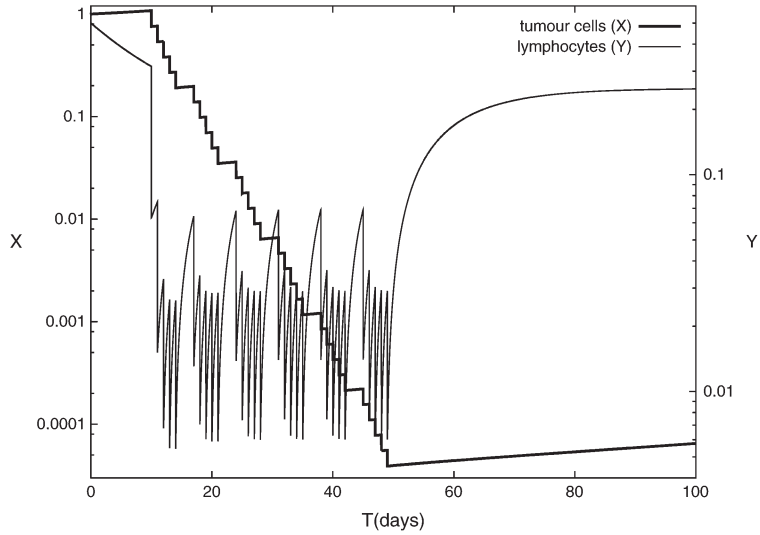

FIG. 2. Evolution of tumour (thick line) and lymphocyte (thin line) populations under radiotherapy treatment. $\lambda = 8.0$, $\sigma = 2.0$, $\kappa = 0.7$, $S_l = 0.2$ and $S_t = 0.7$.

cells survive, they can cause tumour regrowth. It is known that this behaviour is almost independent of tumour size (Steel, 1993) and as an estimation we will assume that the closer L_0 is (in terms of the parameter space of Fig. 1) to the line where it becomes a stable point, the higher the probability of tumour elimination by the immune system will be. Thus, when x becomes small enough (around 100 cells), we will take

$$P(\sigma/\lambda) = \begin{cases} \sigma/\lambda & \text{if} \quad \sigma/\lambda < 1 \\ 1 & \text{if} \quad \sigma/\lambda \geqslant 1, \end{cases} \tag{5}$$

as the probability of tumour regression. If no regression occurs, tumour will regrow as shown in Fig. 2.

We must realize that when the immunodepression term $-kX$ of system (1) is larger than the flux of lymphocytes u, an unattended method to solve the equations will fail to describe a biological system (d'Onofrio, 2005). However, this is a simple way to introduce the immunodepression effect in our equations and can be considered as the first-order Taylor approximation for a more general non-linear function. Furthermore, it provides us a very simple map for the parameter space to select the target tumours of radiotherapy treatments. Finally, the chance of lymphocyte population becoming zero gives us a natural cutoff for our ordinary differential equation (ODE) system. Then, whenever lymphocyte population becomes zero, we will assume the tumour escapes lymphocyte control and grows limited only by space and nutrient existence. At this point, we consider treatment has failed.

3. Simulation

We can mimic different radiation treatments with (4) to simulate tumour evolution. To follow radiotherapy treatment in a realistic way, we apply a radiation session every workday and none in weekends. All treatments (Rades *et al.*, 2006; Khoo, 2005) begin on the 10th day, take 6 weeks of radiotherapy and patients are under observation until 6 months after the end of radiotherapy sessions. We could take up

a sort of tumours, i.e., breast or colon, and knowing their approximate values of α and β, calculate the survival fraction of cells for a 2-Gy dosage. Instead, we prefer to act in a more general way, and ignoring the radiation dose, take a random value for the survival fractions of each patient tumour in the interval shown in Table 2. We generate several virtual patients under treatment taking different values for the parameter values in (4) and use a fourth-order Runge–Kutta method (Press *et al.*, 1992) to integrate them.

