Repopulation: is it inevitably?

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Abstract

A mathematical model of radiotherapy is proposed. The study used the classical 24 hours way of fractionation with a weekend pause. We introduce the matrices of “radiotherapy” and “growth”. We developed an equation of the fraction cell evolution, which we solved numerically. The results indicate that the accelerated growth of cells occurs due to the decrease of the fraction of slowly growing cells and increase of the cells that are fast growing.

Repopulation is a serious problem in cancer radiotherapy. The growth of tumor in final stage of radiation can prevent the healing of a patient. Many studies have shown the importance of timing in radiotherapy \cite{2}. If there is a delay in the treatment caused e.g. by interrupts in radiation then this the increases time given to cells for accelerated growth. It was shown that breaks in radiation especially after fourth weeks of treatment lead to the worse results, approximately 2–4.8 percent growth per day of delay.

Why such a strange phenomenon occurs? Tumor fights for its live and it behaves according to the Lenz rule: the lower number of cells the faster the growth. According to Trott \cite{3} accelerated repopulation occurs when the number of cells in tumor decreases below 1000 cells. It can be explained in a few different ways.

Referring to a recent study there \cite{4} are three theories for explaining reasons for repopulations:

1. Fowler model, in which the author claims that cancer volume doubling time $T_d$ approaches potential time $T_{pot}$ as a result of loosing cells.

2. Jones Model which proposes the following explanation: the tumor possesses sub-populations of cells growing with different velocities (speeds); cells are dying equally but those dividing faster gain advantage during breaks in radiation.

3. Trott–Kummermehr model which can be called Dragon Theory. Like a medieval knight cutting dragon’s head have met next two new heads, here stem cells switch from asymmetrical division to symmetrical one. At each division from one stem cell two are arising.
1 Assumptions

We assume as a basis the Jones model. Cancer tumor is heterogenic; it means that there exists fractions of cells that differ in terms of access to oxygen or nutrition or number of mutations. We assume there are three fractions of cells in the tumor, which we will denote:

- \( x_0 \) – small number of mutations and low growth velocity
- \( x_1 \) – intermediate number of mutations and medium growth velocity
- \( x_2 \) – large number of mutations and fastest growth velocity

where these variables are normalized by

\[
\sum_{i=0}^{2} x_i = 1
\]

In individual fractions there is a well determined number of cell, where 
\( y_i \) number of cells belonging to the \( i \)-th fraction

\[
\sum_{i=1}^{3} y_i = N
\]

and where \( N \) is a total number of cells.

One of mutation factors is the radiation itself [1]. There is no reason to prevent such a phenomenon during radiation. Subsequently to the radiation of tumor after each consecutive dose, the number of cells in tumor will decrease and cells in each individual fraction will undergo mutations. Below is a new model of decreasing of number of cells in each fraction.

Fraction \( x_i^0 \) can be expressed by

\[
x_i^0 = \frac{y_i^0}{N}
\] (1)

Growth of tumor is a result of growth of individual fractions of tumor cells. Each fraction \( x_0^0, x_1^0, x_2^0 \) grows with its own velocity \( v_0, v_1, v_2 \). Time of duplication of tumor \( T_{d,i} \) determines the velocity according to:

\[
v_i = \frac{\ln(2)}{T_{d,i}}
\] (2)

where \( T_{d,i} \) is volume doubling time for individual fraction tumor. There is besides velocity the influence on the tumor growth, on the number of cells in the particular fractions of the tumor. Average velocity of the tumor growth can be described by means of the formula:

\[
\Phi = \sum_{i=0}^{2} v_i x_i
\] (3)
2 Matrix of radiation

The decrease of the tumor volume, i.e. waste of stem cells is described by the linear–quadratic formula:

\[ N = N_0 e^{-\alpha d - \beta d^2} \]  

where \( N \) is the number of survive cells that radiotherapy, and \( N_0 \) is the initial number of cells. Another form of this formula is following:

\[ S = e^{-\alpha d - \beta d^2} \]  

where \( S \) is fraction of surviving cells, \( \alpha, \beta \) are coefficients, \( d \) is a radiation dose. Accordingly

\[ S = N/N_0 \]  

or

\[ S = \sum_i x_i^1 \quad 1 = \sum_i x_i^0 \]  

Here \( x_i^0 \) are initial fractions before radiotherapy and \( x_i^1 \) after first dose of radiation.

\[ \sum_i x_i^1 = \sum_i x_i^0 e^{-\alpha d - \beta d^2} \]  

