

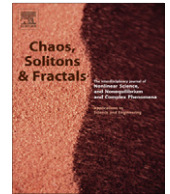


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## Tumour–host dynamics under radiotherapy

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### ABSTRACT

Tumour–host interaction is modelled by the Lotka–Volterra equations. Qualitative analysis and simulations show that this model reproduces all known states of development for tumours. Radiotherapy effect is introduced into the model by means of the linear–quadratic model and the periodic Dirac delta function. The evolution of the system under the action of radiotherapy is simulated and parameter space is obtained, from which certain threshold of effectiveness values for the frequency and applied doses are derived. A two-dimensional logistic map is derived from the modified Lotka–Volterra model and used to simulate the effectiveness of radiotherapy in different regimens of tumour development. The results show the possibility of achieving a successful treatment in each individual case by employing the correct therapeutic strategy.

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### 1. Introduction

In recent decades, many mechanisms of the action of malignant cells against healthy tissue have been discovered. We can model the behaviour of a healthy cell population, the development of a tumour and its evolution under treatment, by calling on experimental and clinical experience. The resulting models are mathematical attempts to generalize the experimental facts.

The interaction of the host cells with tumour cells must be considered a dynamic process. Tumour–host interaction has been modelled as a community where there exist a healthy population and another population of malignant cells. Between these populations, many complex interactions appear. The cell populations fight one against the other for space and resources. In this contribution, this competitive process is described by the Lotka–Volterra (LV) equations, a system of two coupled nonlinear differential equations.

The model was introduced by Volterra [1] to analyze the interaction between a number of different biological species. A version of the model for two species and its rela-

tion with autocatalytic reactions was discussed independently by Lotka [2,3]. This competitive model allows the examination of critical factors in the tumour–host interaction, by viewing the tumour and local tissue as interacting populations of cells analogous to populations of two species in nature.

In the following sections, some of the most important features of the Lotka–Volterra equations are reviewed. The dynamics is investigated by the linear stability method. The action of radiotherapy is introduced into the model and the various responses of the system are simulated. The efficacy of applying radiotherapy in the different regimens in which a tumour can appear is simulated by a two-dimensional map derived from the LV model under the action of radiotherapy. Some recommendations for treatment schedules are derived from the simulations.

### 2. Model

We assume only two populations, normal and malignant cells, and that all cells of the same population are identical. The interaction between populations is described by the LV model. It is assumed that the normal and tumour cells compete for the resources and space in a small volume of tissue [4,5]. The equations are:

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$$\frac{dx}{dt} = ax - bx^2 - cxy \tag{1}$$

$$\frac{dy}{dt} = dy - ey^2 - fxy \tag{2}$$

where  $x$  and  $y$  denote the number of malignant and normal cells, respectively,  $a$  is the rate of multiplication of malignant cells,  $b$  is a factor decreasing the growth rate, due to competition for resources such as nutrient and oxygen or the accumulation of substances released from the cell metabolism. Factor  $c$  is the action of healthy on malignant cells, which may be positive or negative if the net action is inhibitory or stimulatory. The inhibitory effect of the healthy on the malignant cells can be due to the immune response, contact inhibition, induction of terminal differentiation or apoptosis. The stimulatory effect is due to the production of growth factors by the host which stimulate tumour cell growth [4,5]. Analogously, parameter  $d$  is the rate of multiplication of host cells,  $e$  a factor restricting their rate of growth and  $f$  the rate of elimination of the host cells by the activity of malignant cells. The nonlinear interactions between host and tumour cells are able to generate a considerable variety of responses, many of which are observed both experimentally and clinically [4,5].

Although there is no general analytic solution to these equations, phase plane dynamics analysis can be carried out and thus a complete overview of the qualitative behaviour of the model is possible. An important feature of the LV model is that in all regimens growth is limited.

2.1. Analytical approach and linear stability

In spite of the very simple appearance of the LV equations, no general solution is known. There are some cases in which the symmetry of the problem allows the integral of motion to be found. We will review here three such cases. A more complete analysis of the integrability of the two-dimensional LV can be found in a recent article by Pradeep et al. [6] and in the references cited therein.

Case I:  $b = f$  and  $c = e$ . Eqs. (1) and (2) can be combined to give:

$$\frac{dy}{dx} = \frac{dy - cy^2 - bxy}{ax - bx^2 - cxy} \tag{3}$$

By means of the transformation  $y = T/z$  and  $x = 1/z$ , we obtain the linear differential equation

$$\frac{dz}{dT} - \frac{a}{T(d-a)}z = \frac{b}{T(d-a)} - \frac{c}{d-a} \tag{4}$$

and this has the solution

$$z(T) = \frac{a}{b} - \frac{c}{d}T + gT^{\frac{a}{a-d}} \tag{5}$$

Reverting to the original variables

$$\frac{1}{x} = \frac{a}{b} - \frac{c}{d} \frac{y}{x} + g \left(\frac{y}{x}\right)^{\frac{a}{a-d}} \tag{6}$$

The integration constant  $g$  is determined from the initial conditions.

