Immune System – Tumor Efficiency Rate as a new Oncological Index for Radiotherapy Treatment Optimization

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Abstract

A dynamical system model for tumor – 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 Rate (ISTER), is introduced. ISTER dependence of treatment success and other features is studied. Statistical results allow us to give a patient classification scheme. Radiotherapy treatment biological effective dose (BED) is thus optimized based on the patient physical condition, following the ALARA (As Low As Reasonably Achievable) criterion.

1 Introduction

Some approaches to cancer growth and behavior have been made in the past years. Recent techniques try to use a population dynamics model [1, 2, 3, 4] to mathematically describe the tumour behavior and its interaction with the immune system. Some of these works explain tumour behavior under clinical treatments like cytokines [5] or radiovirotherapy [6] and properly explain the qualitative behaviors of several tumours. Even though great efforts had been made to describe cancer radiotherapy treatments [2], they are but vaguely linked to clinical observations and their large number of variables and coefficients make their results hardly transposable to a clinical context.

Radiotherapy and surgery are the most effective treatments for cancer, and even while surgery has a longer tradition, radiotherapy is replacing surgery for the control of many tumours [7]. Those treatments follow strict protocols that often apply a fixed physical radiation dose, hardly taking into account the kind of tumour or 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 and looking for an applicable method, we intend to model a radiotherapy treatment making the simplest possible assumptions. Furthermore we
will introduced the Immune System Tumour Efficiency Rate parameter (ISTER) as a measure of the patient immune system strength to fight back cancer. This parameter allow us to make a patient classification and find the success probability of each patient group following a radiotherapy treatment protocol. Finally, we will use these results to assess the optimized biological effective dose (BED) or tissue effect (E) based on a given patient physical condition.

\section{Model}

In order to describe the tumour evolution, we propose a Lotka-Volterra like model based on some assumptions. Tumour cells 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, $-bXY$. Lymphocytes 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 [8, 9], 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 known equations [5]:

\begin{align}
\dot{X} &= aX - bXY \\
\dot{Y} &= dXY - fY - kX + u
\end{align}  

(1)

The effects of radiation over any tissue are generally classified in three phases [7]. 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 unreparable cells are signaled to die by apoptosis.

Carcinogenesis and other malignant effects, that escape cellular control, can appear as late effects of the biological phase and, to avoid them, radiation doses need to be optimized. This means that higher doses that could reduce the long term overall survival of patients [11], must be avoided whenever possible.

We will collect 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 become appreciable), and so only long term effects will be taken into account in our evolution equations. Then, we are going to assume that lymphocytes die or lose their ability to attack tumour cells immediately, and that radiation dose is concentrated at an infinitesimal instant of time. At that very moment, long term effects start to take place, whereas short term effects instantaneously modify the state of the system.

Thus, we also assume that when a radiation dose is applied at a given instant $T_n$, it induces a fraction $B_n$ of the tumour cells to lose their reproductive endowment and to die exponentially. The fraction $S_n$ of tumour cells not affected by radiation can be computed by the linear-quadratic (LQ) model [4, 10].
\[ S_t = 1 - B_t = \exp[-E] = \exp[-\alpha \Delta - \beta \Delta^2] \]  

where \( E \) is known as the tissue effect, \( \alpha \) and \( \beta \) are Type A and B damage coefficients [7], and \( \Delta \) is the physical radiation dose expressed in Gy, as usual in clinical contexts. Furthermore, a fraction \( B_t \) of lymphocytes is also killed by radiation, in a manner similar to (2) although having different \( \alpha \) and \( \beta \) coefficients.

