A mathematical model to study the effect of drug kinetics on the drug-induced resistance in tumor growth dynamics

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Abstract. Drug resistance is recognized as being the major obstacle to be overcome during the systemic chemotherapy of cancer. Tremendous amounts of molecular mechanisms results in resistance in the cell as they develop. Resistance always arises after drug application. The rate at which resistance occurs under mutation induced by drug is affected by drug kinetics. Yet, it isn’t clear how drug kinetic factors affect the evolution of resistance. Here, we developed a mathematical model to describe the growth of the resistant subpopulation along with the effect of different drugs administrated. In the model, we took into account how two critical kinetic factors for each drug, drug eradication rate and drug-induced resistance mutation rate, determine the treatment result. We calculated the drug dosage threshold for the maximum resistance and found that it only related to eradication rate. The combined analysis of the model and clinical data might give useful information on the treatment strategies and be potentially useful for designing specifically tailored cancer therapies with individual drugs.

1. Introduction
Cancer remains one of the most dangerous illnesses causing many deaths every year. Although new medical techniques have been developed, traditional treatment such as chemotherapy is still one of the main methods applied. However, a persistent barrier to the effective treatments of chemotherapy is the development of resistance to drugs[1,2]. Many mechanisms of drug resistance have been found, for example, drugs can be prevented from entering the cells; drugs can be pumped out of cells; they can be enzymatically inactivated; drug activity can be prevented by mutation or altered expression of the target; and defects in apoptosis, senescence, and repair mechanisms can contribute to resistance[3-5].

Drug resistance is usually divided into two broad categories: intrinsic resistance and acquired resistance. Intrinsic resistance refers to the state wherein the malignancy shows little or no sensitivity to therapeutic agents without having had initial exposure to the drugs. Acquired resistance refers to the process whereby a tumor that was initially sensitive to treatment displays increasing unresponsiveness to the same agent that was initially effective in generating a complete or partial remission. In clinical chemotherapy, usually sees initial decrease in tumor size with application of a cytotoxic drug, but this is eventually followed by the tumor’s regrowth and continued expansion, despite the presence of the
drug. Many drugs, including taxol, methotrexate and imatinib, affect high rates of induced resistance mutation in chemotherapy[6-8]. The mechanisms by which cancer cells achieve resistance are extremely diverse and can vary depending on the mechanisms of action and molecular kinetics of the chemotherapeutic drug. For example, methotrexate caused DHFR gene amplification, which in turn resulted in drug resistance. So it is sometimes assumed that acquired resistance can be directly induced by the chemotherapeutic drug. Resistance acquired during treatment by drug-induced mutation is the key factor to block the successful therapy, modeling of drug-induced resistance dynamics is an active research.

Over the past few decades, various research has been done in the area of modeling tumor drug resistance[9,10]. Goldie and Coldman created the first stochastic model of drug resistance, and then they developed a whole new approach to mathematical treatment of resistance in their subsequent work. Norton and Simon proposed a model in which a particular chemotherapeutic treatment results in a rate of regression in tumor volume that is proportional to the rate of growth for an unperturbed tumor of that size. The chance of eradicating the tumor is maximized by delivering the most effective dose level of drug over as short a time as possible. Thereby, tumors given less time to grow between treatments, are more likely to be eradicated[11,12]. There are models in which partial resistance and its relationship to the concentration of the drug is being addressed created by Gardner and Swierniak et al. Based on this, Gyori considered the resistant cells growth mechanism under periodic dosing cases[13,14]. Some other researchers investigated the tumor growth model by using cellular automata which can include very specific characteristics of the tumor, patient and effectiveness in the model[15-20].

In these works, research of drug-induced resistance was relatively infrequent. Birkhead and Gregory mathematical model investigated induced resistance in small cell lung cancer (SCLC). Their model and experimental data indicated that as many as 36% of sensitive SCLC cells are induced to resistance per dosage[21]. John Carl Panetta described the growth and control of a heterogeneous tumor with the effect of chemotherapy. Panetta took into account induced drug resistance[22]. However, such acquired mathematical models seem incapable of comparing the degree of resistance induced by different chemotherapeutic drugs.

