MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **9**, Number **2**, April **2012**

doi:10.3934/mbe.2012.9.241

pp. **241–257**

DELAY EQUATIONS MODELING THE EFFECTS OF PHASE-SPECIFIC DRUGS AND IMMUNOTHERAPY ON PROLIFERATING TUMOR CELLS

Maria Vittoria Barbarossa, Christina Kuttler and Jonathan Zinsl

Zentrum Mathematik, Technische Universität München
Boltzmannstr. 3, 85748 Garching b. München, Germany

(Communicated by Stephen Gourley)

Abstract. In this work we present a mathematical model for tumor growth based on the biology of the cell cycle. For an appropriate description of the effects of phase-specific drugs, it is necessary to look at the cell cycle and its phases. Our model reproduces the dynamics of three different tumor cell populations: quiescent cells, cells during the interphase and mitotic cells. Starting from a partial differential equations (PDEs) setting, a delay differential equations (DDE) model is derived for an easier and more realistic approach. Our equations also include interactions of tumor cells with immune system effectors. We investigate the model both from the analytical and the numerical point of view, give conditions for positivity of solutions and focus on the stability of the cancer-free equilibrium. Different immunotherapeutic strategies and their effects on the tumor growth are considered, as well.

1. **Introduction.** For years cancer has been a reason for a dramatically high mortality rate in populations. In the last century, enormous efforts have been made by medical doctors, biologists and radiologists in order to understand, treat and cure this disease ([25]). Recently, contributions have also been given by the mathematical biology, with theoretical models for the description and the comprehension of tumor growth. One common idea to almost all these models is the classification of tumor cells in three groups (Fig. 1): necrotic cells (which are dead and located in the most internal part of the solid tumor), quiescent cells (are not dead, but have not enough nutrients for cell growth or division), proliferating cells (the active part, they undergo mitosis). The interested reader can find a review e.g. in [20].

A large class of models for cancer growth focuses on the dynamics of proliferating cells, which are responsible for the extension of the tumoral mass. In particular cell aging and cell cycle (Fig. 2) have been considered in many and different approaches ([12, 13, 16, 26]). The processes of cell aging and cell division can indeed not be neglected when investigating tumor proliferation. All eukaryotic cells undergo the *cell cycle*, a sequence of four phases ([2, 17]). The G_1 *phase* is necessary for the cell to grow up, before the DNA is replicated in the S *phase*. A second growth phase (G_2) follows and the *mitotic phase* (M) concludes the cycle, with division of nucleus and cytoplasm. As a result of a completed sequence, two daughter cells enter the

2000 *Mathematics Subject Classification.* Primary: 34K17, 92B05; Secondary: 92C50.

Key words and phrases. Delay differential equations, tumor, cell cycle, phase-specific drugs, G_0, G_1, immune system, chemotherapy, immunotherapy.

The first author gratefully acknowledges the support of the TUM's Faculty Graduate Center ISAM at Technische Universität München.

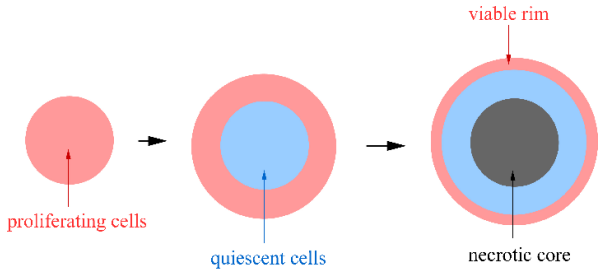


FIGURE 1. Schematic illustration of the different stages of tumor growth.

cycle in G_1. The first three phases are often summed up together and referred to as '*interphase*'. In order to guarantee an error-free replication, there is a biochemical control system which verifies at five different *checkpoints* whether the processes at each phase of the cell cycle have been accurately completed before progression into the next phase. If anything did not work properly, the cycle stops.

Cells may also enter the so-called G_0 *state* in which they live in a quiescent state, neither growing nor dividing. It usually happens that cells lacking growth factors stop at a checkpoint, move from G_1 to G_0 and start the cycle again after a certain time ([8]).

One of the main reasons for cancer is a malfunction of the control system, which leads to uncontrolled growth of a group of cells. In this work we give a mathematical model for tumor growth based on the dynamics of the cell cycle. For a better

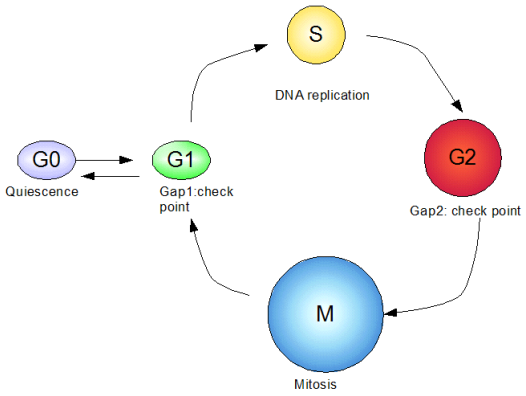


FIGURE 2. Scheme of the cell cycle, its phases and checkpoints.

representation of the real-life problems, many biological phenomena are described by mathematical models which include time delays ([18, 24]). In our model equations (Section 2) a constant delay τ describes the length of the interphase. A similar modeling approach has also been used in [16] and [26]. In both works, mathematical models were developed using the mass action principle, which combined with the delay equation approach leads to incorrectness in the equations. In contrast, we derive our model from a renewal equation, which in turn corresponds to a set of

differential equations with delay ([5, 19]). As a further improvement on the existing delay models, we can also ensure positivity of solutions, choosing the initial functions from a proper set of initial data (Section 3). In Section 4 we present the analysis of the dynamical system, with particular attention to the stability of the tumor-free state. Section 5 is dedicated to the numerical simulation of the model. In Section 6 we investigate the interplay between tumor cells and immune-system effectors. We also simulate the effects of different immunotherapeutic cures on the tumor.

2. **The mathematical model.** To the knowledge of the authors, two mathematical models with delay have been written to date to describe the effects of phase-specific drugs on a solid tumor. The first approach by Villasana and Radunskaya [26] describes proliferating tumor cells which undergo chemotherapy and interact with immune-system effectors. Liu et al. [16] modified and extended the model in [26] including a resting state for the tumoral cells.

