

# A probabilistic model of cancer cell survival rates given arbitrary drug combinations

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## Introduction

Cancer is responsible for the majority of non-accidental deaths in today's humanity and has caused high expenditures to health systems throughout the world. Humanity has invested enormous amounts of research time and resources in the fight against this disease. Although still in early stages, mathematical modelling has readily played an increasingly important place in this endeavour.

The present report begins by a review of the main concepts associated to cancer. A *tumour* is as a cluster of cells with abnormally accelerated reproduction within one or more organs in an organism. A tumour growing toward the exterior of such an organ is called *benign* whereas a tumour which invades the organ is called *malignant* or *cancer*.

Among the methods currently used to treat cancer one can mention surgery, radiotherapy and drug therapy. Drug therapy can exist in the form of chemotherapy or anti-angiogenesis, where the methods of action differ in that the former interferes with the natural life cycle of cells eventually favouring their death while the latter seeks to inhibit the growth of blood vessels near a tumour, hence depleting the nutrient supply while enhancing the flow of other therapy drugs.

Most cells in an organism have a well defined life cycle which will be described in Section 2. Since cancer drugs may target different stages of this cycle, it has been suggested that a combination of two or more treatment drugs or *combination therapies*. Cancer drugs in combination therapies are usually administered at the same time, although their frequency of administration may differ, but a question is raised as to whether it could more effective to administer initially the drugs at different times.

In this work, a discrete dynamical system modelling the cell cycle is introduced and a probabilistic approach to determining some of the parameters of such dynamical system is

described. These two processes are aimed at constructing and studying the dynamics of cancer cell reproduction under the administration of two drugs at variable time intervals.

In principle, this model only contemplates the case where the frequency of administration of the two drugs is the same.

## 1 A model for the dynamics of the cell cycle

The cell cycle has four basic stages. It ought to be noted that a cell is likely to die during either of these stages:

1. A *first gap* stage or  $G_1$  where a cell grows in size.
2. The *synthesis* stage or  $S$  during which DNA is replicated.
3. A *second gap* stage or  $G_2$  where the cell continues to grow.
4. The *mitosis* or  $M$  stage, in which a cell splits into two genetically identical *child* cells, which proceed back to stage  $G_1$ .

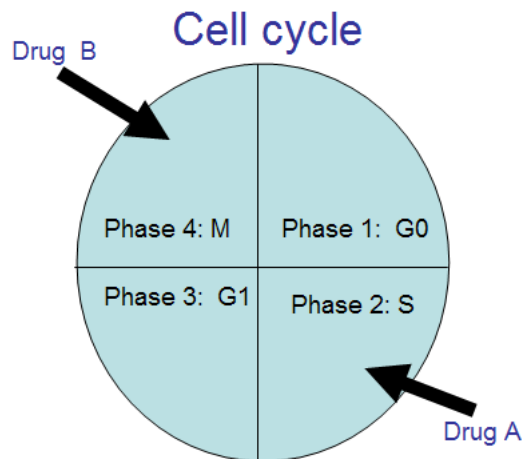


Figure 1: The cell cycle

There are many substages of these stages and this is why it is best for future research to consider this cycle as one having an arbitrary number  $M$  of stages. In the present model, at any time  $t$ , the cell cycle is considered as a series of “buckets”  $S_k$ , each one symbolising a stage of the cycle and containing the portion of all the cells of interest that are currently at that stage. Call  $N_k(t)$  the number of cells at phase  $k$  and time  $t$  and let also

$$N(t) = \sum_{k=1}^M N_k(t)$$

be the total number of cells. Keeping in mind the recovery of the patient, the goal of this model is to force  $N(t)$  to zero in the shortest possible time.

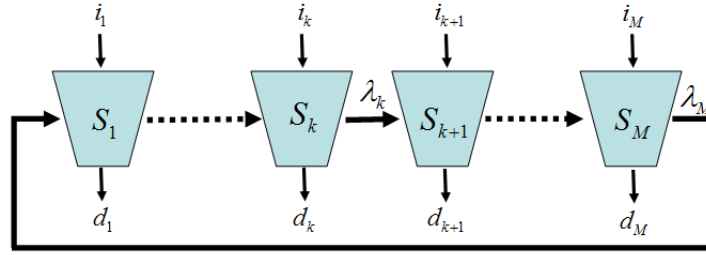


Figure 2: A simplified model for the cell cycle

As the cells undergo their cycle, some of them shall migrate from a certain stage  $S_k$  to the next stage after some time. Let  $\lambda_k$  be the rate at which cells transition from phase  $S_k$  to phase  $S_{k+1 \bmod M}$  within time  $\beta$  after time  $t$ , considering  $\beta$  to be small enough so that no cells migrate stage twice. In addition, let  $d_k(t)$  be the average rate at which cells die, and  $i_k$  be the average rate at which cells divide in phase  $k$  over time  $\beta$  at time  $t$ ; this last is non-zero for exactly one value of  $k$ .

