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Control of Treatment in Tumor Dynamical Model with Hysteresis

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***Abstract*—We consider a problem of the treatment control combining chemotherapy and radiation therapy. In our mathematical analysis we use the dynamical model representing the Norton-Simon hypothesis in tumor cells behavior in presence of chemotherapy. For this model, the bifurcation analysis reveals three parametric zones: (i) monostability zone with the single stable equilibrium corresponding to active tumor; (ii) bistability zone with two coexisting stable equilibria associated with active and dormant tumor states; (iii) monostability zone with the single stable equilibrium regime of dormant tumor. So, the system exhibits specific features of a hysteresis. The results of this bifurcation analysis are used to study the effectiveness of treatment. A parametric diagram in variables associated with the maximum fractional cell kill and concentration of drugs is found for the description of system behavior in presence of chemotherapy. Strategies of treatment combining chemotherapy and radiation therapy are discussed. We show how presence of hysteresis should be taken into account when control treatment strategy is chosen.**

***Index Terms*—tumor dynamics, chemotherapy, hysteresis, control**

I. Introduction

A problem of the description of tumor dynamics and elaboration of the treatment strategies lies in a focus of modern science. Along with experimental studies, a lot of attention is paid to the mathematical modelling of tumor cells dynamics [1]–[5]. Mathematical models of tumor dynamics are actively used when strategies of treatment are chosen [6]–[8]. An understanding of the complex nonlinear tumor dynamics can be achieved through the detailed bifurcation analysis of the appropriate, even simple, mathematical models [9]. Here, an important role is played by the description of attractors, their basins, separatrices, zones of mono- and bistability. In this paper, we show how this analysis can be constructively used in the important problem of the effective control in the treatment program combining chemo- and radiotherapy.

II. Mathematical model of tumor dynamics

In this paper, we study an effect of the chemotherapeutic drugs with the concentration C on the tumor cells with the density $P(t)$ on the basis of the following model:

$$\frac{dP}{d\tau} = \beta + rP\left(1 - \frac{P}{K}\right) - rb\frac{K}{K+sP}\left(1 - e^{-\rho C}\right)P. \quad (1)$$

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Here, a logistic growth with carrying capacity K and rate r is used. A fractional cell kill is described by the term $b(1 - e^{-\rho C})$, where b represents the maximum fractional cell kill and ρ stands for the resistance of the tumor cells to the drugs. The maximum value at the carrying capacity is $r/(1+s)$, so the parameter s controls the Norton-Simon hypothesis. Here,in addition to the model suggested in [9], we suppose that there is a weak non-zero influx β of tumor cells.

After rescaling $x = P/K,\ t = r\tau,\ \alpha = \beta/(rK)$, we get the following model

$$\frac{dx}{dt} = \alpha + x\,(1-x) - \frac{b}{1+sx}\left(1 - e^{-\rho C}\right)x. \quad (2)$$

Further, we put $\alpha = 0.01, \rho = 1, s = 10$ and study system dynamics depending on the parameters b and C.

In absence of the therapy ($C = 0$), the concentration of tumor cells tends to the equilibrium value $\bar{x} = 0.5 + \sqrt{0.25+\alpha} \approx 1.01$ regardless of the initial value of $x(0)$. In the framework of this model, we refer such equilibrium as active tumor with unacceptable level of tumor cells.

III. Results. Control of treatment

Let us consider how the chemical therapy with increasing concentration C of drugs affects the changes in the concentration x of tumor cells for various b. The variation of b implies the transformation of the system from the monostable to bistable regime. Zones of the mono- and bistability of system (2) on the (C, b)-plane are presented in Fig.1. Here, $b_1 = 1.6884, b_2 = 3.1473$ and curves separating these zone are defined by equations

$$b_i(C) = \frac{b_i}{1 - \exp(-\rho C)}, \quad i = 1, 2. \quad (3)$$

In the bottom monostability zone (yellow color), the system (2) has the stable equilibrium $\bar{x}_1$ corresponding to the active tumor (AT). In the upper monostability zone (white color), the system (2) has the stable equilibrium $\bar{x}_2$ corresponding to the dormant tumor (DT). In the middle zone (blue color), the system (2) is bistable and possesses both equilibria $\bar{x}_1$ and $\bar{x}_2$ (AT+DT). Note that borders between these zones are defined by saddle-node bifurcations.