Nowadays, there are as many as hundred kinds of anti-cancer drugs applied in clinical medicine, each drug producing different degrees of resistance. It is not easy to choose the most appropriate drug therapy. Yet, a general relationship between the degree of resistance of the tumor and the different drug applied had not been established.

In this paper, a mathematical model of drug-induced resistant subpopulation evolution dynamics was developed. We used a heterogeneous tumor, which contain compartments for cells sensitive and cells resistant to describe the growth of the cancer along with the effects of chemotherapy. The main aspect of this model is that it takes into account how two critical drug kinetic factors, including drug eradication rate (DER) and drug-induced resistance mutation rate (DMR), affect the evolution of resistant cells. It is suggested to inform the choosing of the most suitable drug when drug-resistant cells inevitably arise. We calculated the dosage threshold for the maximum resistance which led to most ineffective case for treatment with a particular drug. That will give useful information on the diagnosis and the therapy for cancer patients.

2. Methods

2.1 Model of drug-induced resistance arise during tumor cells division with constant drug concentration

Based on the quantitative theories for the development of resistance by Goldie and Coldman[23,24] We established a new model in which the effects of drug kinetic factors have been taken into account. In this model, tumor growth is considered as a population dynamics problem but does not aim to concentrate on a specific kind of cancer. This model focuses on two different cell populations: sensitive cells and resistant cells.
Before exposure to the drug, all the tumor cells were sensitive to drug, there were no resistant cells in existence. The growth of cells was described as exponential growth. The rate of growth was proportional to the tumor size. Resistance developed only at times when the cells had been exposed to the drug. After the time of drug application, we considered two effects of drug kinetic factor: DER and DMR. The sensitive cells would be eradicated by the drug at the certain probability, which denoted the DER. In normal conditions, the death of tumor sensitive cells is delayed with respect to the drug treatment, but here, we assumed that cells could be eradicated at once. The rest of sensitive cells would survive and continue divide. Resistant cells arise via drug-induced mutation with certain probability at the next division of sensitive cells, which defined the DMR. The resistant cells could not be eradicated by the same drug, and the daughter cells of them were all resistant. The sensitive cells would be killed at the certain probability and generated resistant cells at the third division. The remaining divisions could be done in the same manner on the condition of drug existence. For this reason, the resistant cells accumulated more and more during divisions, the proportion of resistant cells increased, the fraction of tumor cells eradicated by drug would decrease through cell division. Both the DER and DMR depended on the drug type and drug concentration applied. The specific relationship of them will be explained in later sections.

In the modeling process, we took several justifiable assumptions. We assumed first that tumor cells couldn’t eliminated by natural death. Second, the concentration of drug at the tumor site was kept constant. Third, only sensitive daughter cells acquired drug resistance by induced mutation. Figure1 showed the growth of hypothetical tumor cells through three synchronized divisions with constant drug concentration application.

![Figure 1](image)

**Figure 1.** The growth of hypothetical tumor cells population through three synchronized divisions. Red circles indicate sensitive cells, blue circles indicate resistant cells, short horizontal lines indicate sensitive cells be killed by drug. The green arrow indicates time drug administration was continued.

Denote the number of tumor cells at beginning by $N_0$, $N_n$ is the number of tumor cells after $n$th divisions. The DMR of sensitive cells in each division is denoted by $\alpha$, the DER is denoted by $\beta$, resistant cells number is denoted by $R_n$. Number of sensitive cells and resistant cells after $n$th divisions has been derived from the model.

\[
N_n = N_0(1 - \beta)^n(2 - \alpha)^{n-1} \quad (1)
\]

\[
R_n = 2R_{n-1} + N_{n-1}\alpha(1 - \beta) \quad (2)
\]