## 2 Modelling the dynamics of cell population under the administration of two drugs.

The fact that different drugs against cancer act on different stages of the cell cycle by disrupting it and eventually killing the cell supported the idea of *combination therapies*, that is, the simultaneous administration of two or more drugs during a certain time frame.

It has been common practice to administer the drugs concurrently, that is, both at the same time, but this might trigger interactions between them. Potentially, separating the administrations would reduce the interactions. This is precisely the motivation of the present work.

Assume that only two drugs,  $A$  and  $B$  are administered where drug  $A$  is administered at time 0 and its effect is assumed to take place  $\alpha_A$  hours later. Let then drug  $B$  be administered at time  $\tau$  and its effect is assumed take place  $\alpha_B$  hours later, in other words,  $\tau$  is the time between the initial administration of the two drugs. Assume further that both drugs are taken with the same periodicity  $T$ . This is summarised in Figure 3, where  $D_A$  and  $D_B$  are the corresponding doses of the drugs.

For clarity purposes and as suggested by Figure 1, it is assumed that drug  $A$  acts on stage 2 and drug  $B$  acts on stage 4. This model can certainly be adapted to the case where the drugs act upon any two distinct stages although further consideration would be in place for the case where both drugs act on the same stage. Figure 4 depicts sketches of the survival probabilities of cells under the action of each of the drugs and for different values of  $\tau$ .

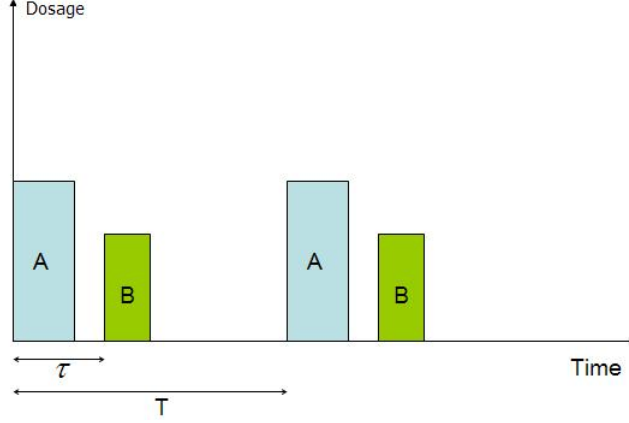


Figure 3: Dosage scenario for combination of two drugs

Returning to the diagram in Figure 2, notice that the number  $N_k(t)$  of cells in stage  $k$  gets increased by the number of cells migrating from the previous stage in the cycle and the number of new cells produced via mitosis. At the same time,  $N_k(t)$  gets decreased by the number of cells migrating to the next stage in the cycle and by those dying due to the action of the drug. In other words,

$$\frac{dN_k}{dt}(t) = \lambda_{k-1}(t) + i_k(t) - \lambda_k(t) - d_k(t) \quad (1)$$

Equation (1) is a statement of conservation of average cancer cell population at stage  $S_k$ , in other words, the rate of change of the average cell population at time  $t_0$  in stage  $S_k$  equals the average rate that cells flow into  $S_k$  minus the average rate that cells flow out of  $S_k$ .