To include long term processes in Eqs. (1), we write a new equation for non-proliferating tumour cells \( Z \) [6], taking into account that lymphocyte population is also stimulated, as \( pZY \), due to interaction with these cells. The number of non-proliferating 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

\[
\begin{align*}
\dot{X} &= aX - bXY - B_t(T)X \\
\dot{Y} &= dXY + pZY - fY - k(X + Z) + u - B_t(T)Y \\
\dot{Z} &= B_t(T)X - rZ - qZY
\end{align*}
\]

where \( B_t(T) = B_t \sum \delta(T - T_n) \) and \( B_t(T) = B_t \sum \delta(T - T_n) \). \( T_n \) are the time instants when radiation doses are applied and \( \delta(T - T_n) \) denotes Dirac’s delta centered at \( T_n \). We have supposed that lymphocytes interact in different ways with \( X \) and \( Z \) cells, although both kind of tumour cells cause the same depression over the immune system.

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

\[
\begin{align*}
\dot{x} &= x - xy - \gamma(\tau)x \\
\dot{y} &= xy + \varepsilon y - \lambda y - \kappa(x + z) + \sigma - \gamma(\tau)y \\
\dot{z} &= \gamma(\tau)x - \rho z - \eta zy
\end{align*}
\]

with \( \gamma = B_t/a, \ \varepsilon = p/d, \ \lambda = f/a, \ \kappa = kb/ad, \ \sigma = ub/a^2, \ \rho = ra/d \) and \( \eta = qa^2/db \).

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 \( \kappa > 1 \) [5]. 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 fulfil the same condition, in other words, if \( \sigma/\lambda \) and \( \kappa \) 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 can not 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 present a low Karnofsky performance scale [11] and will not fulfill physical conditions to be subject under treatment.

However for \( \sigma/\lambda < \kappa < 1 \), tumour will grow exponentially and radiotherapy goal will be to bring it close enough to \( L_0 \) so that immune system can get rid of the tumour.
Figure 1 shows stable and unstable regions of Eqs. (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 Eqs. (4). We can see $\sigma/\lambda$ as the efficiency of immune system over tumour growth and $\kappa$ 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 our system, 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. Although Eqs. (4) allow for infinitesimal $x$ values, in real systems when the number of tumour cells becomes small enough, immune system may kill them [7]. However, in other cases when a few tumour cells survive, they can cause tumour regrowth. It is known that this behavior is almost independent on tumour size and as an estimation we will assume that the closer $L_0$ is (in terms of the phase space of figure 1) to the line where it becomes an stable point, the higher will be the probability of tumour elimination by the immune system. Thus, when $x$ becomes small enough we will take

$$P(\sigma/\lambda) = \begin{cases} 
\sigma/\lambda & \text{if } \sigma/\lambda < 1 \\
1 & \text{if } \sigma/\lambda \geq 1 
\end{cases}$$

(5)

as the probability of tumour regression.

Similarly, whenever lymphocyte population becomes zero we will assume a general failure of immune system. This situation may also occur in some cases where the
tumour is removed but the immune system reaches such an extreme low concentration of lymphocytes that, consequently, the patient dies.

3 Simulation

We can mimic different radiation treatments with Eqs. (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 \[12\] \[13\] begin the tenth day, take 6 weeks of radiotherapy and patients are under observation until 6 months after the end of radiotherapy sessions. We generate several virtual patients under treatment taking different values for the parameter values in Eqs. (4) and use a four step Runge-Kutta method \[14\] to integrate them.

To reproduce tumour evolution resembling that of a clinical case, we need to calculate the correct values of the coefficients appearing in Eqs. (1). Estimation of these coefficients was made in \[15\], and following a similar procedure it would not be too hard for clinical professionals to estimate their values. Figure 2 shows treatment evolution for typical values of the coefficients and under different doses of radiation. We can see how the number of tumour cells capable of mitosis quickly decreases with the radiation therapy. For long enough times, if regression behavior is not accomplished, the tumour regrows quickly.