### 2.2 Model of drug-induced resistance arise during course of chemotherapy

In vivo tumor cells growth is not totally synchronous, in order to fit the experimental tumor growth data in treated animals, we changed model above into model of continuity. In vivo tumor growth models is known to follow exponential growth[25]. Considered a single drug administered repeatedly in the same dosage at constant intervals. The cleaning time of each dosage is shorter then interval, but the death of tumor cells is delayed with respect to the drug treatment, so we assume that the effect of drug worked during delayed time(DT)[26]. Out of DT, drug effect disappeared. Consider that the cells growth and drug effects are continuous. Sensitive cells, resistant cells and tumor total cells at time $t$ are denoted by $N(t), R(t)$ and $X(t)$ respectively. Intrinsic growth rate of sensitive cells and resistance cells are indicated by $r_1, r_2$, which proportional to the population size. $\beta(t)$ represents DER of the drug.
as function of the drug dosage applied, $\alpha(t)$ gives DMR of the drug as function of the drug dosage applied also. The model for evolution of tumor composition during the period covering first three dosages is suggested in Figure 2.

Figure 2. Illustration about the composition of a tumor during the first three dosages. Green block denote the portion of sensitive cells, blue block indicate sensitive cells eradicated by drug, orange block indicate resistant cells. Drug dosage each course is $C_n$.

The model can be expressed in terms of differential equations as follows:

$$
\begin{align*}
\frac{dN(t)}{dt} &= r_1N(t) - \beta(t)N(t) - \alpha(t)dN(t) \quad (3a) \\
\frac{dR(t)}{dt} &= r_2R(t) + \alpha(t)N(t) \quad (3b) \\
X(t) &= N(t) + R(t) \quad (3c) \\
N(0) &= N_0 \quad R(0) = 0 \quad X(0) = N_0 \quad (3d)
\end{align*}
$$

As to different drugs, the relationship of $\alpha(t)$ and drug dosage, ranging from almost zero to nearly 50% of the surviving sensitive cells, was rarely seen in the literature. That might be attributable to the various recruitment rates of the quiescent cells as a response to the cell loss caused by chemotherapy. Sensitive tumor cells have a fixed probability per division of acquiring resistance to a particular drug at a particular dosage [27]. Experiments indicated that as many as 36% of sensitive SCLC cells are induced to resistance per dosage [21]. We assume that DMR is proportion with drug dosage in each of treatment, $\alpha(t) = k_1C(t)$, $k_1$ represent drug-induced mutation coefficient.

The relationship between DER and drug dosage are not the same. In many cases, the dose-response relation is exponential. This relationship is seen most in cells exposed in vitro to various alkylating agents or 5-fluorouracil. The fit is undoubtedly good with cyclophosphamide and 1,3-bis (2-chloroethyl)-1-nitrosourea in vivo [28]. The dose-response curves of L1210 cells in mice treated with methotrexate, or 6-mercaptopurine are not exponential but hyperbolic in form, the product of the surviving fraction and the dose (or a power of the dose) being a constant. There is a log-linear relationship between tumor cell eradicated and drug dose various when tissues of BALB/c mice treated with a single dose of cyclophosphamide (100, 300 or 500mg·kg$^{-1}$) [29]. Each dosage killed sensitive leukemic cells in model mice by means of specific proportion instead of cell number. The fractional eradicated is proportional to drug dosage [30,31]. The first-order kinetics was adopted for $\beta(t)$, the DER is linear in the drug dosage in each course of treatment, $\beta(t) = k_2C(t)$, where $k_2$ denoted drug eradication coefficient.

Substitute the $\alpha(t) = k_1C(t)$ and $\beta(t) = k_2C(t)$ into equation (3a) and (3b), we obtain the following equations.

$$
\frac{dN(t)}{dt} = r_1C(t)N(t) - (k_1 + k_2)C(t)N(t) \quad (4a)
$$
\[
\frac{dR(t)}{dt} = r_2 R(t) + k_1 C(t) N(t) \tag{4b}
\]
\[
C(t) = \int_0^{DT} c(t) \, dt \tag{4c}
\]
\[
X(t) = R(t) + N(t) \tag{4d}
\]

Initial conditions: \( N(0) = N_0 \) , \( R(0) = 0 \), \( X(0) = N_0 \)

In the above equations, \( C(t) \) is the drug dosage in each course, \( c(t) \) is the drug concentration during DT. \( n \) denotes the number of treatment course.