Since  $\lambda_{k-1}$ ,  $\lambda_k$ ,  $i_k$  and  $d_k$  refer to average rates that cells flow between various stages it is natural to expect that these rates can be defined in terms of *transition probabilities*. Let  $F_k(t, \beta)$  be the probability that a cell transitions from stage  $S_k$  to stage  $S_{k+1}$  in time interval  $[t, t + \beta]$ . It is assumed that  $F_k(t, \beta)$  is differentiable. Since  $\beta$  is small, then by the Mean Value Theorem

$$\int_t^{t+\beta} \lambda_k(s) ds = \lambda_k(\tilde{t})\beta = N_k(\tilde{t})F_k(\tilde{t}, \beta) = N_k(\tilde{t})[F_k(\tilde{t}, \beta) - F_k(\tilde{t}, 0)]$$

for some  $\tilde{t} \in [t, t + \beta]$ , which can be assumed equal to  $t$  for small enough  $\beta$ . Therefore,

$$\lim_{\beta \rightarrow 0} N_k(t) \left[ \frac{F_k(t, \beta) - F_k(t, 0)}{\beta} \right] = \lambda_k(t)$$

and finally

$$\lambda_k(t) = N_k(t) \frac{\partial F_k}{\partial \beta}(t, 0) \quad (2)$$

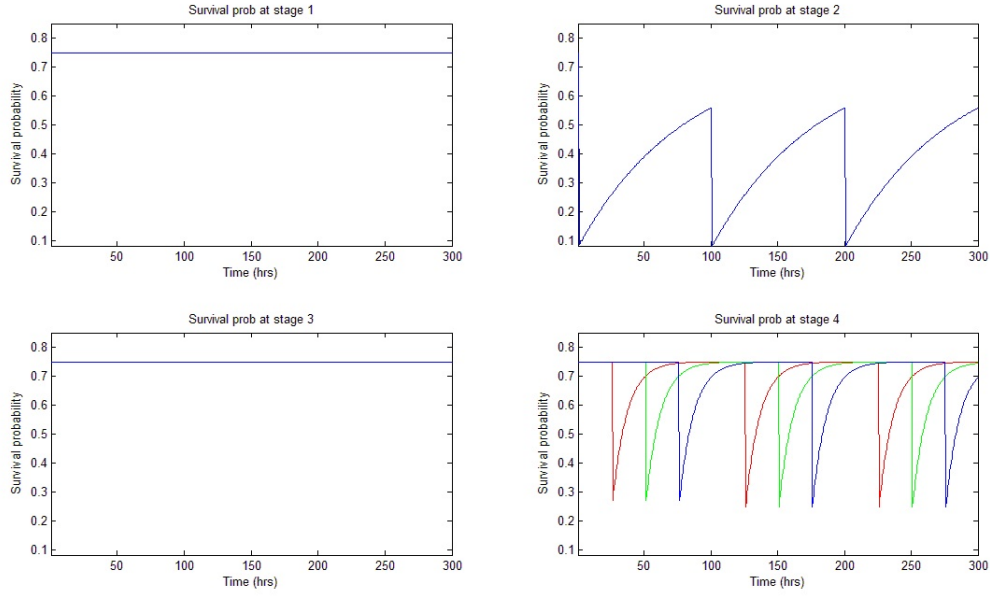


Figure 4:  $T = 100$ ,  $\tau = 25$ ,  $\tau = 50$ ,  $\tau = 75$

By the same reasoning, one finds that

$$i_k(t) = N_k(t) \frac{\partial F_k^i}{\partial \beta}(t, 0) \quad (3)$$

$$d_k(t) = N_k(t) \frac{\partial F_k^d}{\partial \beta}(t, 0) \quad (4)$$

where  $F_k^i(t, \beta)$  is the probability that a cell at time  $t$  divides in time interval  $\beta$  in stage  $S_k$  and  $F_k^d(t, \beta)$  is the probability that a cell at time  $t$  dies in time interval  $\beta$  in stage  $S_k$ . Each of these functions  $F$  will be denoted generically as a *transition probability distribution*. A typical graph of  $F(t, \beta)$  would look the same at time  $t$  appears in Figure 5.

The derivative of  $F$  with respect to  $\beta$  will be generically referred to as the *transition probability density*.

$$P(t, \beta) = \frac{\partial F}{\partial \beta}(t, \beta)$$

A typical graph of  $P(t, \beta)$  is shown in Figure 6, where  $P(t, \beta)$  is a valid probability function for all fixed  $t$ , in other words,  $P(t, \beta) \geq 0$  and  $\int_0^\infty P(t, \beta) d\beta = 1$ .