A standard delay model for an immature population (x_1) and a mature one (x_2) has the structure ([4, 19]):

$$\begin{aligned} \dot{x}_1(t) &= r_1(t) - m_1(t) - d_1(t), \\ \dot{x}_2(t) &= r_2(t) - m_2(t) - d_2(t), \end{aligned} \tag{1}$$

where r_i, m_i, d_i are respectively recruitment, maturation and death factors of population x_i. Recruitment in x_1 is mostly given by a birth function, whereas in x_2 it occurs by maturation only ([19]). Nisbet et al. ([14, 19, 4]) showed that $m_1(t) = r_2(t)$ is indeed a function of $x_2(t-\tau)$, where $\tau > 0$ is the maturation time.

Although modeling basically an immature (interphase cells) and a mature (mitotic cells) population, the system in [16] does not show the standard setting (1): the maturation term m_1 in the immature population equation is undoubtedly missing. In the authors' opinion it should therefore be corrected.

Considering the biology of the cell cycle (Section 1), in the following we derive a DDE model for tumor growth, respecting the standard structure (1).

Our starting point is a tumoral cell population structured by age. Let $p(a,t)$ be the density of proliferating cells in age-class a at time t. For this population, the Lotka-Sharpe model ([22]) is used:

$$\begin{aligned} p_t(a,t) + p_a(a,t) &= -\mu(a)p(a,t), \\ p(0,t) &= \int_0^\infty b(a)p(a,t)\,da, \\ p(a,0) &= \psi_0(a). \end{aligned} \tag{2}$$

System (2) describes the aging process of individuals, with an age-dependent birth-law, given an initial age distribution ψ_0 ([22, 27]). In (2), both birth and death rate do only depend on the age of the individuals. We assume here that these rates are piece-wise constant functions of the age:

$$\begin{aligned} b(a) &= b_1 H_\tau(a), \\ \mu(a) &= \mu_0 + (\mu_1 - \mu_0)H_\tau(a), \end{aligned} \tag{3}$$

where $H_\tau(a)$ is the Heaviside function with jump at $a = \tau$ and $b_1 > 0$, $\mu_0 \geq 0$, $\mu_1 > 0$ are real, nonnegative constants. The value τ corresponds to the length in time of the interphase. Thus, (3) means that interphase cells do not divide and die at rate μ_0, mitotic cells divide at rate b_1 and die at rate μ_1. Even though the interphase duration may be affected by few factors (e.g. drugs concentration [21]),

Variable	Description
$Q(t)$	Number of quiescent (G_0) cells at time t
$U(t)$	Number of mitotic cells at time t
$V(t)$	Number of interphase (G_1, S and G_2) cells at time t
$I(t)$	Number of lymphocytes at time t
$D(t)$	Drug concentration at time t

TABLE 1. List of variables used for the mathematical model.

for the sake of simplicity we assume that τ is a constant value. The biology suggests that τ is nonnegative and bounded, i.e. there exist $\tau_{min} \geq 0$ and $\tau_{max} < \infty$ such that $\tau_{min} \leq \tau \leq \tau_{max}$ holds.

Following the approach introduced in [5], we define the following three populations of cells:

- $V(t) = \int_0^\tau p(a,t)\,da$, the total number of cells in G_1, S and G_2 (interphase). Interphase cells cannot divide, become quiescent at rate μ_Q, die at rate μ_0.
- $U(t) = \int_\tau^\infty p(a,t)\,da$, the total population of mitotic cells. These cells divide at rate b_1 and die at rate μ_1. The biological meaning of the parameters requires $\mu_1 > b_1$.
- $Q(t)$, the total amount of G_0 cells at time t. Quiescent cells do not age, do not divide ([17]). They die at rate μ_{G_0} or enter the cycle again (at rate b_Q), starting from G_1 ([8]).

A list of the model variables is to find in Table 1. Without loss of generality, we consider a time $t > a$ and write the renewal equation for $p(a,t)$:

$$\begin{aligned} p(a,t) &= p(0,t-a)e^{-\int_0^a \mu(s)\,ds} \\ &= p(0,t-a)e^{-\int_0^\tau \mu_0+\mu_Q\,ds}e^{-\int_\tau^a \mu_1\,ds} \\ &= p(0,t-a)e^{-(\mu_0+\mu_Q)\tau}e^{-\mu_1(a-\tau)}. \end{aligned} \tag{4}$$

The birth law for $V(t)$ reads:

$$\begin{aligned} p(0,t) &= \underbrace{\int_0^\infty b(a)p(a,t)\,da}_{\text{result of mitosis}} + \underbrace{b_Q Q(t)}_{\text{from quiescence}} \\ &= 2b_1U(t) + b_Q Q(t). \end{aligned} \tag{5}$$

Substitution in (4) leads to:

$$p(a,t) = \left[2b_1U(t-a) + b_Q Q(t-a)\right] e^{-(\mu_0+\mu_Q)\tau}e^{-\mu_1(a-\tau)}. \tag{6}$$

The total mitotic population at time t is then:

$$U(t) = \int_\tau^\infty \left[2b_1U(t-a) + b_Q Q(t-a)\right] e^{-(\mu_0+\mu_Q)\tau}e^{-\mu_1(a-\tau)}\,da. \tag{7}$$

Differentiation with respect to the time t yields:

$$\dot{U}(t) = \underbrace{\left[2b_1U(t-\tau) + b_Q Q(t-\tau)\right] e^{-(\mu_0+\mu_Q)\tau}}_{\text{maturation}} - \underbrace{\mu_1 U(t)}_{\text{dead cells}}. \tag{8}$$

Equation (8) describes the evolution in time of the mitotic cells population: mitotic cells at time t are those which have been generated by mitosis or came from the

quiescent phase at time $t-\tau$ and did not die nor exit the cycle in $[t-\tau, t]$. The term $\mu_1 U(t)$ expresses the natural death of the mitotic cells. Analogously, we derive a differential equation for interphase cells:

$$\dot{V}(t) = \underbrace{2b_1U(t)}_{\text{from mitosis}} - \underbrace{(2b_1U(t-\tau) - b_QQ(t-\tau))\, e^{-(\mu_0+\mu_Q)\tau}}_{\text{maturation}} + \underbrace{b_QQ(t)}_{\text{from quiescence}} - \underbrace{\mu_0V(t)}_{\text{dead cells}} - \underbrace{\mu_QV(t).}_{\text{enter quiescence}} \tag{9}$$