If in addition, in Eq. (3)  $a = d$  we have

$$\frac{dy}{dx} = \frac{y}{x}$$

Then  $y = g_1x$  with  $g_1 = y(0)/x(0)$ . Placing  $y = g_1x$  in equation (1) and integrating

$$x(t) = \frac{ag_2e^{at}}{(b + cg_1)(1 + g_1e^{at})}$$

This solution shows asymptotic behaviour:  $\lim_{t \rightarrow \infty} x(t) = \frac{ax(0)}{bx(0)+cy(0)}$  and  $\lim_{t \rightarrow \infty} y(t) = \frac{ay(0)}{bx(0)+cy(0)}$ . The motion is bounded and depends on the initial condition. Analyzing the linear stability of the system in the phase plane ( $x, y \geq 0$ ) we find that there is an isolated fixed point at the origin (0,0) which is an unstable node, and a line of fixed points  $y = \frac{a-bx}{c}$  which are stable [7]. Fig. 1 shows a phase plane diagram for this case.

Case II:  $c = 0$ . In this case, Eq. (1) becomes

$$\frac{dx}{dt} = ax - bx^2$$

with the solution

$$x(t) = \frac{ag_1e^{at}}{b + bg_1e^{at}} \tag{7}$$

where  $g_1 = \frac{bx(0)}{a+bx(0)}$ . Inserting (7) in (2), we obtain a Bernoulli equation which can be linearized by the transformation  $z = 1/y$  [7,8]. Finally integrating, the following equation is obtained:

$$z(t) = (1 + g_1e^{at})^{\frac{f}{b}} e^{-dt} \left[ e \int \frac{e^{dt} dt}{(1 + g_1e^{at})^{\frac{f}{b}}} + g_2 \right] \tag{8}$$

where  $g_2$  is a constant of integration which must be determined from the initial conditions. The integral in (8) can be expressed in terms of elementary functions only if  $d/a$  or  $f/b$  is an integer [9]. One particular case in which this integral can be explicitly solved is  $a = d$ .

Case III:  $a = d$ . Eqs. (1) and (2) become

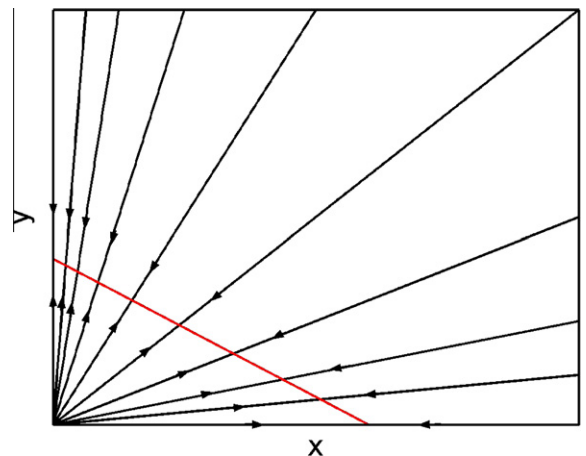


Fig. 1. Phase plane diagram of LV model for  $a = d$ ,  $b = f$  and  $c = e$ . Fixed points  $P1 = (0,0)$  and the line of fixed points  $y = (a - bx)/c$ .

$$\begin{aligned} \frac{dx}{dt} &= ax - bx^2 - cxy \\ \frac{dy}{dt} &= ay - ey^2 - fxy \end{aligned}$$

Using the transformations  $u = at - \ln x$  and  $v = at - \ln y$ , we obtain

$$\begin{aligned} \frac{du}{dt} &= be^{at-u} + ce^{at-v} \\ \frac{dv}{dt} &= ee^{at-v} + fe^{at-u} \end{aligned}$$

These can immediately be rewritten as

$$\frac{du}{dv} = \frac{be^{at-u} + ce^{at-v}}{ee^{at-v} + fe^{at-u}} = \frac{be^{v-u} + c}{e + fe^{v-u}}$$

eliminating  $t$ . Applying the transformation  $z = v - u$ :

$$\frac{dz}{dv} = \frac{(f - b)e^z + e - c}{fe^z + c}$$

Separating variables and integrating, we have

$$\frac{e^{\frac{e}{c}z}}{[(f - b)e^z + e - c]^\gamma} = g_1 e^v$$

where  $\gamma = \frac{e(f-b)-f(e-c)}{(f-b)(e-c)}$ . Returning to variables  $x$  and  $y$ :

$$\left[ \frac{\left(\frac{x}{y}\right)^{\frac{e}{c}}}{(f - b)\frac{x}{y} + e - c} \right]^\gamma = \frac{g_1 e^{at}}{y} \tag{9}$$

In this case, we have an integral of motion that depends on  $x$ ,  $y$  and  $z$ .

The cases in which we can integrate the LV equations or obtain an integral of motion are very restricted. A more general picture of the LV dynamics can, however, be obtained from linear stability analysis.