Using the definition of  $P(t, \beta)$ , the expressions (2),(3) and (4) can be rewritten as

$$\lambda_k(t) = N_k(t) P_k(t, 0) \quad (5)$$

$$i_k(t) = N_k(t) P_k^i(t, 0) \quad (6)$$

$$d_k(t) = N_k(t) P_k^d(t, 0) \quad (7)$$

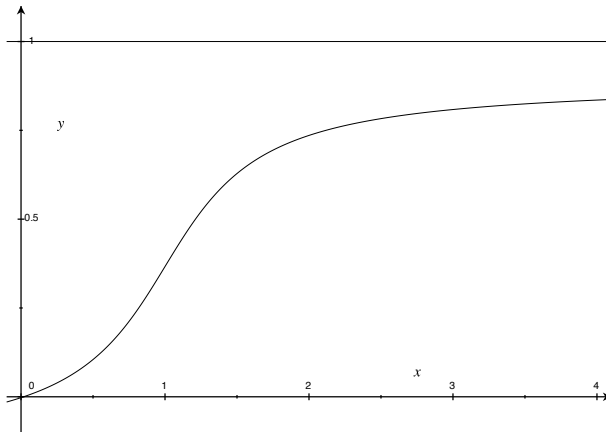


Figure 5: Transition Probability Distribution.

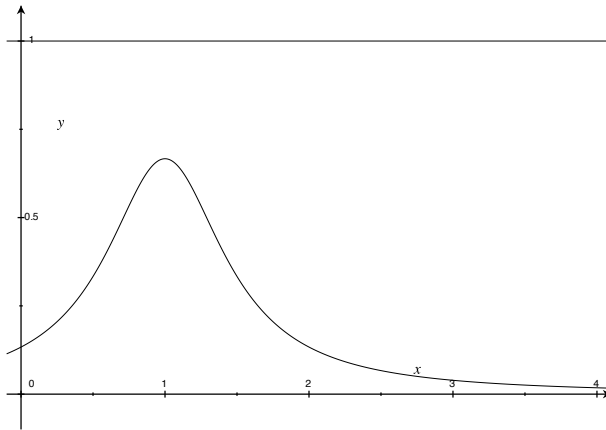


Figure 6: Transition Probability Density

where  $P_k(t, \beta)$  is the transition probability density associated to cell transition from stage  $k$  to stage  $k + 1 \pmod{M}$ ,  $P_k^i(t, \beta)$  is the transition probability density associated to cell replication in stage  $k$  and  $P_k^d(t, \beta)$  is the transition probability density associated to cell death in stage  $k$ . Substituting (5),(6) and (7) into (1) yields

$$\frac{dN_k}{dt}(t) = N_{k-1}(t)P_{k-1}(t, 0) + N_k(t)P_k^i(t, 0) - N_k(t)P_k(t, 0) - N_k(t)P_k^d(t, 0) \quad (8)$$

In order to discretise the time, it would be required to find  $N_k(t + \beta)$  for some small time change  $\beta$  and hence (8) would need to be integrated:

$$N_k(t+\beta) = N_k(t) + \int_t^{t+\beta} [N_{k-1}(s)P_{k-1}(s, 0) + N_k(s)P_k^i(s, 0) - N_k(s)P_k(s, 0) - N_k(s)P_k^d(s, 0)] ds \quad (9)$$

where  $N_k(t)$  is the initial average population of cells (cancer or not) at time  $t$ . Using the Mean Value Theorem and recalling that  $\beta$  is small enough, (9) becomes

$$\begin{aligned} N_k(t + \beta) &= \\ &= N_k(t) + \beta [N_{k-1}(t)P_{k-1}(t, 0) + N_k(t)P_k^i(t, 0) - N_k(t)P_k(t, 0) - N_k(t)P_k^d(t, 0)] \end{aligned} \quad (10)$$

Using (10) one can define the following dynamical system:

$$\begin{bmatrix} N_1(t + \beta) \\ N_2(t + \beta) \\ \vdots \\ N_M(t + \beta) \end{bmatrix} = \begin{bmatrix} 1 + C_1(t)\beta & 0 & \dots & P_M(t, 0)\beta \\ P_1(t, 0)\beta & 1 + C_2(t)\beta & \dots & 0 \\ \vdots & \ddots & \ddots & 0 \\ 0 & \dots & P_{m-1}(t, 0)\beta & 1 + C_M(t)\beta \end{bmatrix} \begin{bmatrix} N_1(t) \\ N_2(t) \\ \vdots \\ N_M(t) \end{bmatrix} \quad (11)$$