The dynamics of quiescent cells is easy to derive, for it is not characterized by age-dependent factors:

$$\dot{Q}(t) = \underbrace{\mu_QV(t)}_{\text{enter quiescence}} - \underbrace{b_QQ(t)}_{\text{start the cycle}} - \underbrace{\mu_{G_0}Q(t).}_{\text{death of } G_0\text{-cells}} \tag{10}$$

This basic model (8)-(10) can be extended by including drugs and immune system agents (a summarizing scheme in Figure 3):

$$\dot{Q}(t) = \mu_QV(t) - b_QQ(t) - \mu_{G_0}Q(t) - k_QI(t)Q(t), \tag{11}$$

$$\dot{U}(t) = (2b_1U(t-\tau) + b_QQ(t-\tau))e^{-(\mu_0+\mu_Q)\tau - k_0\int_0^\tau I(t-\tau+\sigma)d\sigma} - U(t)(\mu_1 + k_2I(t) + k_5(1-e^{-k_3D(t)})), \tag{12}$$

$$\dot{V}(t) = 2b_1U(t) + b_QQ(t) - V(t)(\mu_0+\mu_Q+k_0I(t)) - (2b_1U(t-\tau) + b_QQ(t-\tau))e^{-(\mu_0+\mu_Q)\tau - k_0\int_0^\tau I(t-\tau+\sigma)d\sigma}, \tag{13}$$

$$\dot{I}(t) = k + \rho I(t)\frac{(Q(t)+U(t)+V(t))^n}{\alpha + (Q(t)+U(t)+V(t))^n} - \delta_4I(t) - (c_1Q(t) + c_2U(t) + c_3V(t))I(t) - k_6(1-e^{-k_7D(t)})I(t), \tag{14}$$

$$\dot{D}(t) = -\gamma D(t). \tag{15}$$

Tumor cells are attacked by the immune system: e.g. the term $-k_QI(t)Q(t)$ in (11) models the death of tumoral quiescent cells due to immune system effectors. Similar holds for equations (12) and (13). The terms $e^{-(\mu_0+\mu_Q)\tau}$ and $e^{-k_0\int_0^\tau I(t-\tau+\sigma)d\sigma}$ in (12) describe the probabilities that an interphase cell survives for a period τ, neither becoming quiescent, nor being attacked by the immune system. Further we consider the effects of chemotherapy: the phase-specific drug attacks mitotic tumor cells only. The impact of the drug on the mitotic cells is described by $-U(t)k_5(1-e^{-k_3D(t)})$, where $(1-e^{-k_3D(t)})$ is the probability of tumor-drug interaction. We assume that the drug kills lymphocytes as well, therefore a similar term is to be found in equation (14). The chemotherapeutic treatment is assumed to be a one-time injection at time $t=0$. Drug usage and decay occur at constant loss rate γ ([16, 26]). For the immune system agents we assume that there is a constant production rate k, even in the tumor-free state. In presence of tumor cells, the lymphocyte production is stimulated. Interaction with tumor cells leads to immune system cells loss ([10]).

3. **Nonnegative solutions.** In this Section we give conditions for positivity of the basic delay model (8)-(10). Similar considerations could be done for the extended system (11)-(15) (results not shown here).

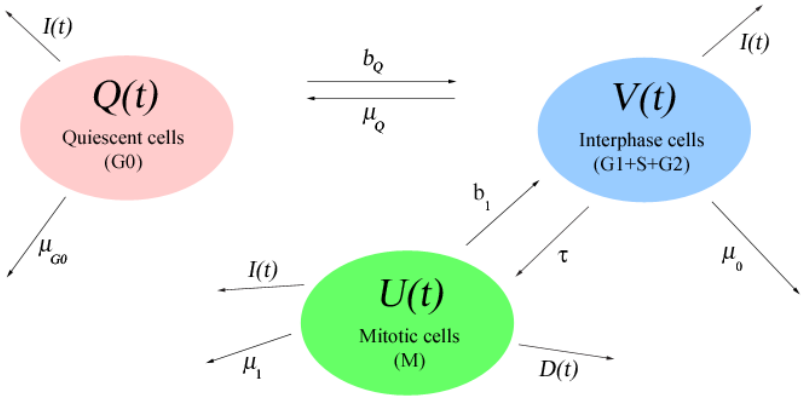


FIGURE 3. Schematic illustration of the mathematical model.

3.1. **The proper initial data.** We consider now the simple delay model (8)-(10) for tumoral cells only. This system holds for all $t \geq \tau$. The challenge at this point is to define what happens for a time $t < \tau$.

We go back for a moment to the PDE model (2). For $t < \tau$, the solution of the balance-equation requires information on the initial distribution $\psi_0(a)$. At this point we recall that only interphase and mitotic cells are age-structured populations. Quiescent cells do not age, indeed ([17]).

Let us define

$$u_0(s) := \psi_0(s), \ \ s < \tau. \tag{16}$$

We indicate by $u_0(\tau - t)$ the density of cells of age $\tau - t$ at time 0. At time t these cells will be of age τ and, consequently, enter the mitotic class. As we are dealing with initial distributions, the previous consideration only holds for the structured populations, thus there is no similar term for the quiescent cells. Quiescent cells enter the cycle form G_1, so we believe them to be of "age zero" when they re-enter the cycle. A quiescent cell which re-enters the cycle should spend a time τ in the interphase, before passing to the mitotic phase. This does not happen for $t < \tau$. All in all, for $t < \tau$ the model equations read:

$$\begin{aligned} \dot{V}(t) &= 2b_1 U(t) + b_Q Q(t) - u_0(\tau - t)e^{-(\mu_0+\mu_Q)t} - (\mu_0 + \mu_Q)V(t), \\ \dot{U}(t) &= u_0(\tau - t)e^{-(\mu_0+\mu_Q)t} - \mu_1 U(t), \\ \dot{Q}(t) &= \mu_Q V(t) - (b_Q + \mu_{G_0})Q(t). \end{aligned} \tag{17}$$

This system gives the appropriate description of the phenomenon in $[0, \tau]$ and it is thus the correct expression of the initial data. Still, there is an inconvenience: the solution of (17) depends on the initial data of the age-structured problem (2). This is the next point we are going to discuss.

3.2. **Nonnegativity of solutions.** A recurrent challenge in mathematical biology is given by the fact that solutions are not allowed to leave the positive cone or a part of it. Although being more and more used in applications, systems of delay equations may show negative solutions, even when the initial data are nonnegative

([24]). In population dynamics, problems concerning nonnegativity of solutions were already considered e.g. in [1, 5].