We are interested only in the first quadrant of the phase plane because negative values of  $x$  and  $y$  are meaningless. In this quadrant, up to four fixed points occur:  $P_1 = (0, 0)$ ,  $P_2 = (0, d/e)$ ,  $P_3 = (a/b, 0)$  and  $P_4 = \left(\frac{cd-ae}{cf-be}, \frac{af-bd}{cf-be}\right)$ .

The stability of these points can be studied by the linear stability method. For simplicity, we will restrict the analysis to nonnegative values of parameters. In order to establish the stability of each of the fixed points, it is necessary to calculate the Jacobian matrix

$$J(x, y) = \begin{pmatrix} a - 2bx - cy & -cx \\ -fy & d - 2ey - fx \end{pmatrix} \tag{10}$$

at the fixed points and then calculate the eigenvalues  $\lambda_i$  directly from the equation

$$\|J - \lambda I\| = \lambda^2 - \text{Tr}(J)\lambda + |J| \tag{11}$$

where  $\text{Tr}(J)$  is the trace of  $J$ . For  $P_1$  we obtain  $\lambda_1 = a$  and  $\lambda_2 = d$ , making this an unstable node, and it appears in all the regimens; for  $P_2$ :  $\lambda_1 = -d$  and  $\lambda_2 = a - cd/e$  if  $cd < ae$  this is a saddle point, otherwise it is a stable node; for  $P_3$ :  $\lambda_1 = -a$  and  $\lambda_2 = d - af/b$  if  $af < bd$  this is a saddle, otherwise it is a stable node; finally, for  $P_4$ :  $\lambda_{1,2} = \frac{1}{2} \left( H \pm \sqrt{H^2 + 4K} \right)$  with  $H = \frac{b(ae-cd)+e(bd-af)}{cf-be}$  and  $K =$

$\frac{(bd-af)(ae-cd)}{cf-be}$ . In this last case, the analysis of the signs of the eigenvalues can be simplified if we assume that  $x$  and  $y$  are positive, so that for  $cf > be$ ,  $cd > ae$  and  $af > bd$  this is a saddle point, and for  $cf < be$ ,  $cd < ae$  and  $af < bd$  it is a stable node, while other cases are not possible.

### 2.2. Regimen I

This regimen occurs when  $cd > ae$  and  $af < bd$ . The point  $P_2$  is a stable node, and  $P_3$  is a saddle point. This corresponds to an immune system that can completely eliminate any malignant formation by itself. If the normal tissue is injured and at the same time a group of malignant cells appears, then the malignant population will immediately begin to diminish, down to  $x = 0$ , while the normal population will grow to  $y = a/b$ , so that equilibrium is established (see Fig. 2). From the clinical point of view, this regimen has no interest because it corresponds to a healthy organism.

### 2.3. Regimen II

For  $cf < be$ ,  $cd < ae$  and  $af < bd$ , both  $P_2$  and  $P_3$  are saddle points, and  $P_4$  is a stable node. In this regimen, the healthy population  $y = \frac{af-bd}{cf-be}$  coexists in equilibrium with the malignant population  $x = \frac{cd-ae}{cf-be}$ , as shown in Fig. 3. In this case, although the malignant population is a latent danger for the organism, the immune system can control the tumour growth. Thus, the tumour can be considered as benign. If a part of the tumour is eliminated, for example by surgery, it can be regenerated unless all the tumour cells are removed.

The parameters can be hand so that the dynamics change to regimen I; then, after surgery, the host can eliminate the remaining tumour cells. One strategy is to enhance the immune activity, which is equivalent to increasing parameter  $c$ . Another would be to use a constant dose of chemotherapy. Mathematically, this can be modelled by adding the terms  $-\gamma C_0 x$  and  $-\delta C_0 y$  to Eqs. (1) and (2), where  $C_0$  is the concentration of the drug [10,11]

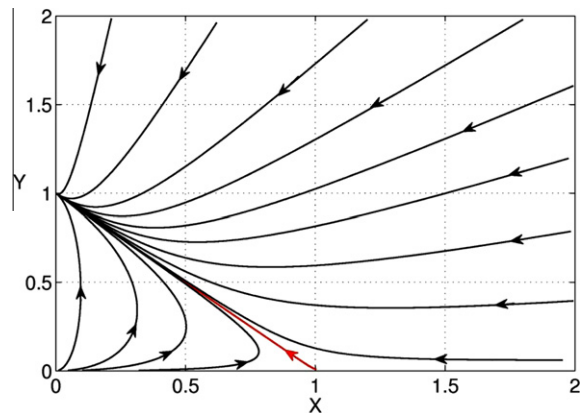
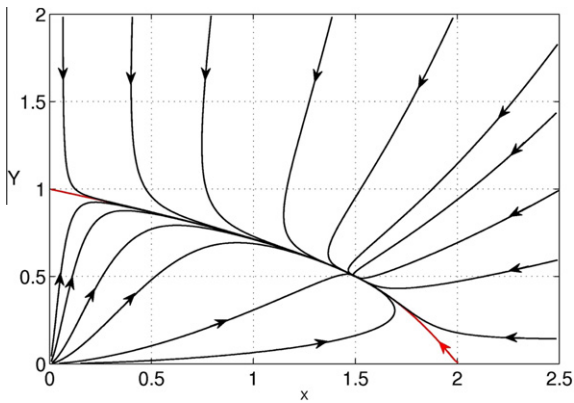


Fig. 2. Phase portrait of LV model in regimen I: the immune system can completely eliminate any malignant formation by itself.  $a = 1$ ,  $b = 1$ ,  $c = 2$ ,  $d = 2$ ,  $e = 2$  and  $f = 1$ . Fixed points  $P_1 = (0, 0)$ ,  $P_2 = (0, 1)$ ,  $P_3 = (1, 0)$ .