In order to accomplish a statistical study of the dependence of treatment success on the dosage, and due to the wide range of possible parameter values in Eqs. (4), their values are drawn randomly from a log-normal distribution, to avoid negative values, but keeping the efficiency of immune system \((\sigma/\lambda)\) always smaller than 1. Survival factors \[4\] \[7\] 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.

| Parameter | Minimum | Maximum |
|-----------|---------|---------|
| \(\lambda\) | \(10^0\) | \(10^3\) |
| \(\sigma\) | \(10^{-1}\) | \(10^3\) |
| \(\kappa\) | \(10^{-2}\) | \(10^4\) |
| \(S_t\) | 0.5 | 0.9 |
| \(S_l\) | 0.1 | 0.4 |

Table 1: Dimensionless parameter values of equations (4) taken from \[15\] \[4\] \[10\].

At this point we can proceed to make statistical predictions by generating a population of “virtual patients” (characterised by their immune system and tumour parameter values) and simulating their treatment evolutions. Tables 3 and 2 show parameter values used to generate virtual patients.
Figure 2: Tumour evolution under radiotherapy treatment for two different tumour survival factors. $\lambda = 5.0, \sigma = 4.0, \kappa = 0.7, S_f = 0.2$

| 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               |

Table 2: Statistical survival factors and initial conditions for tumour cells and T-lymphocytes

| Parameter | log. Mean | log. Standard Deviation |
|-----------|-----------|-------------------------|
| $\lambda$ | 5.0       | 0.5                     |
| $\sigma$  | 2.5       | 0.5                     |
| $\kappa$  | 0.8       | 0.2                     |

Table 3: Statistical parameter values.
4 Results and clinical interpretation

We have created a database consisting of over $3 \times 10^5$ virtual patients. 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 equation (2)) and efficiency of immune system ($\sigma/\lambda$) or ISTER. In Fig 3 a color map of $P_s$ versus $E$ and $\sigma/\lambda$ is represented. This allows us to classify patients based on their $\sigma/\lambda$-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, if a good balance between drawbacks and advantages is presumed for a specific patient.

![Color map of $P_s$ versus $E$ and $\sigma/\lambda$](image)

Figure 3: $P_s$ as a function of $E$ and $\sigma/\lambda$. $E_-$ 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 $\sigma/\lambda$. Marks $E_1 = 0.84$ and $E_2 = 0.24$ represents the tissue effect in the explained examples.

We can see that, for a given value of $\sigma/\lambda$, 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 to the expression,

$$P_s = P_s(\sigma/\lambda, E)$$

and the significant values of $E$ computed as functions of $\sigma/\lambda$. 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 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 $\alpha$ and $\beta$ are generally hard to find, but not impossible, and several values of the ratio $\alpha/\beta$ are reported in the literature [7]. However this is not enough for the clinical application and at least one of them must be found (as explained also in [7]) to proceed. Luckily, to characterize patients, we just need, among all coefficients involved in Eqs. (3), to know the ratio $u/f$, the effective amount of lymphocytes in the absence of tumour effects or immunodepression, and $b/a$, a measure of the effectiveness of lymphocytes over tumour growth. Clinical professionals must determine the inquiries and tests needed to find a patient’s ISTER.

To illustrate a possible clinical application of this result, we are going to suppose two virtual patients with the same ISTER = 0.5 and different tumour sensitivities. We will assume a sensitive tumour [16] with $\alpha = 0.3 \text{ Gy}^{-1}$ and $\alpha/\beta = 5 \text{ Gy}$, and a more resistant tumour with $\alpha = 0.1 \text{ Gy}^{-1}$ and $\alpha/\beta = 10 \text{ Gy}$, so the tumour resistance to radiation is quite different for each case. In both cases the tissue effects, with an usual treatment, are represented in Fig 3, like $E_1$ and $E_2$ respectively.

First, let us consider the case of a sensitive tumour [16] with $\alpha = 0.3 \text{ Gy}^{-1}$ and $\alpha/\beta = 5 \text{ Gy}$. If we apply the typical fractionated radiotherapy used in our calculations, then the biological effective dose ($BED = E/\alpha$), for each radiotherapy session of 2 Gy, will be 2.8 Gy. However, this high dose value does not really increase the success probability. A patient with an immune system efficiency of ISTER = 0.5, has his maximum healing probability for a $BED$ value around 1.5 Gy in each radiotherapy session. Then, we must apply a physical radiation of 1.2 Gy in each radiation session and thus, avoid an useless amount of 24 Gy to be applied in the whole treatment.