The first delay model for tumor growth ([26]) was questioned by Liu et al. ([16]) mainly because it was showing negative solutions in positive time. In [16] the authors gave an alternative system whose structure guarantees positive solutions (cf. [24], Chapter 3). We discussed in Section 2 the reasons why also this second model needs to be improved. However, both our simplified model (8)-(10) and extended model (11)-(15) do not respect the condition given in [24] and thus do not ensure positivity of solutions. We could derive the proper initial system (17) which gives the required information of the initial interval $[0,\tau]$, but we noticed as well that this system depends on the initial distribution $\psi_0(a)$ of (2). If the initial age-distribution is known, one can compute the solution of the initial system (17) and use it as history function for the DDE problem. In this case, positivity is preserved and guaranteed from the well-posedness of the PDE problem ([22, 27]) and the formal derivation of the ODE (17) and DDE (8)-(10) problems. Difficulties arise when we do not know the initial distribution ψ_0. In this case we have to define a set of "good" initial-functions which guarantee preservation of positivity for the solutions of the delay model. We proceed as it was done in [5] for a simpler problem.

Consider the second equation of (17) and transform it as follows:

$$\begin{aligned} \dot{U}(t)+\mu_1 U(t) &= u_0(\tau-t)e^{-(\mu_0+\mu_Q)t}, \\ \frac{d}{dt}\left(U(t)e^{\mu_1 t}\right)e^{(\mu_0+\mu_Q-\mu_1)t} &= u_0(\tau-t). \end{aligned} \tag{18}$$

Condition (18) means that $U(t)e^{\mu_1 t}$ is a nondecreasing function in $[0,\tau]$. Further, integration in $[0,\tau]$ yields:

$$\begin{aligned} \int_0^\tau \frac{d}{dt}\left(U(t)e^{\mu_1 t}\right)e^{(\mu_0+\mu_Q-\mu_1)t}\,dt &= \int_0^\tau u_0(\tau-t)\,dt, \\ U(\tau)e^{(\mu_Q+\mu_0)\tau}-U(0)-\int_0^\tau U(t)e^{(\mu_Q+\mu_0)t}(\mu_0+\mu_Q-\mu_1)\,dt &= \int_0^\tau u_0(z)\,(dz). \end{aligned}$$

So we get:

$$V(0)=U(\tau)e^{(\mu_0+\mu_Q)\tau}-U(0)-(\mu_0+\mu_Q-\mu_1)\int_0^\tau U(t)e^{(\mu_0+\mu_Q)t}\,dt \tag{19}$$

Substitution of the term $u_0(\tau-t)e^{-(\mu_0+\mu_Q)t}$ in $\dot{V}(t)$ yields:

$$\dot{V}(t)=(2b_1-\mu_1)U(t)+b_Q Q(t)-\dot{U}(t)-(\mu_0+\mu_Q)V(t). \tag{20}$$

We solve (20) using variation of constants method and integration by parts and get

$$\begin{aligned} V(t) &= (U(0)+V(0))e^{-(\mu_Q+\mu_0)t}-U(t)+b_Q\int_0^t Q(x)e^{(\mu_0+\mu_Q)(t-x)}\,dx \\ &\quad +(2b_1+\mu_0+\mu_Q-\mu_1)\int_0^t U(x)e^{-(\mu_0+\mu_Q)(t-x)}\,dx. \end{aligned} \tag{21}$$

The third equation of (17) is an ODE, so we have no problem with it, as long as we choose a nonnegative initial value $Q(0)$. The explicit solution for Q is:

$$Q(t)=Q(0)e^{-(b_Q+\mu_{G_0})t}+\mu_Q\int_0^t V(s)e^{(b_Q+\mu_{G_0})(s-t)}\,ds. \tag{22}$$

We define an operator $T : C[0,\tau] \to C[0,\tau]$ so that $(TU)(t) = V(t)$, $t \in [0,\tau]$ and $V(t)$ is given by (21) with $V(0)$ as in (19). At this point we dispose of all elements to define the cone

$$\begin{aligned}\mathcal{K} \quad := \quad & \left\{(V,U,Q) \in (C[0,\tau])^3 : U(0) \geq 0,\, U(t)e^{\mu_1 t} \text{ is nondecreasing in } [0,\tau],\right. \\ & \left. V = TU,\, Q(0) \geq 0\right\}. \end{aligned} \tag{23}$$

Let us sum up the results in the following

Proposition 1. *Consider (2) with the restriction of the initial function (16). The functions $V(t), U(t), Q(t)$ defined in Section 2 satisfy (17) for $t \in [0,\tau]$ and $(V_{[0,\tau]}, U_{[0,\tau]}, Q_{[0,\tau]}) \in \mathcal{K}$.*
Conversely, for functions $(\tilde{V}, \tilde{U}, \tilde{Q}) \in \mathcal{K}$ there is an initial distribution $\psi_0(a) \geq 0$ such that the solution (V,U,Q) of (17) restricted to $[0,\tau]$ corresponds to $(\tilde{V}, \tilde{U}, \tilde{Q})$, i.e. $(V_{[0,\tau]}, U_{[0,\tau]}, Q_{[0,\tau]}) = (\tilde{V}, \tilde{U}, \tilde{Q})$.

4. Stability results.

For biomedical reasons, it is important to look at the long-time behavior of tumoral cell populations. In this Section we investigate the stability of the cancer-free steady state and determine conditions on the model parameters for tumor growth or eradication. As next we analyze the model without delay, then we investigate the (de)stabilizing effects of τ.

4.1. System without delay.

In the following we investigate the ODE system ($\tau = 0$) corresponding to (11)-(15).

4.1.1. *Simple model: Tumor cells, no immunotherapy, no chemotherapy.* For a first investigation, we observe the tumor cells only, neglecting both immunotherapy and chemotherapy. The simplified model reads:

$$\dot{Q}(t) = \mu_Q V(t) - (b_Q + \mu_{G_0})Q(t), \tag{24}$$

$$\dot{U}(t) = 2b_1 U(t) + b_Q Q(t) - \mu_1 U(t), \tag{25}$$

$$\dot{V}(t) = -(\mu_0 + \mu_Q)V(t). \tag{26}$$

This is a linear system with the only stationary state $P_3^* := (0,0,0)$. To check for stability, we calculate the eigenvalues of the coefficient matrix

$$A := \begin{pmatrix} -(b_Q + \mu_{G_0}) & 0 & \mu_Q \\ b_Q & 2b_1 - \mu_1 & 0 \\ 0 & 0 & -(\mu_0 + \mu_Q) \end{pmatrix}. \tag{27}$$

The roots of the characteristic equation are

$$\lambda_1 = -b_Q - \mu_{G_0}, \tag{28}$$

$$\lambda_2 = 2b_1 - \mu_1, \tag{29}$$

$$\lambda_3 = -\mu_0 - \mu_Q. \tag{30}$$

It is trivial to see that all roots are real and that $\lambda_1 < 0$ and $\lambda_3 < 0$. All in all:

Proposition 2. *The stationary state P_3^* is locally asymptotically stable, if $b_1 < \frac{\mu_1}{2}$ holds.*

This means that, if the death rate μ_1 of the mitotic cells is large compared to the division rate b_1, the tumor will vanish at a point.