**Fig. 3.** Phase portrait of LV model in regimen II: healthy and malignant population coexist in equilibrium.  $a = 2, b = 1, c = 1, d = 3, e = 3$  and  $f = 1$ . Fixed points  $P_1 = (0,0), P_2 = (0,1), P_3 = (2,0), P_4 = (1.5,0.5)$ .

and the factors  $\gamma$  and  $\delta$  are related to the responses of tumour and normal cells to the drug (in fact the action of the drug could be more complicated due to the development of resistance in some individuals of the population [12]):

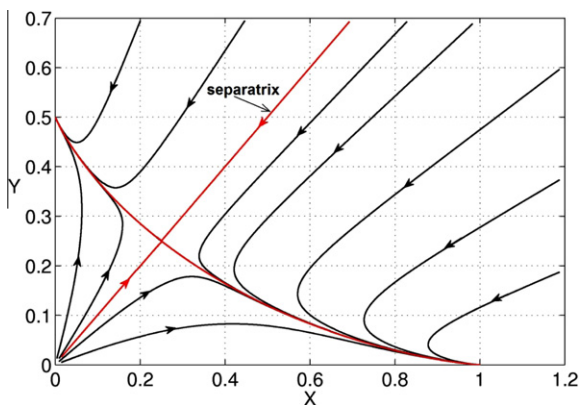
$$\frac{dx}{dt} = (a - \gamma C_0)x - bx^2 - cxy$$

$$\frac{dy}{dt} = (d - \delta C_0)y - ey^2 - fxy$$

Since  $af < bd$ , to change to regimen I it would be necessary that  $(a - \gamma C_0)e < (d - \delta C_0)c$ . Using the fact that  $cd < ae$ , we then have:

$$C_0(\gamma e - \delta c) > ae - cd > 0$$

Then the therapy will be effective if  $\gamma e - \delta c > 0$  and  $C_0 > (ae - cd)/(\gamma e - \delta c)$ . If  $\gamma e < \delta c$  it will fail for any value of  $C_0$ . This result shows that chemotherapy cannot be applied in all cases. In such cases, immunotherapy may be an alternative [13].



**Fig. 4.** Phase portrait of LV model in regimen III: the separatrix divide the phase space into the basins of attraction of nodes  $P_2$  and  $P_3$ .  $a = 1, b = 1, c = 3, d = 1, e = 2$  and  $f = 2$ . Fixed points  $P_1 = (0,0), P_2 = (0,0.5), P_3 = (1,0), P_4 = (0.25,0.25)$ .

2.4. Regimen III

For  $cf > be, cd > ae$  and  $af > bd$ , the points  $P_2$  and  $P_3$  are stable nodes and  $P_4$  is a saddle. In the phase space Fig. 4, it can be seen that the separatrix of positive slope divide the phase space into two regions. The upper region is the basin of attraction of node  $P_2$ , so that any initial condition in this region will have a favourable outcome, because the malignant population will disappear and normal tissue will recover its normal volume, whereas any initial condition located in the basin of attraction of  $P_3$ , the region below the separatrix, will have a fatal outcome.

The equation of the separatrix can be obtained approximately by linearizing around the saddle point [7]:

$$y = y_0 + \frac{\lambda_2 - a_{11}}{a_{12}}(x - x_0) \tag{12}$$

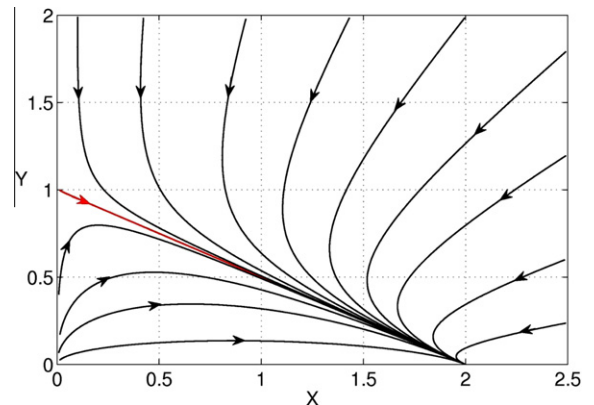
where  $\lambda_2 = \frac{1}{2}(H - \sqrt{H^2 + 4K})$ ,  $a_{11} = b \frac{ae - cd}{cf - be}$ ,  $a_{12} = c \frac{ae - cd}{cf - be}$ ,  $x_0 = \frac{cd - ae}{cf - be}$  and  $y_0 = \frac{af - bd}{cf - be}$ .