2.3 coefficients of \( k_1 \) and \( k_2 \)
The coefficients \( k_1 \) and \( k_2 \) are critical parameters in regard to effectiveness of a particular drug determined by characteristic of the drugs. Drug-induced resistance developed only at times when the cells are exposed to the drug, degree of it determined by dosage and type of drug. The coefficients \( k_1 \) and \( k_2 \) of one drug will differ when this drug is administrated in different tumors. Such as in the experiment of EMT-6 mouse tumor cells located in various tissues of BALB/c mice treated with a single dose of cyclophosphamide, the large variation in response of the tumor cells to the drug depending on tissue location is evident. Anti-cancer drugs will kill the sensitive cells on the one hand, but meanwhile they will continuously induce the remaining sensitive cells to mutate into resistant cells. In another word, the more sensitive cells are killed, the more mutation will be generated from the remaining sensitive cells. Figure.3 demonstrates how the tumor size (cells number) varies with different coefficients \( k_1 \) and \( k_2 \).

![Figure 3](image)

Figure 3. Tumor cells growth with two parameter values varied during treatment with constant concentration of a drug. Red, blue and green lines indicate resistant cells, sensitive cells and tumor total cells respectively (a) \( N_0 = 6 \times 10^8, r_1 = 0.05 \text{day}^{-1}, r_2 = 0.06 \text{day}^{-1}, k_1 = 5 \times 10^{-5}, k_2 = 0.01 \) \( c=10\text{mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1} \). For the remaining curves, one of the parameters is changed from those used in (a) as follows: (b) \( k_1 = 5 \times 10^{-4} \) (c) \( k_1 = 5 \times 10^{-3} \) (d) \( k_2 = 0.05 \).

2.4 Drug dosage threshold led to maximum resistance in continued drug administration
If one drug is fixed for the tumor, what drug dosage must be administered for maximum resistance? It is necessary to ignore the time course of growth of the tumor and just use the growth of the tumor as an index of development of the system. Considering \( X \) being an approximately continuous variable, we will derive equations that describe the size of \( R \) for any particular value of \( X \). \( X \) replaces \( t \) as an index of the overall process. We will consider what happens when the total number of tumor cells \( X \) increases to \( X + \Delta X \). \( R \) may be expanded about the point \( X \) using Taylor's theorem.
\[ R(X + \Delta X) = R + \frac{dR}{dx} \Delta X + 0(\Delta X^2) \]  \hspace{1cm} (5)

If the total tumor population increases by \( \Delta X \), then there will be an expected \( \frac{R}{X} \Delta X \) growth in the resistant number, an increase of \( k_1 C(1 - k_2 C) \left( 1 - \frac{R}{X} \right) \Delta X \) due to new mutation. Therefore, the expected number of mutant cells is

\[ R(X + \Delta X) = R + \frac{R}{X} \Delta X + k_1 C(1 - k_2 C) \left( 1 - \frac{R}{X} \right) \Delta X + 0(\Delta X^2) \]  \hspace{1cm} (6)

Equating (5) and (6), dividing by \( \Delta X \), and taking limit \( \Delta X \to 0 \) yields

\[ \frac{dR}{dx} = \frac{R}{X} + k_1 C(1 - k_2 C)(1 - \frac{R}{X}) \]  \hspace{1cm} (7)

Using the condition \( \mu = 0 \) when \( X = 1 \), then formula becomes

\[ R = \left[ 1 - (R + N)^{-k_1 C(1-k_2 C)} \right] (R + N) \]  \hspace{1cm} (8)

So we obtain the threshold dosage of drug which result in the most resistance cells

\[ C_b = \frac{1}{2k_2} \]  \hspace{1cm} (9)