4.1.2. *Model with immunotherapy, no chemotherapy.* In this paragraph, we include immunotherapeutic effects into the basic ODE model (24)-(26):

$$\dot{Q}(t) = \mu_Q V(t) - b_Q Q(t) - \mu_{G_0} Q(t) - k_Q I(t) Q(t), \tag{31}$$

$$\dot{U}(t) = 2b_1 U(t) + b_Q Q(t) - U(t)(\mu_1 + k_2 I(t)), \tag{32}$$

$$\dot{V}(t) = -V(t)(\mu_0 + \mu_Q + k_0 I(t)), \tag{33}$$

$$\begin{aligned}\dot{I}(t) = k + \rho I(t) \frac{(Q(t)+U(t)+V(t))^n}{\alpha + (Q(t)+U(t)+V(t))^n} \\ - \delta_4 I(t) - (c_1 Q(t) + c_2 U(t) + c_3 V(t)) I(t).\end{aligned} \tag{34}$$

Since our interest focuses on tumor growth (or eradication) in the long-time behavior, we investigate the stability of the cancer-free equilibrium $P_4^* := (0, 0, 0, \frac{k}{\delta_4})$. The Jacobian matrix at the stationary point is:

$$B := J(P_4^*) = \begin{pmatrix} -(b_Q + \mu_{G_0} + \frac{k_Q k}{\delta_4}) & 0 & \mu_Q & 0 \\ b_Q & 2b_1 - \mu_1 - \frac{k_2 k}{\delta_4} & 0 & 0 \\ 0 & 0 & -(\mu_0 + \mu_Q + \frac{k_1 k}{\delta_4}) & 0 \\ -\frac{c_1 k}{\delta_4} & -\frac{c_2 k}{\delta_4} & -\frac{c_3 k}{\delta_4} & -\delta_4 \end{pmatrix}. \tag{35}$$

From the characteristic polynomial

$$\begin{aligned}p_B(\lambda) = \frac{1}{\delta_4^3}(\lambda + \delta_4)(\delta_4\lambda + \mu_1\delta_4 + k_2 k - 2b_1\delta_4)\,(k_1 k + \delta_4\lambda \\ + \mu_0\delta_4 + \mu_Q\delta_4)\,(k_Q k + \delta_4\lambda + b_Q\delta_4 + \mu_{G_0}\delta_4),\end{aligned} \tag{36}$$

we get the eigenvalues

$$\lambda_1 = -\delta_4, \tag{37}$$

$$\lambda_2 = -\frac{1}{\delta_4}(\mu_1\delta_4 + k_2 k - 2b_1\delta_4), \tag{38}$$

$$\lambda_3 = -\frac{1}{\delta_4}(k_1 k + \mu_0\delta_4 + \mu_Q\delta_4), \tag{39}$$

$$\lambda_4 = -\frac{1}{\delta_4}(k_Q k + b_Q\delta_4 + \mu_{G_0}\delta_4). \tag{40}$$

It is easy to verify that all eigenvalues are real and λ_1, λ_3 and λ_4 are always negative. The stability of P_4^* depends on the real part $Re(\lambda_2)$.

Proposition 3. *The tumor-free equilibrium P_4^* is locally asymptotically stable if $\delta_4(\mu_1 - 2b_1) + k_2 k > 0$.*

When $\mu_1 - 2b_1 > 0$, it is $\delta_4(\mu_1 - 2b_1) + k_2 k > 0$ and the tumor would be defeated even without immune system interaction (Section 4.1.1). In case $\mu_1 - 2b_1 < 0$, a low death rate δ_4 of the lymphocytes, a high lymphocytes production rate k or a high immunotherapy effectiveness k_2 is necessary for tumor eradication. The stability condition for the tumor-free steady state can be as well written as $k > \frac{\delta_4}{k_2}(2b_1 - \mu_1)$. It is indeed practical to have a stability condition in terms of the parameter k, as that can be controlled from the outside, for example with immunotherapeutic treatments (see also Section 6).

4.1.3. *Model with immuno- and chemotherapy.* Now we consider the complete model (11)-(15), for $\tau = 0$. The tumor-free steady state is

$$P_5^* := (0, 0, 0, \frac{k}{\delta_4}, 0).$$

The corresponding Jacobian matrix is

$$C := J_5\left(P_5^*\right) = \begin{pmatrix} & & B & & 0 \\ & & & & 0 \\ & & & & 0 \\ & & & & -\frac{k_6 k}{\delta_4} \\ 0 & 0 & 0 & 0 & -\gamma \end{pmatrix}, \tag{41}$$

where B is the Jacobian in (35). The spectrum of C is $\sigma(C) = \sigma(B) \cup \{-\gamma\}$. Because of $\gamma > 0$, the stability conditions of (3) stay unchanged even if chemotherapy is included.