This expression could be very interesting from a theoretical point of view, because any therapeutic schedule capable of taking the system over the separatrix would ensure a favourable evolution.

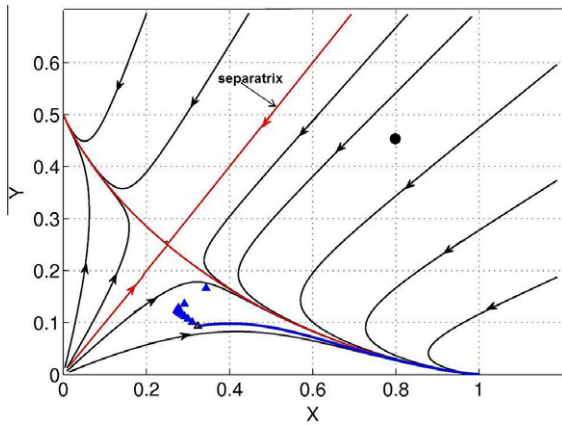
2.5. Regimen IV

For  $cd < ae$  and  $af > bd$ , the point  $P_2$  is a saddle and  $P_3$  is a stable node (see Fig. 5). In this regimen, the tumour is very aggressive, it evades the control of the immune system and the proliferation of its cells completely destroys the healthy tissue. In this regimen, surgery and radiotherapy fail completely, unless all malignant cells are eliminated before the tumour destroys the host. If a part of the tumour is removed it will be regenerated. On the other hand, the damage caused to healthy tissues by radiation or surgery could benefit the malignant population.

By increasing parameter  $c$ , it is possible to carry the system from regimen IV to regimen III. This might be achieved by enhancement of the immune response.



**Fig. 5.** Phase portrait of LV model in regimen IV: the tumour is very aggressive; the growth of its population completely destroys the healthy tissue.  $a = 2, b = 1, c = 1, d = 1, e = 1$  and  $f = 1$ . Fixed points  $P_1 = (0,0), P_2 = (0,1), P_3 = (2,0)$ .



**Fig. 6.** Incorrect schedule of radiotherapy due to inappropriate choice of doses and period. The triangles represent the state of the system just before each application of radiation:  $D = 2$ ,  $T = 1.3502$ ,  $a = 1$ ,  $b = 1$ ,  $c = 3$ ,  $d = 1$ ,  $e = 2$  and  $f = 2$ . Fixed points are the same as in Fig. 4.

Another strategy could be to promote normal cell expansion (augment  $d$ ) by the use of growth factors that stimulate normal but not tumour cells.

For the sake of simplicity we restricted our analysis to nonnegative values of parameters, although the tumour–host interaction may stimulate or inhibit the tumour growth, so parameter  $c$  can be positive or negative. In the case  $c < 0$ , the fixed point  $P_2$  is a saddle and only regimens II and IV can exist.

### 3. Radiotherapy

The effects of radiotherapy can be included by modifying Eqs. (1) and (2). Radiotherapy kills cells from both populations and as a consequence reduces their growth rates. The fraction of a population killed by a dose  $D$  of radiation can be modeled by the linear quadratic model [14]. If the time of exposure to radiation is very short, compared to the period  $T$  between sessions, the radiotherapy dose can be modelled in the time domain by the Dirac delta function.

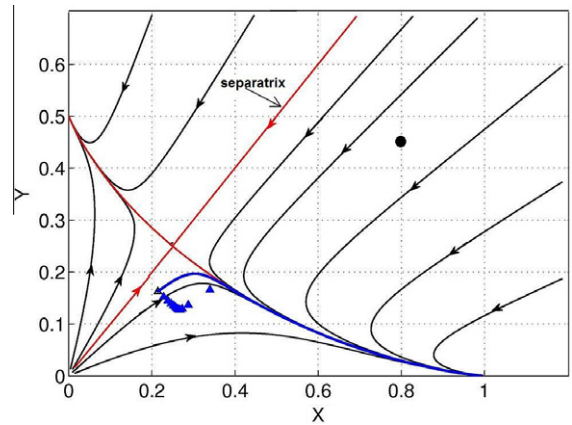
The evolution of the population under radiotherapy is expressed by the equations:

$$\frac{dx}{dt} = ax - bx^2 - cxy - x \sum_j (\alpha_x D + \beta_x D^2) \delta(t - jT) \quad (13)$$

$$\frac{dy}{dt} = dy - ey^2 - fxy - y \sum_j (\alpha_y D + \beta_y D^2) \delta(t - jT) \quad (14)$$

where  $\alpha$  and  $\beta$  are parameters that depend on the characteristics of the cells,  $D$  is the dose applied,  $T$  is the period between doses and  $\delta(t)$  is the Dirac delta function.