Define the ratio \( \frac{R}{X} \) describe the degree of tumor resistance under the condition of most ineffective dosage, denotes the maximum resistance rate, so we have the resistance rate at time \( t \)

\[ P(t)_b = \left\{ 1 + \frac{k_1 + k_2}{k_1} \left[ e^{\frac{k_1 + k_2}{2k_2}t} - 1 \right] \right\}^{-1} \]  \hspace{1cm} (10)

Meanwhile the maximum resistant cells number obtained as follows

\[ R(t) = \frac{N_0 e^{rt}}{k_1 + k_2} \left( k_1 + k_2 e^{\frac{k_1 + k_2}{2k_2}t} \right) \]  \hspace{1cm} (11)

3. Result and discussion

To evaluate the practical applicability of the model, the experiment that anti-tumor activity of irinotecan (CPT-11), a DNA topoisomerase I inhibitor, was evaluated in 5 advanced stage subcutaneous medulloblastoma xenografts in nude mice, using different schedules of administration retrospectively surveyed[32]. 5 medulloblastoma xenografts include IGRM11, IGRM13, IGRM21, IGRM33 and IGRM34 derived from primary tumors of the posterior fossa by subcutaneous transplantation of small fragments in previously irradiated athymic mice. CPT-11 was administered three schedules (1) short course treatment: 27 and 40 mg ∙ kg⁻¹ doses were given daily over 5 consecutive days (1 cycle). (2) sequential schedule treatment: CPT-11 (13.5, 20 and 40 mg ∙ kg⁻¹ ∙ day⁻¹) was given in two 5-day cycles (days 0–4 and days 28–32). (3) protract-schedule treatment: CPT-11 (6.75 and 10 mg ∙ kg⁻¹ ∙ day⁻¹) was given in four 5-day cycles (days 0–4, days 7–11, days 21–25 and days 28–32). One week rest was required in the middle of the treatment period to resolve local toxicity at the site of the I.V. Injection. During these three schedules, the same total dosages (135 and 200 mg ∙ kg⁻¹) were administered over the same period.

According to the evolution of the mean tumor volume for each group of mice, IGRM11 proved to be the most sensitive xenograft. IGRM13 proved to be the lowest sensitive xenograft. We applied our model on experimental data of xenograft IGRM34, assuming that tumor cells are sensitive prior to treatment, drug administered was completely exposed to the tumor. The cleaning time of 40mg ∙ kg⁻¹ ∙ day⁻¹ CPT-11 was approximate 2.5hours, meaning that the concentration of drug vanished when the therapeutic effect becomes negligible. But experiments proved that the efficacy of a treatment is delay, so the efficacy time of a treatment may be measured using the delayed time. According to experiment, the DT of CPT-11 is about 17days. Tumor cells growth was exponential out of time DT.

We have chosen parameters in ranges consistent with the literature. In Fig.4, the observed and the model-fitted average tumor cells growth curves are shown in control and CPT-11-treated nude mice in three different schedules. (a) daily×5, received saline or CPT-11 at dose of 40mg ∙ kg⁻¹ ∙ day⁻¹(b) daily×5, received saline or CPT-11 at dose of 27mg ∙ kg⁻¹ ∙ day⁻¹(c) days 0–4 and days 28–32.
received saline or CPT-11 at dose of 40mg · kg⁻¹ · day⁻¹ (d) days 0–4 and days 28–32 received saline or CPT-11 at dose 27mg · kg⁻¹ · day⁻¹ (e) days 0–4, 7–11 and days 21–25, 28–32 received either saline or CPT-11 at a total dose of 200mg · kg⁻¹ respectively (f) days 0–4, 7–11 and days 21–25, 28–32 received either saline or CPT-11 at a total dose of 135mg · kg⁻¹ respectively. 1mm³ tumor contains 10⁸ cells[33].

Figure 4. The observed and the model-fitted average tumor growth curves are shown in control and CPT-11-treated in advanced stage subcutaneous medulloblastoma xenograft IGRM 34 in nude mice, in three different schedules (r₁ = 0.1096 day⁻¹, r₂ = 0.1096 day⁻¹, k₁ = 2.5 × 10⁻⁹, k₂ = 9 × 10⁻⁴).