When move from fractions to the number of cells then the equations take the form:

\[ \begin{align*}
    y_0^1 &= y_0^0 (e^{-(\alpha d + \beta d^2)}) \\
    y_1^1 &= y_1^0 e^{-(\alpha d + \beta d^2)} \\
    y_2^1 &= y_2^0 e^{-(\alpha d + \beta d^2)}
\end{align*} \]  

In matrix notation we have:

\[ \begin{pmatrix} y_0^1 \\ y_1^1 \\ y_2^1 \end{pmatrix} = \begin{pmatrix} e^{-\alpha d - \beta d^2} & 0 & 0 \\ 0 & e^{-\alpha d - \beta d^2} & 0 \\ 0 & 0 & e^{-\alpha d - \beta d^2} \end{pmatrix} \begin{pmatrix} y_0^0 \\ y_1^0 \\ y_2^0 \end{pmatrix} \]  

The matrix is diagonal and it shows that each fraction decreases according to the linear-quadratic formula and there is no exchange of cells between individual fractions.

This description suggests that all cells behave the same way and are equally sensitive to the absorbed dose gained by the tumor. Investigations show that cancer tumor does not possess uniform cells the individual cells differ in access to the oxygen or nutritious means. One of mutation factors is the ion radiation. During radiation surviving cells inherit improved conditions of oxygenations and nutrition and are undergoing rapid mutation. All these changes lead both to the decrease in the number of cells in individual fractions and also to the change of the proportions of individual fractions. We introduce coefficients \( Q \) and \( P \) to describe the probability that the cells from fractions \( x_0^0, x_1^0 \) will shift to fraction \( x_0^1 \) and \( x_2^0 \) respectively.
Equation describing this process have the following form:

\[
y_0^1 = y_0^0(e^{-\alpha d - \beta d^2} - Q)
\]

\[
y_1^1 = y_1^0(e^{-\alpha d - \beta d^2} - P) + Qy_0^0
\]

\[
y_2^1 = y_2^0e^{-\alpha d - \beta d^2} + Py_1^0
\]

Situation after \(n\) steps is described by the following equations:

\[
y_0^{(n)} = \left(e^{-(\alpha d + \beta d^2)} - Q\right)y_0^{(n-1)}
\]

\[
y_1^{(n)} = Qy_0^{(n-1)} + \left(e^{-(\alpha d + \beta d^2)} - P\right)y_1^{(n-1)}
\]

\[
y_2^{(n)} = P(y_1^{(n-1)} + y_2^{(n-1)}e^{-(\alpha d + \beta d^2)})
\]

or in matrix notation:

\[
\begin{pmatrix}
y_0^{(n)} \\
y_1^{(n)} \\
y_2^{(n)}
\end{pmatrix} =
\begin{pmatrix}
e^{-\alpha d - \beta d^2} - Q & 0 & 0 \\
Q & e^{-\alpha d - \beta d^2} - P & 0 \\
0 & P & e^{-\alpha d - \beta d^2}
\end{pmatrix}^n
\begin{pmatrix}
y_0^{(0)} \\
y_1^{(0)} \\
y_2^{(0)}
\end{pmatrix}
\]

We will call the matrix appearing above a radiation matrix and we will denote it \(\mathcal{R}\):

\[
\mathcal{R} = \begin{pmatrix}
e^{-\alpha d - \beta d^2} - Q & 0 & 0 \\
Q & e^{-\alpha d - \beta d^2} - P & 0 \\
0 & P & e^{-\alpha d - \beta d^2}
\end{pmatrix}
\]

It can be shown by induction that for each \(n\) after summing up rows we obtain following equations:

\[
N = N_0 e^{-n(\alpha d + \beta d^2)}
\]

It means that the matrix \(\mathcal{R}\) describes the diminishment of tumor cells after radiation according to the linear quadratic form. Additionally it shows how individual fractions change in time during radiation. Coefficients \(Q\) and \(P\) allows exchange of cells between individual fractions.