The simulation was carried out with the parameters of regimen III. In Fig. 6, a system that initially has a fatal prognosis (black spot) is shown. The dose and period were incorrect (the triangles show the evolution). The same situation is seen in Fig. 7, except that the period was diminished: the evolution was again fatal because the number of therapy sessions was not enough to cross the separatrix. In this case, when radiotherapy was interrupted the

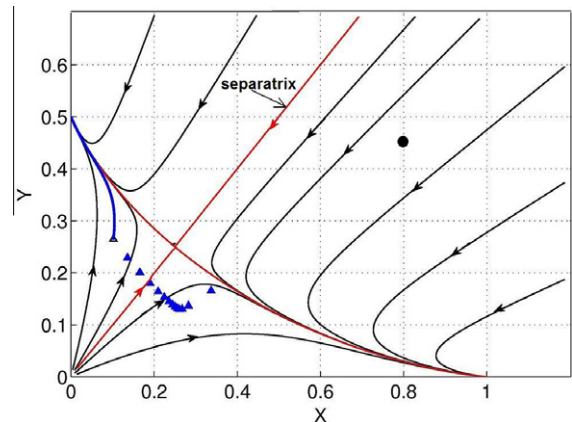


**Fig. 7.** Incorrect schedule of radiotherapy due to insufficient sessions:  $(n = 14)D = 2$ ,  $T = 1.3501$ ,  $a = 1$ ,  $b = 1$ ,  $c = 3$ ,  $d = 1$ ,  $e = 2$  and  $f = 2$ . Fixed points are the same as in Fig. 4.

tumour was regenerated and the result could be worse. Finally, with a larger number of sessions with of same dose and period, it was possible to cross the separatrix and achieve a total regression of the tumour Fig. 8.

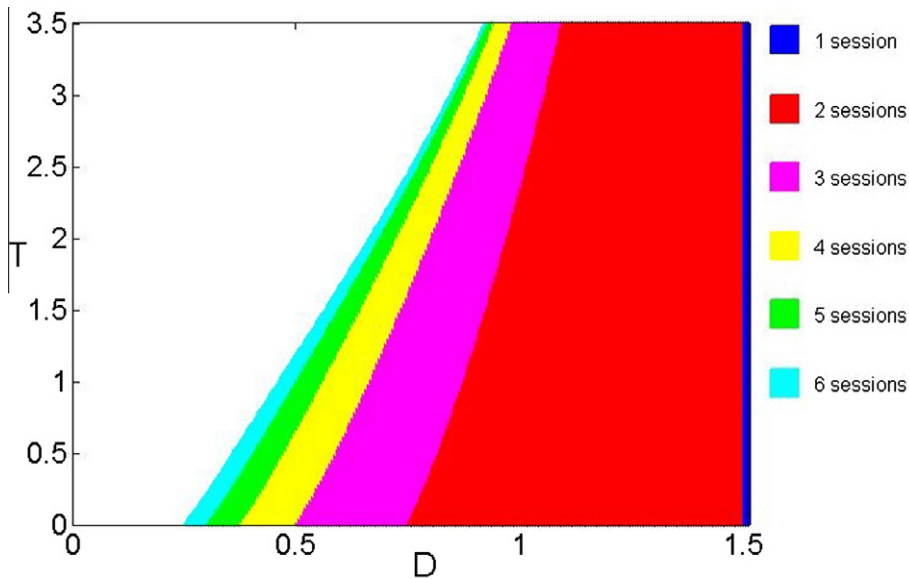
The simulation results demonstrate the need to know the initial state of the patient accurately. It is thus essential to check the state of patients before each radiotherapy session. A control theory based on measurement of the state of the system and on the control of parameters  $D$  and  $T$  has to be developed.

Fig. 9 shows the  $D - T$  parameter space built for certain initial conditions. Different tones were used to indicate the number of sessions necessary to cross the separatrix for each combination of  $D$  and  $T$ . It can be seen that there exists a minimum doses for which only one session is necessary to induce a complete cure. For smaller values  $D$  of more sessions are necessary. As  $T$  is increased, the number of sessions slowly rises. So, here we can opt for two different strategies: either to use a large single dose or several small doses with a maximum frequency  $1/T$ . The first has



**Fig. 8.** Correct schedule of radiotherapy. Parameters are the same as in the previous figure but more radiation sessions are applied. After the therapy is interrupted, the system evolved to the fixed point  $(0, d/e) = (0, 0.5)$ , i.e., the malignant population disappears completely.





**Fig. 9.**  $D$  vs  $T$  for the initial conditions  $x(0) = 0.6$  and  $y(0) = 0.4$ . For smaller values of  $D$  more sessions are necessary. As  $T$  is increased, the number of sessions slowly rises. The parameters used are:  $a = 1, b = 1, c = 3, d = 1, e = 2, f = 2, \alpha_x = 0.33, \beta_x = 0.02, \alpha_y = 0.06$  and  $\beta_y = 0.02$ .

the risk of a possible overdose which could be lethal. The second is more secure and parameters can be chosen to minimize the damage to health tissues. This kind of schedule has long been used in clinical practice and is known as dose fractionation [15–22].