Red dotted line, blue dotted line and green line indicate nude mice received saline, CPT-11 and model-fitted tumor cells growth curves.

In order to compare the effective of treatment with the same drug, we matched the curves of IGRM11, 13, 21 and 33 by the least square method, obtained the estimated coefficients r₁, k₁ and k₂ (Table 1)

Table 1 Coefficients of r₁, k₁ and k₂

| coefficients | IGRM11 | IGRM13 | IGRM21 | IGRM33 | IGRM34 |
|--------------|--------|--------|--------|--------|--------|
| r₁ (day⁻¹)   | 0.0456 | 0.0474 | 0.0441 | 0.0523 | 0.1096 |
| k₁ (CPT-11)  | 9 × 10⁻⁶ | 4 × 10⁻⁶ | 3 × 10⁻⁵ | 7 × 10⁻⁶ | 2.5 × 10⁻⁹ |
| k₂ (CPT-11)  | 0.0018 | 0.00016 | 0.00046 | 0.0015 | 0.0009 |

Drug dosages which develop the maximum resistance cells under steady concentration of each type xenografts were 277.78, 277.78, 1086.96, 333.33, 555.56 (mg · kg⁻¹) respectively.

The model was fitted experiment date well when applied on experiment about anti-tumor activity of irinotecan (CPT-11). We obtained the threshold dosage which lead to the number of drug-induced resistant cells and resistance rate both reached maximum levels. From this it may be seen that, assume r₁ = r₂, the resistance rate related to drug kinetic coefficients k₁ and k₂ which is irrelevant to intrinsic growth rate or tumor burden. So if we have fixed the drug for a particular tumor, then the model can act as a predictor for how to avoid the most ineffective therapy while at the same time predicting the time to switch to the second non-cross-resistant drug.

We have considered two of the main critical drug kinetic factors including DER and DMR. Model shown how drug kinetics effect drug-induced resistant subpopulation evolution, the coefficient of DER and DMR both determined by drug type, they are differ when different tumor treatment with one drug. These parameters are important to know because, if the clinical data does not allow us to determine
them either directly or implicitly, then the model will have little hope of being of any use in estimating effective chemotherapeutic treatments.

As for the tumor growth, the exponential function has been used in our model. But the general framework is independent of this choice calculations can be carried out using other functions for growth rate such as Gompertz function or power-law function. We adopted linear relationships between the two parameters and drug dosage, but there have been alternative relationship such as the exponential and power-law in different condition. Our intention is to provide a framework for the analysis of response of the tumor to chemotherapeutic drugs that might help to devise better treatment strategies; potentially useful for designing specifically tailored cancer therapies with individual drugs.

4. Conclusions
Resistant to chemotherapy is a key impediment to successful cancer treatment that has been studied intensively for the last three decades. In most cases, development of resistance is inevitable. In this paper, a heterogeneous tumor with chemotherapy and drug-induced resistance is discussed. It is hope that, by a close investigation of this model, we will come to a better understanding of the dynamic of drug-induced resistance subpopulation evolution and be able to help determine more effective methods of delivering chemotherapeutic drugs.