To reproduce tumour evolution resembling that of a clinical case, one needs to calculate the correct values of the coefficients appearing in (1). Numerical estimation of these coefficients was already made in Rodríguez-Pérez *et al.* (2007) (and also in de Pillis *et al.*, 2005, for a slightly different model) based on clinically available data showing a possible procedure for clinical professionals to estimate their values.

Figure 2 shows treatment evolution for tumour cells and lymphocytes. We can see how the number of tumour cells capable of mitosis quickly decreases with the radiation therapy. For long enough times, if regression behaviour is not accomplished, the tumour regrows exponentially.

An statistical study of the dependence of treatment success on the dosage was performed. Due to the wide range of possible parameter values in (4), their values are drawn randomly from a log-normal distribution, to avoid negative values, but keeping the efficiency of immune system (σ/λ) always smaller than 1. Survival factors (Enderling *et al.*, 2006; Steel, 1993) are also taken as random values within the interval shown in Table 1. As initial conditions we have supposed, for simplicity, that the number of tumour cells is higher than the number of lymphocytes and that both populations are distributed as normal random numbers with parameters shown in Table 2. We have also tested other distributions for the initial conditions as well as for coefficient values to verify that the choice does not affect the qualitative nature of our results.

At this point, we can proceed to make statistical predictions by generating a population of 'virtual patients' (characterized by their immune system and tumour parameter values) and simulating their treatment evolutions. Tables 2 and 3 show parameter values used to generate virtual patients.

TABLE 1 *Dimensionless parameter values of (4), taken from Rodríguez-Pérez et al. (2007), Enderling et al. (2006) and Düchting et al. (1996)*

Parameter	Minimum	Maximum
λ	10^0	10^3
σ	10^{-1}	10^5
κ	10^{-2}	10^4
S_t	0.5	0.9
S_l	0.1	0.4

TABLE 2 *Statistical survival factors and initial conditions for tumour cells and T lymphocytes*

Coefficient	Mean	Standard deviation
S_t	0.6	0.1
S_l	0.18	0.06
x_0	1.0	0.1
y_0	0.5	0.1

4. Results and clinical interpretation

We have created a database consisting of over 3×10^5 virtual patients, as far as we did not observe any change in our results when more patients were generated. We have calculated the probability of treatment success (P_S) as the fraction of patients without tumour at the end of treatment. We have represented this probability P_S as a function of tissue effect E (see (2)) and ISTER $= \sigma/\lambda$. In Fig. 3, a colour map of P_S versus E and σ/λ is represented. This induces a classification of patients based on their ISTER value and to assess those patients to whom, having an extremely low success probability, the application of high radiation doses would render useless. Radiotherapy is not the appropriate treatment for those patients, although it could be used as a palliative treatment, if a good balance between drawbacks and advantages is presumed for a specific patient.

We can see that, for a given value of σ/λ, two significant values of E can be defined: E_-, below which P_S is very small (less than 1%) and E_+, above which P_S is almost constant (with less than 1% of change). Results can be fitted (see Appendix A) to one expression of the form,

$$P_S = P_S(\sigma/\lambda, E), \tag{6}$$

and the significant values of E computed as functions of σ/λ. These two threshold values (E_- and E_+) divide the phase space $(\sigma/\lambda, E)$ into three regions as shown in Fig. 3. The success probability is