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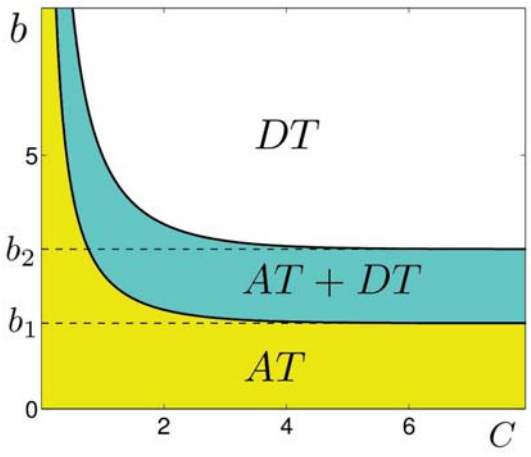

Fig. 1. Mono- and bistability zones of system (2). Here, $b_1 = 1.6884, b_2 = 3.1473$

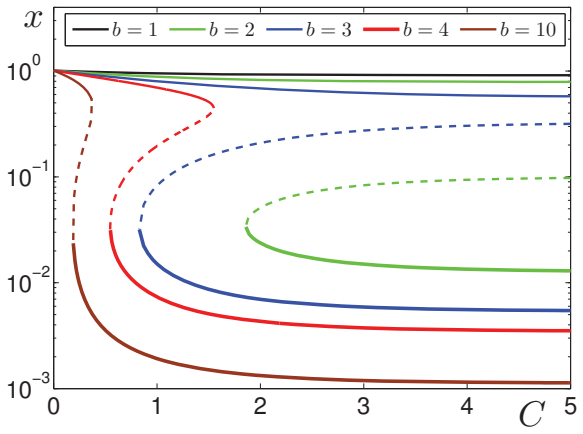

Fig. 2. Equilibria of system (2): stable (solid) and unstable(dashed).

In Fig.2, we plot stable (solid) and unstable (dashed) equilibria of the system (2) for several values of the parameter b versus parameter C.

For $0 < b < b_1$, for any C, the system (2) is monostable with the high concentration of tumor cells: for any initial data, tumor stabilizes to the equilibrium $\bar{x}_1(C)$ that is the active state (see, e.g., black curve for the parameter $b = 1$ which belongs to AT-zone).

As the parameter b passes the value b_1, the system becomes bistable: in the zone $AT + DT$, along with the equilibrium $\bar{x}_1$, a second stable equilibrium $\bar{x}_2$ appears. The value of $\bar{x}_2$ is several orders of magnitude smaller than $\bar{x}_1$, so the equilibrium $\bar{x}_2$ can be interpreted as a dormant tumor. Examples of such behavior are shown in Fig.2 for $b = 2$ (green) and $b = 3$ (blue).

A basin of attraction of the dormant tumor is separated from the active tumor by the unstable equilibrium $\tilde{x}$ (dashed line). Dynamics of this bistable system depends on the initial value of the concentration x_0 of tumor cells. If $x_0 < \tilde{x}$, then the concentration $x(t)$ of tumor cells under increasing t tends to the state $\bar{x}_2$ of the dormant tumor. Otherwise, for $x_0 > \tilde{x}$, the system transits to the state $\bar{x}_1$ of the active tumor. So, for $b_1 < b < b_2$, the increasing C results in the transition from monostability AT-zone to the bistability $AT + DT$-zone.

When the parameter b becomes greater than b_2, under increasing C one can observe more complex transitions: monostability AT-zone $\rightarrow$ bistability $AT + DT$-zone $\rightarrow$ monostability DT-zone (see Fig.1). These double transitions result in the appearance of the hysteresis. Examples of such hysteresis curves are shown in Fig.2 for $b = 4$ (red) and $b = 10$ (brown).

Consider now an effectiveness of the drug therapy in dependence on the parameter b that characterizes the intensity of the influence of drugs on the tumor cell kill.

For $0 < b < b_1$, as shown above, even large doses of drugs only slightly decrease the level of tumor cells. This means that drug therapy with such value of the parameter b is not able to push the system out of the active tumor state.

Some strategies of the treatment taking in account the bistability can be suggested. Here, two zones of the parameter b should be distinguished: $b_1 < b < b_2$ and $b > b_2$.