However, in the case of a tumour having a higher resistance to radiation, e.g. with $\alpha = 0.1 \text{ Gy}^{-1}$ and $\alpha/\beta = 10 \text{ Gy}$, the same patient with an ISTER = 0.5, attains a maximum success probability for a $BED$ = 4.5 Gy, and needs a physical dose of 3.4 Gy to be applied in each session. Besides, the minimum $BED$ value is 2.2 Gy, corresponding to 1.85 Gy of physical radiation per session. Table 4 shows the optimal calculated values of physical radiation dose for the two examples of tumour with a ISTER = 0.5.

The oncologist, should decide the amount of radiation to apply, by evaluating Eq. (6) to know the treatment success probability, and taking into account any other clinical factors implied.

| Kind of tumour | $BED$ for $\Delta = 2 \text{ Gy}$ | Optimal $E$ | Optimal $BED$ | Optimal $\Delta$ per session |
|---------------|---------------------------------|-------------|---------------|-----------------------------|
| Sensitive tumour | $\alpha = 0.3 \text{ Gy}$ $\alpha/\beta = 5 \text{ Gy}$ | 2.8 Gy | 0.45 | 1.5 Gy | 1.2 Gy |
| Less sensitive tumour | $\alpha = 0.1 \text{ Gy}$ $\alpha/\beta = 10 \text{ Gy}$ | 2.4 Gy | 0.45 | 4.5 Gy | 3.4 Gy |

Table 4: Optimal values for two different tumours with a rate ISTER = 0.5.

The presented results match with those reported in [11], that show that the long term survivance 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
5 Conclusions

The proposed method, allows us to find the success probability of a fractionated radiotherapy treatment, using the patient \( ISTER \) parameter, as a new oncological index, 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 his/her immunological characteristics (\( ISTER \)) relative to the tumour. Tissue effect has to be tuned to be larger than \( E_- \), otherwise no success will be achieved, but needs not to be larger than \( E_+ \), because no improvement will be obtained for larger radiation doses. Thus, in accordance with the ALARA (\textit{As Low As Reasonably Achievable}) principle \[17\], the physical radiation doses should be adjusted to bring \( E \) as close as possible to \( E_+ \) but without out-ranging it. This optimization process could be performed once the clinical professionals find a way to evaluate the \( ISTER \) index experimentally for a given patient. On other hand, the values of \( \alpha \) and \( \beta \) (in Eq. \[2\]) are known or feasible to find for many kinds of tumour.

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A Fitting result data to an analytical function

We used a Levenberg-Marquardt \cite{14} method to fit the result data, showed in figure 3, to the analytical function,

\[
\frac{P_s(\sigma/\lambda, E)}{\sigma/\lambda} = \left( \theta + \phi \left( 1 + \left( \frac{E + \psi}{\phi} \right)^4 \right)^{-1} \right)
\]  

(7)

for each value of computed $\sigma/\lambda$. This expression gives us a family of functions related to each other through coefficients $\theta$, $\phi$, $\psi$ and $\varphi$. These coefficients are functions of only $\sigma/\alpha$ and can be easily fitted using the same numerical method.

We have found the following numerical expressions for these coefficients,

\[
\begin{align*}
\theta &= 0.950271 \times (1 - \exp(-4.66627\frac{\sigma}{\lambda} - 0.24319)) \\
\phi &= -0.935012 + \exp(-4.71719\frac{\sigma}{\lambda} - 0.289458) \\
\varphi &= 0.0450091 \frac{\sigma}{\lambda} + 0.091267 \\
\psi &= 0.0159581 \frac{\sigma}{\lambda} - 0.141425
\end{align*}
\]  

(8)

Merging all this expressions, it is possible analyze the behaviour of the success probability $P_s(\sigma/\lambda, E)$. 

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