TABLE 3 *Statistical parameter values*

Parameter	Log. mean	Log. standard deviation
λ	5.0	0.5
σ	2.5	0.5
κ	0.8	0.2

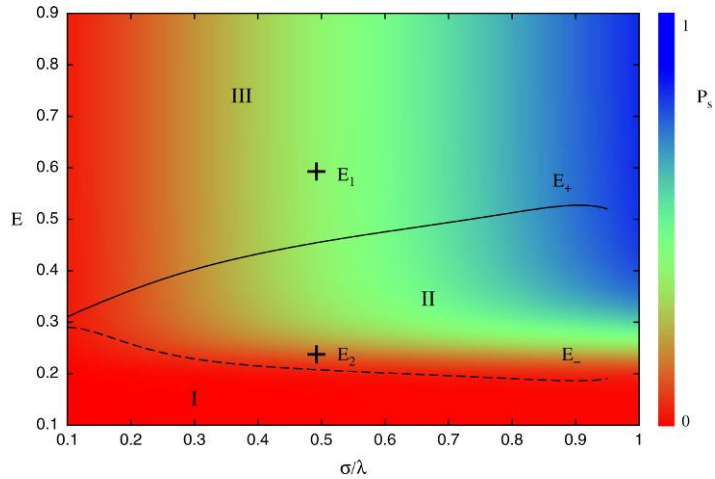

FIG. 3. P_S as a function of E and σ/λ (ISTER). E_- curve corresponds to the minimum values of tissue effect for which $P_S > 0$. E_+ curve represents the values of tissue effect for which P_S reaches its maximum value, given a fixed σ/λ. Marks (+) $E_1 = 0.6$ and $E_2 = 0.24$ represents the tissue effect in the explained examples.

negligible in Region I, below E_-, while it almost attains its maximum value above E_+, in Region III. However, on the intermediate Region II, as E grows, P_s increases faster towards its maximum value (above the E_+ curve).

The coefficients α and β are generally hard to find. Several values of the ratio α/β are reported in the literature (Steel, 1993). However, this is not enough for the clinical application and at least one of them must be found (as explained in Steel, 1993) to proceed.

To characterize patients, we only need, among all coefficients involved in (3), to know the ratio u/f, the effective amount of lymphocytes in the absence of tumour effects or immunodepression, and a/b, the opposition of tumour to be annihilated by lymphocytes. Clinical professionals must determine the inquiries and tests needed to find a patient's ISTER $= \sigma/\lambda = \frac{u/f}{a/b}$. Even though we realize this index definition only applies to a basic context, we think the concept could be useful to classify patients by the strenght of their immune system against tumour proliferation.

4.1 *Illustrative examples*

To show a possible clinical application of this result, let us consider two patients with the same ISTER $= 0.5$ and different tumour repair rate capacities described by the α/β parameter value (Abou-Jaoude & Dale, 2004). We will assume a low repair rate capacity tumour with $\alpha = 0.1\ \text{Gy}^{-1}$ and $\alpha/\beta = 1$ Gy and a high repair rate capacity tumour with $\alpha = 0.1\ \text{Gy}^{-1}$ and $\alpha/\beta = 10$ Gy, so the tumour repair rate capacities under radiation are different for each case. In both cases, the tissue effects, with an usual 2-Gy dose per day treatment, are represented in Fig. 3, like E_1 and E_2, respectively, and the maximum healing probability, calculated by expression (6) at the point corresponding to curve E_+ for $\sigma/\lambda = 0.5$, is $P_s = 0.43$. Table 4 shows the optimal calculated values of radiation dose for these two examples of tumour.

First, let us consider the case with $\alpha = 0.1\ \text{Gy}^{-1}$ and $\alpha/\beta = 1$ Gy. If we apply a typical dosage of 2 Gy per session of fractionated radiotherapy in our calculations, then the tissue effect will be $E_1 = 0.6$. However, this high tissue effect value does not really increase the success probability above P_s. A patient with an immune system efficiency of ISTER $= 0.5$ has his maximum healing probability for an E_+ value around 0.45 in each radiotherapy session. Then, we must apply a lower dose of 1.7 Gy in each radiation session and thus avoid an useless excess amount of 9 Gy to be applied in the whole treatment, i.e., a 15% dose reduction.

However, in the case with $\alpha = 0.1\ \text{Gy}^{-1}$ and $\alpha/\beta = 10$ Gy, the same patient with an ISTER $= 0.5$ needs a dose of 3.4 Gy to be applied in each session to attain the maximum healing probability $P_s = 0.43$. Besides the minimum E_- value is 0.22 corresponding to 1.9 Gy of physical radiation

TABLE 4 *Optimal values for two different tumours with ISTER* $= 0.5$, $E = 0.45$

Kind of tumour	E for $\Delta = 2$ Gy	Optimal Δ per session (Gy)
Low repair rate capacity tumour $\alpha = 0.1$ Gy $\alpha/\beta = 1$ Gy	0.6	1.7
High repair rate capacity tumour $\alpha = 0.1$ Gy $\alpha/\beta = 10$ Gy	0.24	3.4

per session (see Table 4). The oncologist should decide the amount of radiation to apply taking into account the treatment success probability, estimated by (6), and the radiosensitivity of the surrounding tissue.