4.2. **System with delay.** Now we consider the delay model and compare the results to the previous ones. For simplicity, consider first the model with no immunotherapy nor chemotherapy and neglect the quiescent state:

$$\dot{U}(t) = 2b_1 U(t-\tau)e^{-\mu_0 \tau} - \mu_1 U(t), \tag{42}$$

$$\dot{V}(t) = 2b_1 (U(t) - U(t-\tau)e^{-\mu_0 \tau}) - \mu_0 V(t). \tag{43}$$

In this case the only stationary point is $(U^*, V^*) = (0, 0)$. To determine stability, it is not necessary to investigate the roots of the characteristic equation of the system. As it can be easily recognized, equation (42) is autonomous and for the structure of (43), it is sufficient to determine stability conditions for $U^* = 0$ to have the corresponding conditions for the trivial equilibrium. Equation (42) is linear and has a "positivity structure", indeed, whenever $U(t) = 0$ the right hand-side is non-negative (compare [23], Section 5.1). In this case, the dominant root of the characteristic equation must be real ([23, 24]). Therefore it is sufficient to investigate the real characteristic roots of

$$z + \mu_1 - 2b_1 e^{-\mu_0 \tau} e^{-z\tau} = 0. \tag{44}$$

The real roots $z \in \mathbb{R}$ of (44) are given by the intersections of the line $y = z + \mu_1$ with the curve $y = 2b_1 e^{-\mu_0 \tau - z\tau}$. If $2b_1 e^{-\mu_0 \tau} < \mu_1$, then there is no intersection in the positive half-plane and so no characteristic root z with $Re(z) > 0$. If the parameter values are such that $2b_1 e^{-\mu_0 \tau} > \mu_1$, then the two curves intersect at some point z such that $Re(z) > 0$ and the fixed point becomes unstable. An equivalent condition for instability can be formulated in terms of the delay:

$$2b_1 e^{-\mu_0 \tau} > \mu_1 \Leftrightarrow ln\left(\frac{2b_1}{\mu_1}\right) > \mu_0 \tau \Leftrightarrow \tau < \widehat{\tau} := \frac{1}{\mu_0} ln\left(\frac{2b_1}{\mu_1}\right).$$

Let us summarize our results in a proposition:

Proposition 4. *Consider the delay system (42)-(43) for mitotic and interphase tumor cells. The stability of the tumor-free steady state depends on the parameters as follows:*

- *For all $\tau > \widehat{\tau} := \frac{1}{\mu_0} ln\left(\frac{2b_1}{\mu_1}\right)$ the dominant characteristic root of (44) lies in the negative half-plane and the stationary point is stable.*
- *For $\tau < \widehat{\tau}$ the tumor-free equilibrium is unstable.*

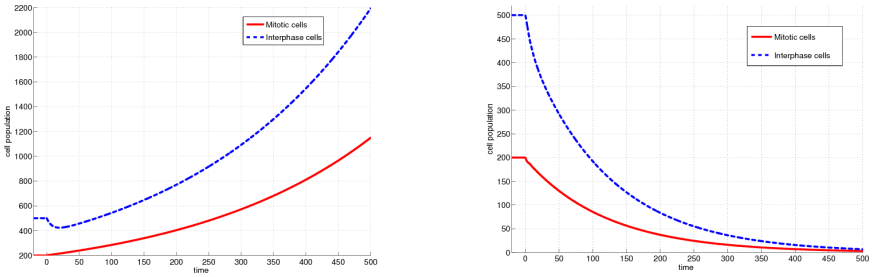
Symbol	Description	Value
μ_{G_0}	death rate of G_0-cells ($\frac{1}{[\text{time}]}$)	$0.1 \cdot 10^{-4}$
μ_Q	transition rate from G_1 to G_0 ($\frac{1}{[\text{time}]}$)	0.02
k_Q	effectiveness of immune system on G_0-cells ($\frac{1}{[\text{cells}\cdot\text{time}]}$)	$0.1 \cdot 10^{-8}$
b_Q	transition rate from G_0 to G_1 ($\frac{1}{[\text{time}]}$)	0.2
b_1	division rate of M-cells ($\frac{1}{[\text{time}]}$)	see text
μ_0	death rate of G_1-cells ($\frac{1}{[\text{time}]}$)	0.11
k_0	effectiveness of immune system on G_1-cells ($\frac{1}{[\text{cells}\cdot\text{time}]}$)	10^{-8}
μ_1	death rate of M-cells ($\frac{1}{[\text{time}]}$)	0.28
k_2	effectiveness of immune system on M-cells ($\frac{1}{[\text{cells}\cdot\text{time}]}$)	$0.4 \cdot 10^{-8}$
k_5	drug degradation rate on M-cells ($\frac{1}{[\text{time}]}$)	0.7
k_3	effectiveness of drugs on M-cells ($\frac{1}{[\text{concentration}]}$)	$0.25 \cdot 10^{-3}$
k	production rate of lymphocytes ($\frac{[\text{cells}]}{[\text{time}]}$)	$0.15 \cdot 10^{6}$
ρ	stimulation rate of I due to the tumor ($\frac{1}{[\text{time}]}$)	0.2
n	non-linearity of tumor-immune system interplay	3
α	threshold for the immune system activation ($[\text{cells}]^n$)	$0.5 \cdot 10^{6}$
δ_4	death rate of lymphocytes ($\frac{1}{[\text{time}]}$)	0.3
c_1	loss of lymphocytes by interaction with G_0-cells ($\frac{1}{[\text{cells}\cdot\text{time}]}$)	$0.2 \cdot 10^{-6}$
c_2	loss of lymphocytes by interaction with G_1-cells ($\frac{1}{[\text{cells}\cdot\text{time}]}$)	$0.8 \cdot 10^{-7}$
c_3	loss of lymphocytes by interaction with M-cells ($\frac{1}{[\text{cells}\cdot\text{time}]}$)	$0.108 \cdot 10^{-6}$
k_6	drug degradation rate on lymphocytes ($\frac{1}{[\text{time}]}$)	0.3
k_7	effectiveness of drug on lymphocytes ($\frac{1}{[\text{concentration}]}$)	$0.5 \cdot 10^{-2}$
γ	degradation rate of drug ($\frac{1}{[\text{time}]}$)	$0.3 \cdot 10^{-2}$

TABLE 2. Model parameters, descriptions and values chosen for simulations.

In other words, if cells divide too often (i.e. the interphase is too short), the tumor size will explode because of the large number of mitotic cells. For $\mu_1 < 2b_1$ and $\tau > \widehat{\tau}$ there is no real characteristic root $z \in \mathbb{R}_+$.

5. **Numerical simulations.** In this Section numerical simulations of the models in Section 2 and Section 4 are shown. The algorithm for solving systems of delay differential equations is a *continuous Runge-Kutta* ([3]) based on an explicit method for ODEs. Parameter values are mostly taken directly from [16, 26] or derived from these works. An overview of the model parameters and their values is given in Table 2. In all our plots the time scale is shifted of τ, i.e. we move the starting point to $t = 0$. This shifting is of course possible because of time-invariance in autonomous systems ([24], Chap. 5).