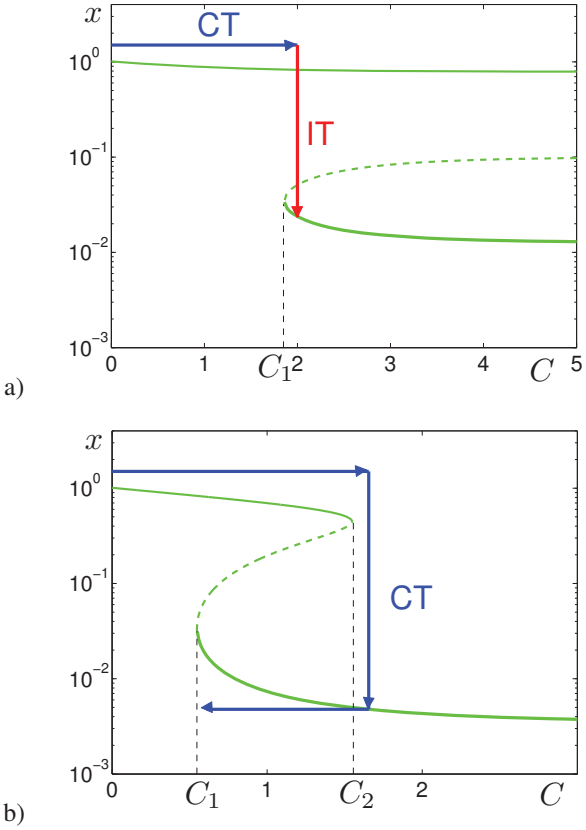

Fig. 3. Two variants of treatment for a) $b = 2$, b) $b = 4$.

Consider in details the first case $b_1 < b < b_2$, for example, with $b = 2$. In Fig.3a, zones of mono- and bistability are detached by the point $C_1 = 1.8592$. For $C < C_1$, the system is

monostable and independently of the initial value x_0 stabilizes in the state $\bar{x}_1$ of the active tumor. For $C > C_1$, the system is bistable, and two stable states of the active and dormant tumor coexist.

In absence of chemotherapy ($C = 0$), the concentration of tumor cells is high. As can be seen in Fig.3a (upper green curve), a significant increase of the drug concentration C only slightly decreases the concentration of tumor cells x. It means that even intensive chemotherapy can not remove the system from the unwanted regime of the active tumor. In these circumstances, the treatment that combines the chemotherapy (CT) and the impulse (radiation) therapy (IT) may provide a positive result. The radiation therapy has an extremely hard effect on living tissues. It allows to decrease sharply the concentration of tumor cells but has many side effects, so it is used when chemotherapy alone is already ineffective.

In our conceptual study, we restrict ourselves by a case of the single use of the radiation therapy. Note that the impulse radiation therapy for $C < C_1$ is meaningless: in this zone of monostability, even after a sharp decrease of the concentration x, the tumor returns to the active state.

Here, the following constructive strategy of the treatment can be suggested. First, we transfer the system from the monostability zone to the bistability zone using the chemotherapy with the drug concentration, for example, $C = 2 > C_1$ (see blue arrow in Fig.3a). Further, we apply the intensive impulse therapy which allows to decrease sharply the concentration of tumor cells (see red arrow in Fig.3a). An intensity of the impulse therapy should be chosen so as to obtain $x < \tilde{x}$, where $\tilde{x}$ is the unstable equilibrium (green dashed line). Then, being in the basin of attraction of the stable equilibrium $\bar{x}_2$ corresponding to the dormant tumor, we continue to provide the drug therapy with $C = 2$. This allows us to keep the system in the state of the dormant tumor. Note that in this regime, it makes no sense to increase the dose of drugs, since this practically does not reduce the concentration of tumor cells (lower green curve in Fig.3a).

Here, it is interesting to compare two programs of the treatment (see plan A in Fig.4a and plan B in Fig.4b). In the top panel, temporal programs of the treatment are shown in blue. We suppose that in the interval $0 < t < T_C$ the concentration of drugs is $C = 0$, and the treatment starts at the time $t = T_C$: for $t > T_C$, the concentration of drugs is $C = 2$. These programs of chemotherapy are the same in Fig.4a and Fig.4b. The difference is only in the points in time when the impulse therapy is applied (marked by red triangles). In the plan A, the impulse therapy is applied before the chemotherapy starts ($T_R < T_C$), and in the plan B the impulse therapy is applied after the chemotherapy starts ($T_R > T_C$).

In the bottom panel, results of these two treatment programs are shown (result A and result B). It is supposed again that the initial state of the system is $x_0 = \bar{x}_1(0)$.

Result A shows that the impulse therapy gives a sharp decrease of the tumor cells, however in absence of the chemotherapy, the population of tumor cells is quickly restored to its original active state. In these circumstances, the subsequent chemotherapy can not remove the system from this active state.