Inserting here values for \(\alpha, \beta, P, Q\) the number of cells \(N\) and values of fractions \(x_0, x_1\) we can calculate the rate of decrease of the number of cells in each fraction. From computer simulations it follows that the vector \((x_1, x_2, x_3)\) tends to the equilibrium state \((0, 0, x_2)\). From this we conclude, that radiation of the tumor leads to the selection of cells which are the most mutated and which grow with the largest speed. In the limit of large \(n\) this equation has the form:

\[
\Phi = v_2d_2^{(n)}
\]

It means that speed of tumor growth is larger when the tumor diminishes, and this effect cannot be avoided.
3 The growth matrix

We describe the rate of tumor growth according to the Sole [5]. We make use of the results of the paper [5] in which it was shown that the equations for growth of the cell fractions can be written as:

\[
\begin{align*}
\frac{dx_0}{dt} &= v_0 x_0 (1 - Q') - x_0 \Phi(x_0, x_1, x_2) \\
\frac{dx_1}{dt} &= v_1 x_1 (1 - P') + v_0 x_0 Q' - x_1 \Phi(x_0, x_1, x_2) \\
\frac{dx_2}{dt} &= v_2 x_2 + v_1 x_1 P' - x_2 \Phi(x_0, x_1, x_2)
\end{align*}
\]

or in the matrix notation:

\[
\dot{x} = \mathcal{M} x
\]

(24)

where \( \dot{x} \) is the time derivative of the \( x = (x_1, x_2, x_3)^T \), 1 is the identity matrix and mixing matrix \( \mathcal{M} \) is given by

\[
\mathcal{M} = \begin{pmatrix}
    f_0(1 - Q') - \Phi(x_0, x_1, x_2) & 0 & 0 \\
    f_0 Q' & f_1(1 - P') - \Phi(x_0, x_1, x_2) & 0 \\
    0 & f_1 P' & f_2 - \Phi(x_0, x_1, x_2)
\end{pmatrix}
\]

(25)

and we denote this matrix \( \mathcal{M} \) as the growth matrix. Equations of Sole describe how ratios of fractions are changing during radiotherapy. However growth of the cell number in each fraction which occurs during the pauses in radiotherapy we obtain through the following procedure: The result of the Sole equation expressed in fractions \( x \) we convert to the integer valued number of cells \( y \) (see below). Obtained number of cells we multiply by factor \( e^{\ln(2) \cdot v_i} = 2^{v_i} \) and next we pass from the number of cells back to fractions:

\[
\begin{pmatrix}
y_0' \\
y_1' \\
y_2'
\end{pmatrix} = \begin{pmatrix}
2^{v_0} & 0 & 0 \\
0 & 2^{v_1} & 0 \\
0 & 0 & 2^{v_2}
\end{pmatrix} \begin{pmatrix}
y_0 \\
y_1 \\
y_2
\end{pmatrix}
\]

(26)

Here \( y_i' \) is the number of cells after division during pause between consecutive pulses of radiotherapy. Let

\[
\mathcal{D} = \begin{pmatrix}
    2^{v_0} & 0 & 0 \\
    0 & 2^{v_1} & 0 \\
    0 & 0 & 2^{v_2}
\end{pmatrix}
\]

(27)

denote the division matrix. The growth matrix we construct from mixing and division in the following way:

\[
\mathcal{G}(y_i, x_i) = \mathcal{D}(y_i) \mathcal{M}(x_i)
\]

(28)

We introduce the dependence of \( v_2 \) on \( v_1 \):

\[
v_2 = a v_1 \psi(\theta, Q, P, Q', P', d, n).
\]

(29)
where
\[
\psi(\theta, Q, P, Q', P', d, n) = e^{\Theta - n(\sqrt{Q^2 + P^2 d + \sqrt{Q'^2 + P'^2 d^2}})}
\] (30)

This form is for radiation period, during weekend the form is different:
\[
\psi(\theta, Q', P', d, n) = e^{\Theta - n(\sqrt{Q'^2 + P'^2}})
\] (31)

It contains a threshold after crossing this threshold velocity \( v_2 \) decreases, in accordance velocity \( \Phi \) also diminishes. In the paper by Sole at al [5] it is shown for which parameters \( Q', P', M' \) the fraction \( x_2 \) exists.

4 The radiation

The act of radiation consists of:

a. time of radiation — pulse radiation
b. time between consecutive exposures

These equations describe growth of tumor from the moment of ending of radiation till the next exposures. In classical fraction this time is 24 hours. The radiation lasts for a very short period of time: a few minutes, in comparison to 24 hour waiting period between consecutive fractions. Exposition after Wheldon [6] we can call pulse radiotherapy. In the remaining time, tumor cells repair damage from radiotherapy and they divide. The tumor growth appears.