5.1. **Delay 2D model.** Consider the simple delay model (42)-(43) with constant delay $\tau > 0$. In this Section we are particularly interested in showing the qualitative behavior of the solutions, which validates the stability analysis of Section 4. We set the parameter values as in Table 2 and change the value of b_1 and τ to show stability switches. Further we choose constant history functions $U_0(t) = 200$ [cells], $V_0(t) = 500$ [cells] for $t \in [-20, 0]$. More realistic initial values are considered in Section 6. With $b_1 = 0.25, \mu_1 = 0.28, \mu_0 = 0.11$ a stability switch occurs at $\tau = \widehat{\tau} \approx 5.27$ (Proposition 4): for $\tau = 5$ the cancer-free equilibrium is unstable (Figure 4(a)), whereas for $\tau = 6$ it is stable (Figure 4(b)).



(a) Instability of $(0,0)$ for $\tau = 5$.

(b) Stability of $(0,0)$ with $\tau = 6$.

FIGURE 4. Stability switches due to the delay.

5.2. **Delay 3D model.** Consider the three-dimensional basic model (8)-(10). To confirm the positivity conditions given in Proposition 1, we choose constant history functions and compute the values of $U(0)$, $V(0)$ and $Q(0)$ according to Section 3. For $Q(0) = 100$ [cells] and $U(0) = 200$ [cells], the solution curve remains in the positive cone (Figure 5).

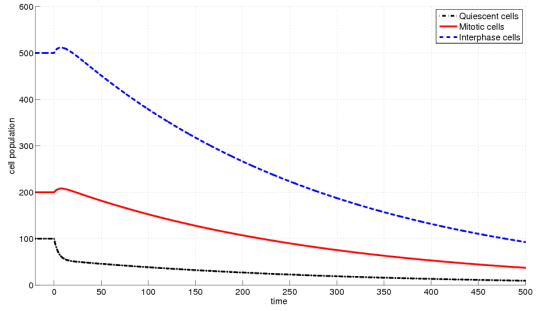


FIGURE 5. Preservation of positivity.

6. **Effects of periodic immunotherapy.** In this Section we focus on cancer treatments. In particular, we shall investigate the effects of immunotherapy which aims to stimulate the immune system in order to better fight the tumor. More and more immunotherapeutic treatments are preferred over chemotherapy, since the effectors of the immune system are more specific than drugs in their actions: they target indeed cancer cells only and leave the vast majority of other healthy cells untouched ([6]).

As suggested in [10], a constant immunotherapy is not really applicable, but is rather an idealization of a periodic treatment which can instead be easily carried out. To simulate the effects of immunotherapy, we generalize the equation for $I(t)$ by introducing a function θ for the stimulation of the immune system over time:

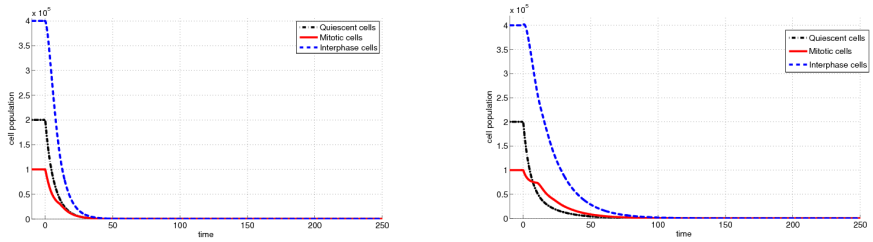
$$\begin{aligned}\dot{I}(t) = &\theta(t) + \rho I(t)\frac{(Q(t)+U(t)+V(t))^n}{\alpha+(Q(t)+U(t)+V(t))^n} - \delta_4 I(t) \\ &- (c_1 Q(t) + c_2 U(t) + c_3 V(t))I(t).\end{aligned} \tag{45}$$

We choose expressions for θ from those proposed in [9, 10, 11]:

- $\theta(t) = \theta_0(t) := k$ constant immunotherapy. Its effects have been investigated in Section 4.
- $\theta(t) = \theta_1(t) := k(1 + \cos(\frac{2\pi}{T}t))$, an idealized T-periodic therapy which is reminiscent of periodic forcing.
- $\theta(t) = \theta_2(t) := k\exp(-\frac{1}{\gamma_I}\mathrm{Mod}(t,T))$ is a more realistic T-periodic therapy: here k is the delivered drugs concentration, γ_I the degradation rate of drugs in the body and T the time between two consecutive deliveries. The term $\mathrm{Mod}(t,T)$ is the result of $t \mod T$, i.e. $\mathrm{Mod}(t,T) = t - T\lfloor\frac{t}{T}\rfloor$.

In the following, we simulate the administration of each one of these treatments on a tumoral mass and assume that the patient undergoes immunotherapy from the very beginning. Unless other specifications are made, we use the parameter values as in Table 2 and choose history functions $Q(t) = 2\cdot 10^5$, $U(t) = 1\cdot 10^5$, $V(t) = 4\cdot 10^5$, $I(t) = 3\cdot 10^5$, $D(t) = 100$, for $t \in [-20, 0]$.

6.1. **Constant treatment $\theta_0(t)$.** We start with the numerical investigation of the effects of constant treatment $\theta(t) = \theta_0(t)$. If the time between one mitosis and the next one is large enough and the division rate is small, then the tumor vanishes independently of the delivered dose (cf. Section 4), see Figure 6. However, cancer



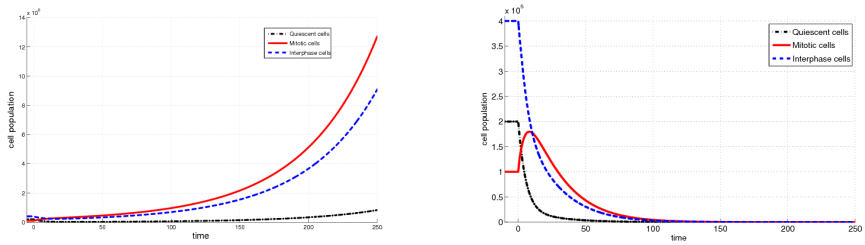
(a) Constant immunotherapy dose $k = 2\cdot 10^6$. (b) Constant immunotherapy dose $k = 2\cdot 10^4$.

FIGURE 6. Constant immunotherapy θ_0: with large delay ($\tau = 10$) and small division rate ($b_1 = 0.12$), the tumor vanishes independently of the immunotherapy.

is due to the uncontrolled growth of cells, so a large division rate ($b_1 = 0.20$) is plausible. Further, we assume the interphase duration to be very short ($\tau = 2$) and we look at the effects of a constant immunotherapy. Increasing the dose can be a winning strategy: the tumor vanishes when the immune system is highly stimulated (Figure 7).