The evolution of the system under radiotherapy can be represented by rather simple discrete relations. To a first approximation, the solution of the LV equation system can be found by the method of successive approximations. We convert Eqs. (1) and (2) to the integral equations

$$x(t) = x(0) + \int_0^t (ax - bx^2 - cxy) d\tau$$

$$y(t) = y(0) + \int_0^t (dy - ey^2 - fxy) d\tau$$

Successive approximate solutions can be found by the recurrent relations:

$$x_{n+1}(t) = x(0) + \int_0^t (ax_n - bx_n^2 - cx_n y_n) d\tau \tag{15}$$

$$y_{n+1}(t) = y(0) + \int_0^t (dy_n - ey_n^2 - fx_n y_n) d\tau \tag{16}$$

Consider the zero order approximation

$$x_0(t) = x(0)e^{at} \tag{17}$$

$$y_0(t) = y(0)e^{dt} \tag{18}$$

which are the solution of the linear system  $\frac{dx}{dt} = ax$  and  $\frac{dy}{dt} = dy$ . Substituting the zero order solution (17) and (18) in Eqs. (15) and (16), we obtain

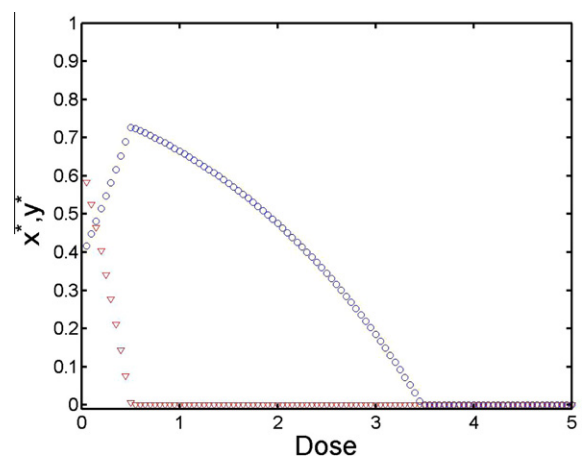
$$x(t) = \frac{bx(0)^2}{2a} + \frac{cx(0)y(0)}{a+d} + x(0)e^{at} - \frac{bx(0)^2}{2a}e^{2at} - \frac{cx(0)y(0)}{a+d}e^{(a+b)t}$$

$$y(t) = \frac{ey(0)^2}{2d} + \frac{fx(0)y(0)}{a+d} + y(0)e^{dt} - \frac{ey(0)^2}{2d}e^{2dt} - \frac{fx(0)y(0)}{a+d}e^{(a+d)t}$$

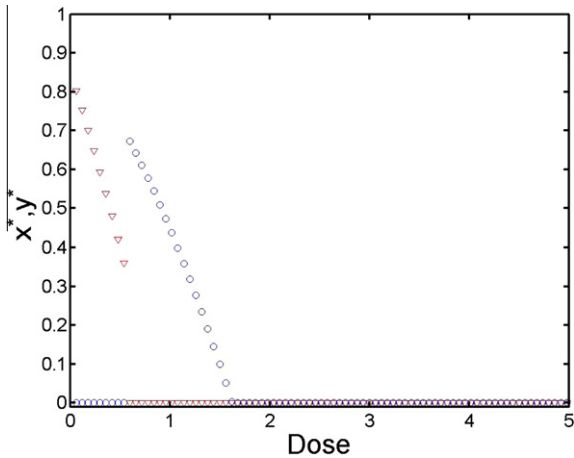
Following a dose  $D$  at  $t = T$ , we have

$$x(T) = S_x \left[ \frac{bx(0)^2}{2a} + \frac{cx(0)y(0)}{a+d} + x(0)e^{aT} - \frac{bx(0)^2}{2a}e^{2aT} - \frac{cx(0)y(0)}{a+d}e^{(a+b)T} \right]$$

$$y(T) = S_y \left[ \frac{ey(0)^2}{2d} + \frac{fx(0)y(0)}{a+d} + y(0)e^{dT} - \frac{ey(0)^2}{2d}e^{2dT} - \frac{fx(0)y(0)}{a+d}e^{(a+d)T} \right]$$



**Fig. 10.** Evolution of 20,000 initial values of  $x^*$  and  $y^*$  selected at random in the unitary square ( $0 \leq x^* \leq 1, 0 \leq y^* \leq 1$ ), for regimen II. The circles and triangles represent the values of  $y^*$  and  $x^*$ , respectively. Each initial value is iterated 10,000 but only last 1000 are shown. The parameters used are:  $a = 2, b = 1, c = 1, d = 3, e = 3, f = 1, T = 0.01, \alpha_x = 0.33, \beta_x = 0.02, \alpha_y = 0.06$  and  $\beta_y = 0.02$ .