where  $C_k(t) = P_k^i(t, 0) - P_k(t, 0) - P_k^d(t, 0)$ ,  $k = 1, \dots, M$ . Notice further that the system can be rewritten in the somewhat more convenient form

$$\begin{bmatrix} N_1(t + \beta) \\ N_2(t + \beta) \\ \vdots \\ N_m(t + \beta) \end{bmatrix} = \left\{ \begin{bmatrix} 1 + T_0(t)\beta & 0 & \dots & P_M(t, 0)\beta \\ P_1(t, 0)\beta & 1 + T_1(t)\beta & \dots & 0 \\ \vdots & \ddots & \ddots & 0 \\ 0 & \dots & P_{m-1}(t, 0)\beta & 1 + T_M(t)\beta \end{bmatrix} - \begin{bmatrix} P_0^d(t, 0)\beta & 0 & \dots & 0 \\ 0 & P_1^d(t, 0)\beta & \dots & 0 \\ 0 & \ddots & \ddots & \\ 0 & \dots & 0 & P_M^d(t, 0)\beta \end{bmatrix} \right\} \begin{bmatrix} N_1(t) \\ N_2(t) \\ \vdots \\ N_M(t) \end{bmatrix} \quad (12)$$

where  $T_k(t) = P_k^i(t, 0) - P_k(t, 0)$ ,  $k = 1, \dots, m$ . The first matrix encodes the evolution of the cell population due to intrinsic (natural) causes whereas the second one encodes the

influence of the drugs in the cell population. Either of equations (11) or (12) can be applied recursively in order to determine the vector

$$\mathbb{N}(t) = [N_1(t), N_2(t), \dots, N_M(t)]$$

describing the cell populations of all states. Of primary importance is  $N(t)$ . From (10) this gives

$$N(t + \beta) = \sum_{k=1}^M \{N_k(t) + \beta N_k(t) [P_k^i(t, 0) - P_k^d(t, 0)]\}$$

or

$$N(t + \beta) = N(t) + \beta \sum_{k=1}^M N_k(t) [P_k^i(t, 0) - P_k^d(t, 0)]$$

Cell death due to natural causes will be the objective of further study and for the time being it is assumed that the probability of a cell surviving through time  $\beta$  within any stage of its life cycle is a constant 0.95. It is well known that the concentration of either drug over time can be modelled by exponential decay. Assuming a linear relationship between the concentration of the drug and the probability that it kills a cell, the survival probability under the effect the two drugs combined is given by

$$F_k^s(t, \tau) = \begin{cases} 0.95 - \gamma_A D_A e^{-\delta_A(t-\alpha_A)} & k = \sigma_A \\ 0.95 - \gamma_B D_B e^{-\delta_B(t-\alpha_B-\tau)} & k = \sigma_B \\ 0.95 & \text{elsewhere} \end{cases}$$

where  $\delta_j$  is the decay rate and  $\gamma_j$  is the proportionality constant for the linear relationship between killing probability and concentration for drug  $j = A, B$ , and  $\sigma_j$  is the phase in which drug  $j$  acts. This survival probability is closely related to the cell death probability by simply  $F_k^d(t, \tau) = 1 - F_k^s(t, \tau)$ . For the time being, the interaction between the two drugs is overlooked.

### 3 An example of the implementation of the model

A combination of two chemotherapy drugs was considered at random. Known data for these drugs appears in Table 1. These parameters along with the artificial ones for the two drugs shown in Table 2 and the artificial data for the cell cycle shown in Table 3 were time-plotted through MATLAB using  $T = 100$  and the initial departures  $\tau = 25, 50$  and  $75$  for three administration periods, obtaining in Figure 7 a description of the behaviour for each of the four cell stages.

In addition, the dynamics of the quantity  $N(t)$  giving the total number of cells is presented in Figure 8, showing the effect of the drugs during three administrations. This suggests that the time of separation between the initial administration of the two drugs does play a role in the overall cell mortality.

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<sup>1</sup>The value of the decay rate was computed using an average half-life of 7.5 hours.