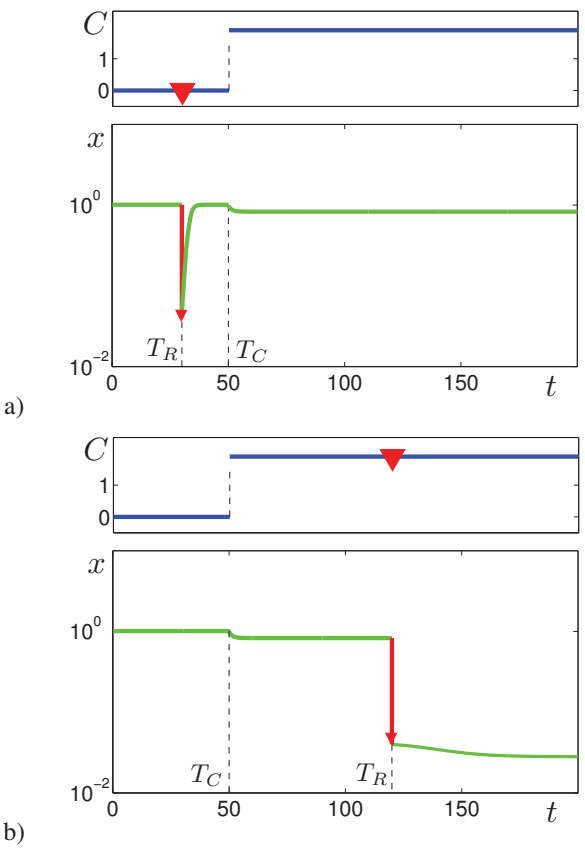

Fig. 4. Two programs of treatment in system (2) with $b = 2$.

Result B with another impulse point in time is much more positive. At first glance, the chemotherapy $C = 2$ applied at T_C is ineffective, since the concentration of tumor cells decreases slightly. However, after the application of the same intensity of the impulse therapy, as in the plan A, the same level $C = 2$ of the chemotherapy keeps the system in the dormant state.

Consider now the case $b > b_2$ where the bistability zone has a hysteresis form. This case is illustrated in the Fig.3b for $b = 4$. Here, the bistability zone is (C_1, C_2) where $C_1 = 0.5483$ and $C_2 = 1.5456$ are saddle-node bifurcation points. For $0 < C < C_1$, the system is monostable and possesses the single stable equilibrium $\bar{x}_1$ corresponding to the active tumor. In the zone $C_1 < C < C_2$, the system is bistable and possesses two stable equilibria $\bar{x}_1$ and $\bar{x}_2$ corresponding to the active and dormant tumor. For $C > C_2$, the system is monostable and exhibits the single stable equilibrium $\bar{x}_2$ corresponding to the dormant tumor. In the zone of the bistability, basins of attraction of dormant and active tumor are separated by the unstable equilibrium $\tilde{x}$ (green dashed line).

In absence of chemotherapy ($C = 0$), the concentration of tumor cells is high. Under gradual increasing drug concentration C till C_2, the system continues to be in the active

tumor state although the concentration of tumor cells slightly decreases. When the drug dose exceeds C_2, the system exhibits a sharp fall down to the regime of the dormant tumor state (see Fig.3b). A further increase of C is meaningless because the concentration of tumor cells almost does not change.

It is interesting to see what will happen if we will further reduce C. First, due for hysteresis, the system remains in the dormant tumor state (lower branch) until $C = C_1$. When C becomes less than C_1, the system exhibits a sharp jump up to the regime of the active tumor. This is the characteristic feature of the hysteresis-type behavior. Thus, the transition of the system from the active to dormant tumor can be achieved without intensive impulse therapy. Indeed, for example, by increasing C up to $C = 1.6 > C_2$, we transfer the system to the zone with the dormant tumor only (see upper and vertical blue arrows in Fig.3b). After that, a dose of drugs can be decreased, for example, to $C = 0.8$ (see lower arrow), but the system still stays in the regime of the dormant tumor. This program of treatment without impulse therapy is illustrated in detail in Fig.5a.