**Fig. 11.** Evolution of 20,000 initial values of  $x^*$  and  $y^*$  selected at random in the unitary square, for regimen IV. The circles and triangles represent the values of  $y^*$  and  $x^*$ , respectively. Each initial value is iterated 10,000 but only last 1000 are shown. The parameters used are:  $a = 2, b = 1, c = 1, d = 1, e = 1, f = 1$ ; other parameters are the same as in previous figure.

where  $S_x = e^{-(\alpha_x D + \beta_x D^2)}$  and  $S_y = e^{-(\alpha_y D + \beta_y D^2)}$  are the fraction of cells that survive the radiation. Putting  $x_n, y_n, x_{n+1}$  and  $y_{n+1}$  in place of  $x(0), y(0), x(T)$  and  $y(T)$ , we have

$$x_{n+1} = Ax_n^2 + Bx_n y_n + Cx_n \tag{19}$$

$$y_{n+1} = Ey_n^2 + Fx_n y_n + Gy_n \tag{20}$$

where  $A = S_x \frac{b}{2a} (1 - e^{2aT}), B = S_x \frac{c}{a+d} (1 - e^{(a+d)T}), C = S_x e^{aT}, E = S_y \frac{e}{2d} (1 - e^{2dT}), F = S_y \frac{f}{a+d} (1 - e^{(a+d)T})$  and  $G = S_y e^{dT}$ . Map (19) and (20) are a generalization of the logistic map.

The map given by Eqs. (19) and (20) works as a good approximation to (13) and (14) for sufficiently small values of  $T$ . The behaviour of this map can vary from very simple motion to chaos [23]. The map has the advantage over the differential equations that it allows the evolution of thousands of initial conditions to be investigated numerically by varying the set of parameters of the system. One intriguing question is whether a complete cure is possible in regimen II and IV, using radiotherapy. In these regimens, when therapy is stopped the tumour is regenerated. Thus the question is: is it possible to eliminate the whole malignant population before the organism is destroyed?

Numerical experiments with the map show that it is possible, for low doses and an increased number of sessions. In the simulation, we chose a small fixed period,  $T = 0.01$ , and the doses were varied. The results are shown in Fig. 10, for regimen II. We have assumed that the maximum values of normal and malignant populations are  $y_0 = d/e$   $x_0 = a/b$ , respectively, and in the diagram we used the normalized variables  $x^* \equiv xb/a$  and  $y^* \equiv ye/d$ . For each dose value 20,000 initial conditions were chosen at random in the unitary square ( $0 \geq x^* \geq 1, 0 \geq y^* \geq 1$ ) with a uniform distribution. For each initial condition, the maps were iterated 10,000 times, only the last 1000 iterations being shown in the diagram in Fig. 10. In this diagram, we can see an interval of doses for which it is possible to eliminate the malignant population; of course, we have assumed that the survival fraction of the normal

population is greater than that of the malignant population:  $S_y > S_x$ .

There are differences between the two populations, such as their rate of multiplication and the capacity for self-repair of damaged cells. Hence, survival fraction will differ between populations. Survival fractions are given by the linear quadratic model  $S = e^{-(\alpha D + \beta D^2)}$  [14] where the parameters  $\alpha$  and  $\beta$  are associated with direct lethal lesions produced by radiation in cells (specifically in DNA) and the fatal misrepair of such damage (indirect effect) [24]. The multiplication rate of malignant cell is in general higher than normal cells so we can expect that effect of misrepair of radiation damage is enhanced in malignant cells, thus  $S_y > S_x$ .

Fig. 11 shows a similar simulation for regimen IV. We can see that there exists an interval of doses in which it is possible to kill all malignant cells, while outside this interval the evolution of the system is fatal for the host. It is curious that there is an abrupt change of behaviour in both populations, around  $D = 0.6$ , which resembles a phase transition.

#### 4. Conclusions

Several mathematical models developed in cancer research have been used to design new treatments. In this contribution tumour–host interactions are modelled by LV equations. By using the qualitative theory of differential equations and introducing into the model the action of radiation, we reach conclusions as a result of the simulations with implications for the design of treatments. These results draw attention to the control of some parameters that are sometimes ignored, leading to a fatal outcome.

The LV model shows how the nonlinear interactions between the host and the tumour are able to generate a number of different kinds of response that can be observed clinically. The LV model describes the growth dynamics of the tumour and all the stages of development. One distinctive feature, with respect to many other models, is that in all regimens growth is limited [11].

One important result derived from the LV model is that in certain regimes allow self-cure by appropriate radiation schedules. We can also appreciate that in some cases, it would be advisable to use other strategies, such as stimulation of the immune system or a combination of radiotherapy and chemotherapy, depending on the specific characteristics of the system.

Cancer is not merely the disorganized growth of a population that has suffered some genetic transformation; rather it is a complex network of interactions established between the original population and the transformed one. Therefore, in the design of new treatments it is necessary to take the complexity of this phenomenon into account. Radiotherapy simulation may lead to the development of a more effective and efficient schedule, if it is combined with dynamical system control theory and the monitoring of microscopic and macroscopic variables by means of techniques such as X-ray radiography, nuclear magnetic resonance, lymphograms and leukograms. Summing up, the use of tumour evolution data before and during the treatment and computer simulation could help to improve the final outcome.

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