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Reference
[1] Lu, H. W.; Gratzl, M. Analytical Chemistry, 71 (14), 2821-2830. (1999)
[2] Hrabakova, R.; Kollareddy, M.; Tyleckova, J.; Halada, P.; Hajduch, M.; Gadher, S. J.; Kovarova, H. Journal Of Proteome Research, 12 (1), 455-469. (2013)
[3] Bronchud, M. H.; Foote, M. A.; Peters, W. P.; Robinson, M. O. Principles of Molecular Oncology. Humana.Totowa, NJ: (2000);
[4] Kruh, G. D. Oncogene, 22 (47), 7262-7264. (2003)
[5] Wang, X.; Li, J.; Wang, Y.; Koenig, L.; Gjyrezi, A.; Giannakakou, P.; Shin, E. H.; Tighiouart, M.; Chen, Z.; Nie, S.; Shin, D. M. Acs Nano, 5 (8), 6184-6194. (2011)
[6] Shannon, K. M. Cancer Cell, 2 (2), 99-102. (2002)
[7] G., M., C., D. Trends Cell Biol, 11, S22-S26. (2001)
[8] R.T.Schimke. Cancer Res, 44, 1735-1742. (1984)
[9] Tredan, O.; Galmarini, C. M.; Patel, K.; Tannock, I. F. Journal Of the National Cancer Institute, 99 (19), 1441-1454.(2007)
[10] Michor, F.; Nowak, M. A.; Iwasa, Y. Current Pharmaceutical Design, 12 (3), 261-271. (2006)
[11] Norton, L.; Simon, R. Cancer Treatment Reports, 70 (1), 163-170. (1986)
[12] Norton, L.; Simon, R. Cancer Treatment Reports, 61 (7), 1307-1318. (1977)
[13] Swierniak, A.; Kimmel, M.; Smieja, J. European Journal Of Pharmacology, 625 (1-3), 108-121. (2009)
[14] Gyori, I.; Michelson, S.; Leith, J. Bulletin of Mathematical Biology, 50 (6), 681-696. (1988)
[15] Castorina, P.; Carco, D.; Guiot, C.; Deisboeck, T. S. Cancer Research, 69 (21), 8507-8515. (2009)
[16] Gerlee, P.; Anderson, A. R. A. Journal Of Theoretical Biology, 246 (4), 583-603. (2007)
[17] Goldie, J. H.; Coldman, A. J.; Gudauskas, G. A. Cancer Treatment Reports, 66 (3), 439-450. (1982)
[18] Kansal, A. R.; Torquato, S.; Harsh, G. R.; Chiocca, E. A.; Deisboeck, T. S. Journal Of Theoretical Biology, 203 (4), 367-382. (2000)
[19] Kansal, A. R.; Torquato, S.; Harsh, G. R.; Chiocca, E. A.; Deisboeck, T. S. Biosystems, 55 (1-3), 119-127. (2000)
[20] Monro, H. C.; Gaffney, E. A. Journal Of Theoretical Biology, 257 (2), 292-302. (2009)
[21] Birkhead, B. G.; Gregory, W. M. Mathematical Biosciences, 72 (1), 59-70. (1984)
[22] Panetta, J. C. Mathematical Biosciences, 147 (1), 41-61. (1998)
[23] Gold, J. H.; Coldman, A. J. Cambridge University Press, New York: (1998).
[24] Coldman, A. J.; H, G. J. Math. Biosci, 65, 291. (1983)
[25] Bissery, M. C.; Vrignaud, P.; Lavelle, F.; Chabot, G. G. Anti-Cancer Drugs, 7 (4), 437-460. (1996)
[26] Simeoni, M.; Magni, P.; Cammia, C.; De Nicolao, G.; Croci, V.; Pesenti, E.; Germani, M.; Poggesi, I.; Rocchetti, M. Cancer Research, 64 (3), 1094-1101. (2004)
[27] Goldie, J. H.; Coldman, A. J. Cancer Treat. Rep. 69(10), 1041-1045. (1985)
[28] Berenbaum, M. C. British journal of cancer, 23 (2), 426-33. (1969)
[29] Teicher, B. A. Molecular Cancer Therapeutics, 5 (10), 2435-2443. (2006)
[30] Wilcox, W. S.; Schabel, F. M., Jr.; Skipper, H. E. Cancer research, 26 (5), 1009-14. (1966)
[31] Pittillo, R. F.; Schabel, F. M., Jr.; Wilcox, W. S.; Skipper, H. E. Cancer chemotherapy reports. Part I, 47, 1-26. (1965)
[32] Vassal, G.; Boland, I.; Santos, A.; Bissery, M.-C.; Terrier-Lacombe, M.-J.; Morizet, J.; Sainte-Rose, C.; Lellouch-Tubiana, A.; Kalifa, C.; Gouyette, A. International Journal of Cancer, 73 (1), 156-163. (1997)
[33] Akanuma, A. European Journal of Cancer, 14 (16), 681-688. (1978)