In classical radiotherapy we radiate once a day during the 4-7 weeks, depending on the radiation dose quantity. Duration of radiation is very short (a few minutes), remaining time is spent on the repair of post-radiation damage. Symbolically we can demonstrate this in the following form:

\[
(growth\ radiation)^5\ growth^2\ ...growth^2(growth\ radiation)^5|\ N_0 >=
\]
\[
((growth\ radiation)^5)(growth^2(growth\ radiation)^5)^{n-1}|\ N_0 >
\]

where \( n \) is the number of weeks of radiotherapy and \( N_0 \) is initial number of tumor cells, i.e. \( |N_0 > = \ initial\ number\ of\ tumor\ cells \ > \)

Radiation is represented by the matrix:
\[
\mathcal{R} = \begin{pmatrix}
 e^{-\alpha d - \beta d^2} - Q & 0 & 0 \\
 Q & e^{-\alpha d - \beta d^2} - P & 0 \\
 0 & P & e^{-\alpha d - \beta d^2}
\end{pmatrix}
\] (32)

and
\[
\mathcal{M} = \begin{pmatrix}
 f_0(1 - Q') - \Phi(x_0, x_1, x_2) & 0 & 0 \\
 f_0Q' & f_1(1 - P') - \Phi(x_0, x_1, x_2) & 0 \\
 0 & f_1P' & f_2 - \Phi(x_0, x_1, x_2)
\end{pmatrix}.
\] (33)
The radiation process can be described by the following equation:

\[ y^{(n+1)} = R y^n \]  

This equation describes the diminishing of the number of cells in fractions after a pulse of radiation. Next we can write the equation which describe the rise of tumor until next exposition. First we describe the change in proportion in fractions in tumor cells. To this aim we change the variable from \( y \) to \( x \). We assume that the proportion of \( y(t + \text{next day})/y(t) \) is the same as normalized variables:

\[ \frac{y(t + \text{next day})}{y(t)} = \frac{x(t + \text{next day})}{x(t)} \]  

The Sole equations describe change of proportion during growth of tumor between expositions:

\[ \frac{dx^{n+1}}{dt} = M x^n \]  

Differential equations were solved on the interval of one working day and on the interval of three days during weekend. We change solutions of this equation again into the number of cells. Then we calculate how many new cells arise during the pause between radiations. We again pass from \( x \) back to \( y \) as before and we use following equation:

\[ \overline{y}^{n+1} = V \overline{y}^{n+1} \]  

We repeat this procedure during prescribed cure time expressed in weeks.

5 Results

We performed numerical calculations for two different sets of parameters: in the first case the probability coefficients of \( Q, P, Q', P' \) were zero, in the second they were different from zero and were \( Q = 0.0005, P = 0.0005, Q' = 0.1, P' = 0.1 \). We took the parameters \( \alpha = 0.2, \beta = 0.02, d = 2Gy, n = 30, v_0 = 0.01, v_1 = 0.016 \). \( v_2 \) was calculated from the formula ?? for \( m = 5 \) and threshold \( \theta = 0.005 \). At \( Q, P, Q', P' \) equal zero velocity of growth rising of tumor was initially slower, and next faster. The conclusion is simply: the fact of existence of the population of cells of with different growth rates is sufficient for the tumor to grow faster as the corollary of the radiation and intervals between the fraction radiotherapy. At this point the faster growing cells are gaining the population dominance over the slower growing cells and finally lead to the accelerated growth tumor. After introduction the \( P, Q, Q', P' \) different from zero the velocity of the tumor growth was also larger. According to this model probabilities \( Q, P, Q', P' \) are responsible for the velocity change via the change of the cell population \( x \) from \( x_0 \) and \( x_1 \) to \( x_2 \). Fraction \( x_2 \) is the fastest growing. Biologically it can be explained that fraction \( x_2 \) gains the best condition for growth due to the improvement of oxygenation and better nutrition. Additionally fraction \( x_2 \) is built from the most undifferentiated cells and most mutated
cells. The factor that causes the decrease fractions $x_0$ and $x_1$ and increase of the fraction $x_2$ is the radiotherapy which leads to the death of cells and simultaneously by causing the shift of mutation from $x_0$ and $x_1$ to $x_2$. In this way additional radiation influence leads to some differences between situation when the ionization energy is the cause of destroying only cells in fractions $(Q = 0, P = 0, Q' = 0, P' = 0)$ and leads to the shift of cells from one fraction to another $(Q \neq 0, P \neq 0, Q' \neq 0, P' \neq 0)$. These differences can be seen after subtraction of two graph, see Figs. 1 and 2. In this way we can see how the change of the oxygenation, better nutrition and mutation influence growth velocity. According to the assumption about the existence of the threshold $\Theta$ the influence of the coefficients $(Q \neq 0, P \neq 0, Q' \neq 0, P' \neq 0)$ is as following: In the first stage we see that they accelerate tumor growth and next they cause the slowing down of the tumor growth. On this example we see a new mechanism leading to the death of the tumor. Namely the existence of the $\Theta$ threshold, Namely the existence of the theta threshold, causes that growth mutation not only shifts cells to faster growing fraction but also crossing sufficient threshold causes slower growth of tumor.