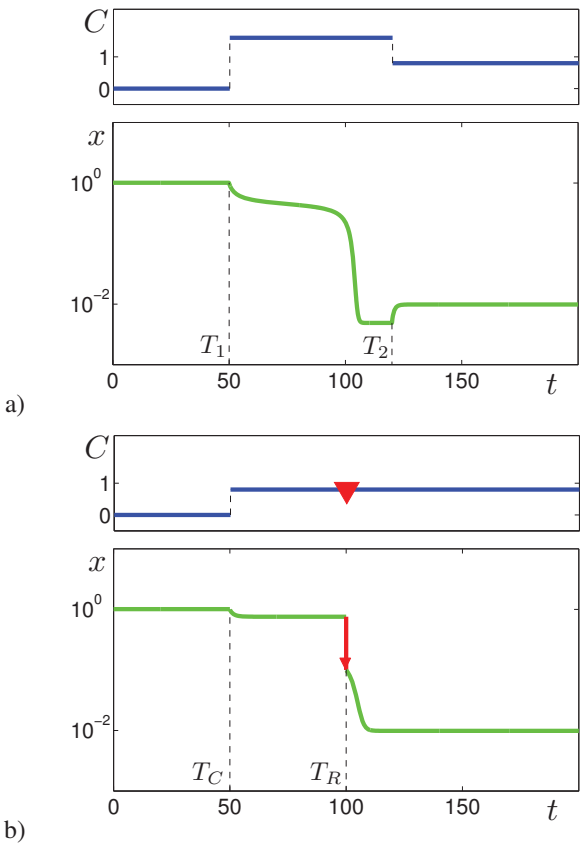

Fig. 5. Two programs of treatment in system (2) with $b = 4$.

Here, in the top panel, a temporal program of the treatment is shown in blue. We suppose that in the interval $0 < t < T_1$ the concentration of drugs is $C = 0$, and the treatment with the drug intensity $C = 1.6$ starts at the point of time $t = T_1$ and continues up to T_2. At the point T_2, we reduce the drug concentration till $C = 0.8$. In the bottom panel, we show results of this chemotherapy. As can be seen, this program reduces the concentration of tumor cells in two orders. The same result can be achieved by the chemotherapy with the lower concentration of drugs $C = 0.8$ and one application of the low dose impulse therapy at $t = T_R$ (see Fig.5b). So, the peculiarities of the mutual arrangement of attractors and their basins play an important role in the choice of the reasonable control strategy in treatment.

IV. Discussion and Conclusion

The vital problem of cancer treatment was considered on the base of the dynamical model following Norton-Simon hypothesis. In the process of treatment, it is important to choose the reasonable strategy combining chemotherapy and radiation therapy. In the present paper, it was shown that this strategy depends on the specific features of the tumor dynamics connected with bistability in the hysteresis form. Mathematical analysis of the treatment control is based on the description of attractors, their basins, and bifurcations. It was also shown how these mathematical results can be effectively used in the choice of the time protocol for the treatment program combining chemo- and radiotherapy. It is highly important to develop such type analysis for higher-dimensional models that take into account the interaction of tumor cells with the immune system in the presence of unavoidable random disturbances.

References

[1] D. Wodarz and N. L. Komarova, "Dynamics of cancer: mathematical foundations of oncology," World Scientific Publishing, 2014.
[2] N. Bellomo, N. K. Li, and P. K. Maini, "On the foundations of cancer modelling: selected topics, speculations, and perspectives," Math. Models Methods Appl. Sci., vol. 18, pp. 593–646, 2008.
[3] L.G. De Pillis and A. Radunskaya, "The dynamics of an optimally controlled tumor model: a case study," Math. Comput. Model., vol. 37, pp. 1221–1244, 2003.
[4] Á. G. López, J. M. Seoane, and M.A.F. Sanjuán, "Bifurcation analysis and nonlinear decay of a tumor in the presence of an immune response," Int. J. Bifurc. Chaos, vol. 27, p. 1750223, 2017.
[5] I. Bashkirtseva and L. Ryashko, "Analysis of noise-induced phenomena in the nonlinear tumor–immune system," Physica A, 2019, in press, https://doi.org/10.1016/j.physa.2019.123923.
[6] A. D'Onofrio, A. Gandolfi, and S. Gattoni, "The Norton-Simon hypothesis and the onset of non-genetic resistance to chemotherapy induced by stochastic fluctuations," Physica A, vol.391, pp. 6484–6496, 2012.
[7] P. A. Valle, K. E. Starkov, and L. N. Coria, "Global stability and tumor clearance conditions for a cancer chemotherapy system," Commun. Nonlinear Sci. Numer. Simul., vol.40, pp. 206–215, 2016.
[8] A. J. Coldman and J. M. Murray, "Optimal control for a stochastic model of cancer chemotherapy," Math. Biosci., vol.168, pp.187–200, 2000.
[9] Á. G. López, K. C. Iarosz, A. M. Batista, J. M. Seoane, R. L. Viana, and M.A.F. Sanjuán, "Nonlinear cancer chemotherapy: Modelling the Norton-Simon hypothesis," Commun. Nonlinear Sci. Numer. Simulat., vol. 70, pp. 307–317, 2019.