Table 1: Known data for a combination therapy

Drug	Doxorubicin	Cyclophosphamide
Stage of action, $\sigma_D$	<b>G1</b>	<b>M</b>
Dosage in mg, $D_j$	2000	500
Half-life in hours	55	3 to 12
Decay rate, $\delta_j$	.0126	.0924 <sup>1</sup>

Table 2: Artificial data for a combination therapy

Drug	Doxorubicin	Cyclophosphamide
Proportionality constants (slopes) between concentration and effectiveness (kill rate), $K_j$	1/3000	1/1000
Delay between drug application and its effect in hours, $\alpha_j$	0.5	0.5

Table 3: Artificial data for the cell cycle

Stage	<b>G<sub>1</sub></b>	<b>S</b>	<b>G<sub>2</sub></b>	<b>M</b>
Transition probabilities $P_k$	1/4	1/4	1/4	1/4
Replication probabilities $P_k^i$	0	0	0	1/4
Initial number of cells per stage $N(0)$	50	50	50	50

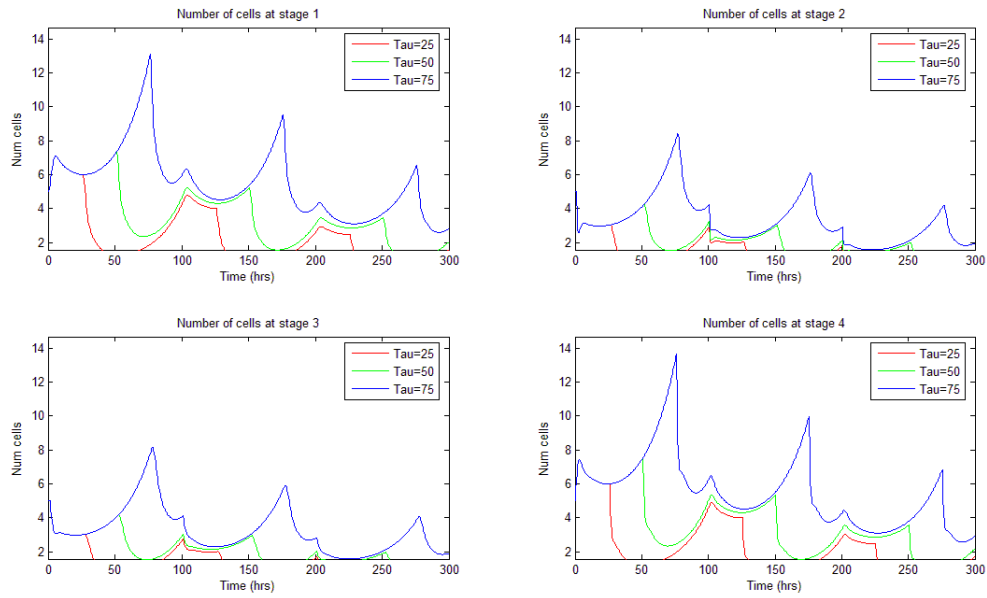


Figure 7:  $T = 100$ ,  $\tau = 25$ ,  $\tau = 50$ ,  $\tau = 75$

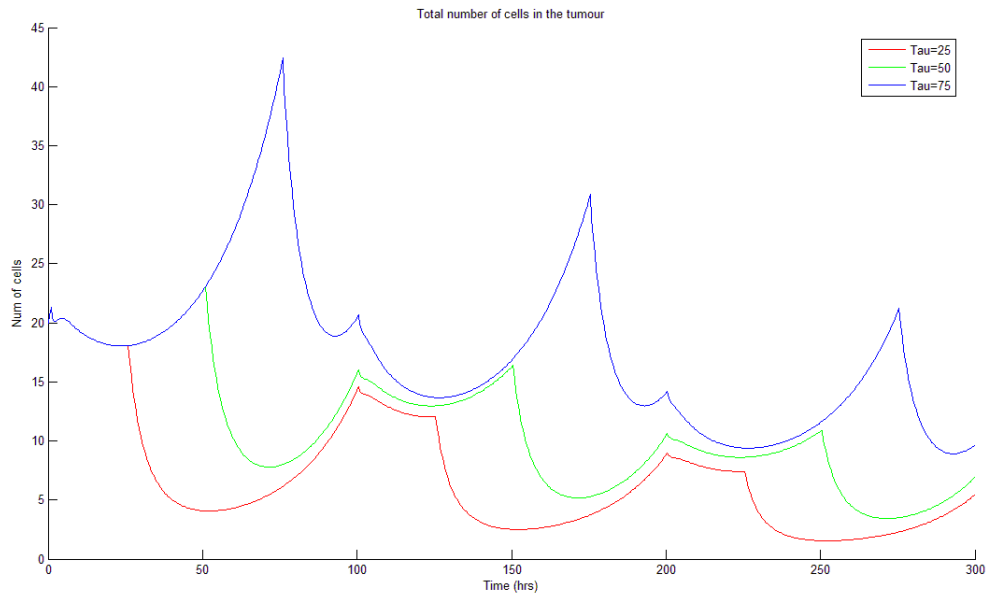


Figure 8:  $T = 100$ ,  $\tau = 25$ ,  $\tau = 50$ ,  $\tau = 75$

Although this example might suggest that the closer the two drugs are administered, the more effective the combination treatment will be, it should be kept in mind that the present model does not yet consider drug interactions.

## 4 Parameter Estimation

Post introduction of the drug, many events happen over time. In a particular phase, some of the main events include:

- Annihilation: The cancer cells are annihilated at each time.
- Migration: The cells in that phase transform into next phase and Some cells enter into the phase from the previous phase.

Since the number of cells are large (order of  $10^5$ ) and probability of a cell either dividing or getting killed is small, the process can be characterised as a Poisson process. Hence, at a given time  $t$ , the annihilation and migration events can be characterised:

The probability that  $k_1$  cells are killed at time  $t$  is the random variable  $A$ ,

$$p(A = k_1) = \frac{\lambda_1^{k_1} \times \exp^{-\lambda_1}}{k_1!} \quad (13)$$

The probability that  $k_2$  cells transform into next phase at time  $t$  is the random variable  $T$ ,

$$p(T = k_2) = \frac{\lambda_2^{k_2} \times \exp^{-\lambda_2}}{k_2!} \quad (14)$$

The probability that  $k_3$  cells infuse into current phase at time  $t$  is the random variable  $I$ ,

$$p(I = k_2) = \frac{\lambda_2^{k_2} \times \exp^{-\lambda_2}}{k_2!} \quad (15)$$

The time taken for a cell that has just entered to migrate into next phase is large compared to time for an existing cell to transform into next phase and hence these events can be assumed to be independent. The drugs are known to destroy a select portion of the tumour such as portion of the outer layer. Hence, each of these processes can be assumed to be independent.