6 Conclusions

Our model explains accelerated growth tumor according to Jones model. The existence of cells fraction of different growth velocity is the cause of the accelerated growth tumor. During the radiation therapy because of the interrupts, cells have time to take advantage of the differences in the velocities of growth and increase the number of cells in fastest growing fraction. In the course of radiation the living conditions of cells are changing: the oxygenation and nutrition is better and additionally mutations appear. Together these factors causes the change of the number of cells in the particular fractions. We have described these changes by the coefficients $P$ and $Q$ responsible for the changes during the radiation pulse and coefficients $Q', P'$ responsible for the changes occurring between different fractions. These coefficients are modifying the tumor growth: in the beginning they accelerate and after crossing the threshold $\Theta$ they slow down. The existence of the threshold $\Theta$ could explain the benefits from the simultaneous radiochemotherapy. Chemotherapy has the mutagen function. This mechanism in conjunction with radiotherapy facilitates the crossing of the threshold $\Theta$ after which the tumor growth is slowing down. From the model it follows that natural state of the tumor is the state described by the vector $(0, 0, 1)$, it means that it tends to the fastest fraction. The fastest and least differentiated fraction gains the crucial dominance. It seems to be in accordance with the clinical experience that often the revival of the tumor is more malicious and less differentiated.

Model that we introduced is the enlargement of the linear–quadratic model. When we take into account only total number of cells it describes the diminishing of the cells tumor exactly the same way as the linear–quadratic model. However it allows to see how the numbers of cells in each fractions change during the radiation and which influence on the velocity of the tumor growth is the appearance of the threshold $\Theta$ mutation.
It is possible to apply our model to arbitrary doses, time of radiation and breaks in radiations time.