The presented results match with those reported in Sundstrom *et al.* (2004) and show that the long-term survival of patients is not better at higher doses of radiation. On the contrary, the higher number of long-term survival patients is reached at intermediate doses (between 2 or 3 Gy), even with a smaller total amount of radiation.

5. Conclusions

The proposed method allows to find the success probability of a fractionated radiotherapy treatment using the patient ISTER parameter and the survival fraction S_t of tumour cells, even if other parameters involved are unknown. This calculation provides a way to classify patients based on their ISTER value and to approach to the optimum treatment.

The radiotherapy treatment must be designed for each patient taking into account the immunological features (ISTER) of each patient. Tissue effect has to be tuned to be larger than E_- (otherwise no success will be achieved) but needs not to be larger than E_+ (tissue effect at optimal treatment dosage) because no improvement will be obtained for higher radiation doses. Thus, in accordance with the ALARA (*As Low As Reasonably Achievable*) principle (Martin & Harbison, 1998), the physical radiation doses should be adjusted to bring E as close as possible to E_+ but without outranging it. This optimization process could be performed once the clinical professionals find a way to clinically evaluate the ISTER parameter value for a given patient. On the other hand, the values of α and β in (2) are already known or feasible to find for many kinds of tumour.

We must remark that the method used in this work does not depend on the chosen model (1) or the regression probability description given by (5). A more realistic model for both processes could give us a more accurate expression (6) but even using the simple form used in this work, it is possible to show that an optimized radiotherapy treatment can be found for a given patient. The robustness of the overall methodology would allow an oncologist to fit any tumour–immune system growth model to his clinical data and thus estimate the optimal dosage for a given patient in a real clinical context.

We must note that there are quite complete models that represent to a better extent tumour evolution (Matzavinos & Chaplain, 2004; Matzavinos *et al.*, 2004) and the ODE model presented here is comparatively simple. Nevertheless, although a very complex model could be fitted to represent the precise evolution of tumour cells together with their lymphocyte interaction, the experimental or clinical measurement of the coefficients involved would not be very precise. A simple model could certainly underestimate some characteristics of this evolution but may provide a conceptual framework to clinical professionals. We hope that the work presented in this paper will stimulate experimental research groups to further investigate the immune system importance in radiotherapy success.

Acknowledegments

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Appendix A

A.1 *Fitting result data to an analytical function*

We used a Levenberg–Marquardt (Press *et al.*, 1992) method to fit the result data shown in Fig. 3 to a suitable expression of the form,

$$\frac{P_s(\sigma/\lambda, E)}{\sigma/\lambda} = \left(\theta + \phi\left(1 + \left(\frac{E+\psi}{\varphi}\right)^4\right)^{-1}\right) \tag{A.1}$$

for each of the values σ/λ computed. This expression gives us a family of functions related to each other through the coefficients θ, ϕ, ψ and φ. These coefficients are functions of only σ/λ and can be easily fitted using the same numerical method. We have found the following numerical expressions for these coefficients,

$$\begin{aligned}
\theta &= 0.950271 \times \left(1 - \exp\left(-4.66627\tfrac{\sigma}{\lambda} - 0.24319\right)\right), \\
\phi &= -0.935012 + \exp\left(-4.71719\tfrac{\sigma}{\lambda} - 0.289458\right), \\
\varphi &= 0.0450091\tfrac{\sigma}{\lambda} + 0.091267, \\
\psi &= 0.0159581\tfrac{\sigma}{\lambda} - 0.141425.
\end{aligned} \tag{A.2}$$

Merging all these expressions, it is possible to analyse the behaviour of the success probability $P_s(\sigma/\lambda, E)$ in terms of σ/λ with no need to resort to more numerical simulations.