In order to find the joint probability of the events, one must maximise the likelihood of the above processes

$$\begin{aligned} L &= \{p[I = k_2] \times p[A = k_1] \times p[D = k_3]\} \\ &= \prod_{i=1}^4 \frac{\lambda_i^{-k_i} \exp^{-\lambda_i}}{k_i!} \\ \text{Log}(L) &= \sum_{i=1}^4 \{(-k_i \log(\lambda_i) - \lambda_i) - \log(k_i!)\} \end{aligned}$$

for which experimental data could be put into this process to determine the mentioned parametres.

## 5 Conclusion

This final section contains some thoughts on potential future directions for the model described in this work. The authors concede that this is a quite general model and that further instantiation must take place in order to apply it to a real situation, but at the same time, they believe that the generality described herein might potentially allow for a wider variety of applications.

It is a fact that the example of this model suggests a dependency of the effectivity of a combination treatment upon the time separation between the initial administration of the two drugs involved. A first task would be to evaluate the validity of the present model using real parameters, that is, determining all the parameters of the model for drugs that are actually used in cancer therapy.

Certainly, the probabilistic process involved in modelling the migration probabilities discussed in Section 4 is general enough to estimate these parameters for any type of cells; moreover, even for healthy cells. Estimating these parameters from real data to fit a specific cancer type is certainly a challenge.

Once the real parameters are established for a specific type of cancer and a particular treatment against this disease, it would be in place to evaluate the impact of side effects on the patient and to quantify the interaction of the drugs depending on the departure between treatments  $\tau$ . This model would then be able to describe the expectancy of improvement in patients and serve as a guideline for more effective clinical trials of combination therapies. Further, by varying dosage times as well as initial departures might eventually sharpen the effectivity expectation and suggest even better clinical trials.

In a longer time, drug resistance could be implemented into the model. The authors believe that this can be done by keeping the relatively simplistic approach of modelling through a discrete dynamical system. This would in turn allow to model and optimise the overall quality of life of the patient and the cancer cell population depletion with respect to multiple drug treatment scenarios.

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