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| day | fraction 1 | fraction 2 | fraction 3 | velocity |
|-----|------------|------------|------------|----------|
| 1   | 371270035  | 210386353  | 37127004   | 0.000000000 |
| 1   | 371476229  | 212652573  | 41821898   | 0.016515136 |
| 2   | 229863321  | 131585880  | 25878696   | 0.016515136 |
| 2   | 229878511  | 132938244  | 29136931   | 0.017018336 |
| 3   | 142177843  | 83060670   | 20288506   | 0.017571932 |
| 4   | 87977288   | 51396563   | 12554190   | 0.017571932 |
| 4   | 87883740   | 51866147   | 14118852   | 0.018180004 |
| 5   | 54380999   | 32093910   | 8736511    | 0.018180004 |
| 5   | 54287929   | 32366123   | 9818991    | 0.018846713 |
| 6   | 53706425   | 32541035   | 11729058   | 0.019269721 |
| 7   | 52692848   | 32602887   | 14884639   | 0.019715495 |
| 8   | 32566127   | 20174125   | 9210367    | 0.022962204 |
| 8   | 32380128   | 20263716   | 10310082   | 0.022962204 |
| 9   | 20036285   | 12538511   | 6379707    | 0.022962204 |
| 9   | 19900781   | 12581216   | 7133890    | 0.024044202 |
| 10  | 12314273   | 7785047    | 4414332    | 0.024044202 |
| 10  | 12217058   | 7802451    | 4930553    | 0.025208646 |
| 11  | 7559712    | 4828027    | 3059444    | 0.025208646 |
| 11  | 7490861    | 4832904    | 3403560    | 0.026457045 |
| 12  | 4635221    | 2990521    | 2106067    | 0.026457045 |
| 12  | 4587001    | 2989628    | 2346407    | 0.027789957 |
| 13  | 4457412    | 2952492    | 2753154    | 0.028616727 |
| 14  | 4249783    | 2878036    | 3399291    | 0.029472506 |
| 15  | 2629695    | 1780881    | 2103425    | 0.029472506 |
| 15  | 2583253    | 1767292    | 2326276    | 0.035259776 |
| 16  | 1598474    | 1093571    | 1439461    | 0.035259776 |
| 16  | 1567496    | 1083298    | 1588182    | 0.037028960 |
| 17  | 969941     | 670345     | 983359     | 0.037028960 |
| 17  | 949425     | 662867     | 1083679    | 0.038852571 |
| 18  | 587489     | 410171     | 670562     | 0.038852571 |
| 18  | 573996     | 404843     | 737601     | 0.040720840 |
| 19  | 355179     | 250510     | 456415     | 0.040720840 |
| 19  | 346366     | 246788     | 501095     | 0.042622914 |
| 20  | 326744     | 236600     | 570777     | 0.043757469 |
| 21  | 297833     | 220498     | 673761     | 0.044897230 |
| 22  | 184294     | 136440     | 416912     | 0.044897230 |
| 22  | 178080     | 133186     | 453545     | 0.051789508 |
| 23  | 110193     | 82413      | 280646     | 0.051789508 |
| 23  | 106278     | 80297      | 304735     | 0.053649548 |
| day | fraction 1 | fraction 2 | fraction 3 | velocity  |
|-----|-----------|-----------|-----------|----------|
| 24  | 65763     | 49686     | 188565    | 0.053649548 |
| 24  | 63311     | 48322     | 204376    | 0.055462791 |
| 25  | 39176     | 29901     | 126465    | 0.055462791 |
| 25  | 37648     | 29028     | 136826    | 0.057219673 |
| 26  | 23296     | 17962     | 84665     | 0.057219673 |
| 26  | 22349     | 17408     | 91445     | 0.058911922 |
| 27  | 20408     | 16155     | 100824    | 0.059878183 |
| 28  | 17720     | 14341     | 113371    | 0.060818297 |
| 29  | 10965     | 8874      | 70152     | 0.060818297 |
| 29  | 10444     | 8539      | 75231     | 0.065925766 |
| 30  | 6463      | 5284      | 46552     | 0.065925766 |
| 30  | 6148      | 5078      | 49860     | 0.067155054 |
| 31  | 3805      | 3142      | 30853     | 0.067155054 |
| 31  | 3615      | 3017      | 33006     | 0.068300215 |
| 32  | 2237      | 1867      | 20424     | 0.068300215 |
| 32  | 2123      | 1790      | 21826     | 0.069362910 |
| 33  | 1314      | 1108      | 13506     | 0.069362910 |
| 33  | 1246      | 1061      | 14418     | 0.070345563 |
| 34  | 1112      | 962       | 15538     | 0.070889546 |
| 35  | 934       | 826       | 16893     | 0.071407364 |
| 36  | 578       | 511       | 10453     | 0.071407364 |
| 36  | 546       | 488       | 11117     | 0.074038283 |
| 37  | 338       | 302       | 6879      | 0.074038283 |
| 37  | 319       | 288       | 7312      | 0.074629103 |
| 38  | 197       | 178       | 4524      | 0.074629103 |
| 38  | 186       | 170       | 4806      | 0.075165861 |
| 39  | 115       | 105       | 2974      | 0.075165861 |
| 39  | 109       | 100       | 3158      | 0.075652632 |
| 40  | 67        | 62        | 1954      | 0.075652632 |
| 40  | 63        | 59        | 2074      | 0.076093354 |
| 41  | 56        | 53        | 2209      | 0.076335559 |
| 42  | 46        | 45        | 2362      | 0.076597666 |
| 43  | 29        | 28        | 1461      | 0.076597666 |
| 43  | 27        | 26        | 1548      | 0.07673641 |
| 44  | 17        | 16        | 958       | 0.077673641 |
| 44  | 16        | 15        | 1015      | 0.077915957 |
| 45  | 10        | 10        | 628       | 0.077915957 |
| 45  | 9         | 9         | 665       | 0.078133711 |
| 46  | 6         | 6         | 412       | 0.078133711 |
| 46  | 5         | 5         | 436       | 0.078329254 |
| 47  | 3         | 3         | 270       | 0.078329254 |
| 47  | 3         | 3         | 285       | 0.078504740 |
| 48  | 3         | 3         | 303       | 0.078599769 |
Figure 1: Plot of velocity of the tumor growth as a function of time (days) of radiotherapy. Here $Q, P, Q', P'$ are zero.

Figure 2: Plot of velocity of the tumor growth as a function of time (days) of radiotherapy. Here $Q, P, Q', P'$ are different from zero.
Figure 3: Plot of velocity for zero valued parameters subtracted from velocity for parameters different from zero.