6.2. **Periodic treatment.** As a constant immunotherapy is not really possible ([10]), we shall include in the model the effects of an idealized periodic treatment $\theta(t) = \theta_1(t) = k(1 + \cos(\frac{2\pi}{T}t))$, where k is the mean value of θ over one period of length T.

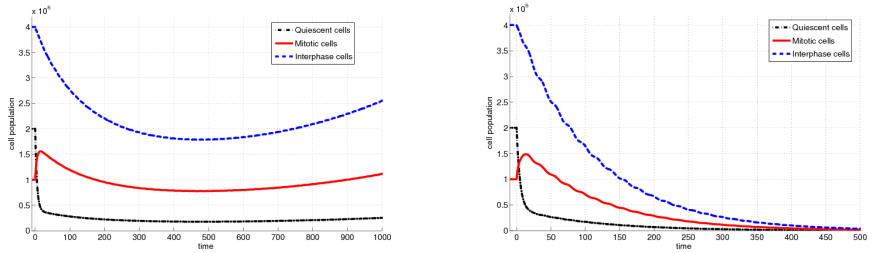
Assume cell division occurs at rate $b_1 = 0.27$. When considering the simple 2D model (42)-(43) with the chosen parameter values there is a stability switch at $\widehat{\tau} \approx 5.97$: for $\tau < \widehat{\tau}$ the tumor-free stationary point is unstable. So we choose $\tau = 5.5$ and investigate the effects of therapies on the tumor. Assume a period $T = 20$ for the treatment and choose $k = 2\cdot 10^4$ as the mean value for the therapy.



(a) Constant immunotherapy dose $k = 2 \cdot 10^4$. (b) Constant immunotherapy dose $k = 2 \cdot 10^6$.

FIGURE 7. Constant immunotherapy θ_0: short interphase duration ($\tau = 2$) and large division rate ($b_1 = 0.2$) lead to tumor growth (left panel). Immunotherapy helps in eradicating the tumor (right panel).

This strategy is unfortunately not effective and the tumor escapes the immunosurveillance (Figure 8(a)). However, if we administer a larger dose, e.g. $k = 2 \cdot 10^6$, the tumor vanishes (Figure 8(b)). Tumor eradication is still possible when an intermediate drug concentration ($k = 5 \cdot 10^4$) over a longer time period ($T = 50$) is sustained (Figure 9). This would be a sort of "compromise" between the two strategies: not too much medicament nor too often! Similar results hold for a T-periodic



(a) Periodic immunotherapy $T = 20$, $k = 2{\cdot}10^4$. (b) Periodic immunotherapy $T = 20$, $k = 2{\cdot}10^6$.

FIGURE 8. Effects of the periodic immunotherapy $\theta_1(t)$.

treatment in the form $\theta(t) = \theta_2(t)$. This expression is more correct that the one given by $\theta_1(t)$, as it takes into account the degradation of drugs over time. Here, k describes the immunotherapy dose at time $t = nT$, for $n \in \mathbb{N}_0$. Drug decay occurs at constant rate $\frac{1}{\gamma_I}$ ($\gamma_I \approx 0$ corresponds to a very fast decay). For $\gamma_I \to \infty$, $\theta_2(t)$ approaches a constant therapy. The mean value of θ is given by $[\theta] = k\gamma_I \frac{1-e^{-T/\gamma_I}}{T}$ ([11]).

From the medical point of view, varying the decay parameter γ_I might be difficult. For the numerical simulation, we choose a fixed value $\gamma_I = 20$ in order to investigate the effects of T and τ. As for the periodic therapy $\theta_1(t)$, we choose $b_1 = 0.27$ and $\tau = 5.5$. For $T = 20$ and $k = 2 \cdot 10^4$ (Figure 10(a)) or $k = 4 \cdot 10^4$ (Figure 10(b)) the tumor grows larger. By reducing the gap between two consequent deliveries or giving a larger dose to the patient, tumor eradication would be possible, as in the limit the constant therapy θ_0 is approached (data not shown).

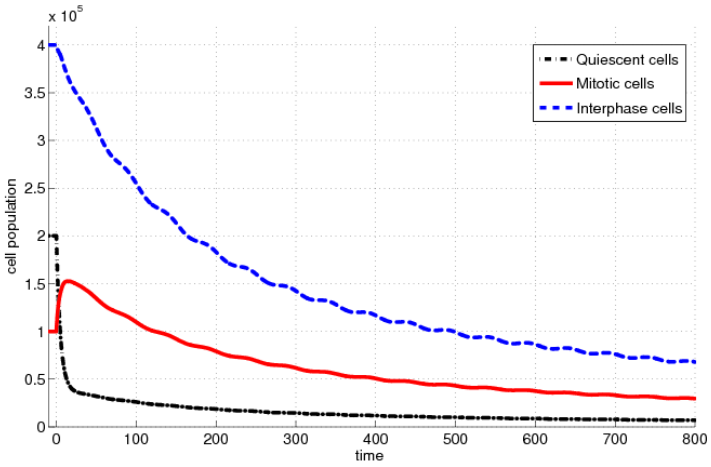
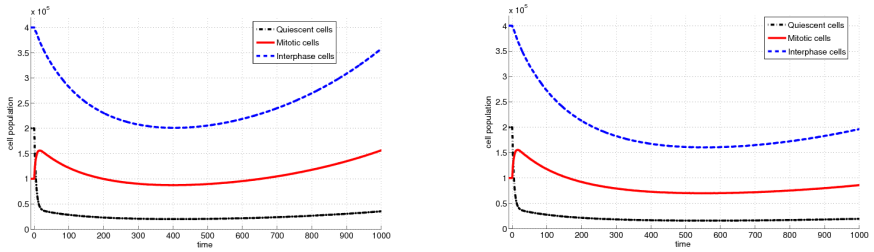


FIGURE 9. Periodic immunotherapy $\theta_1(t)$: an effective treatment with a intermediate drug concentration ($k = 5 \cdot 10^4$) over a period $T = 50$.

But we would like to achieve a compromise, as in the case of the θ_1-therapy. Indeed, this is possible: e.g. a weekly ($T = 7$) dose of $k = 4 \cdot 10^4$ [cells]/[time] is sufficient to reduce the tumor size (Figure 11(a)). Similar results are also possible, when giving to the patient a larger dose ($k = 6 \cdot 10^4$) every 15 days (Figure 11(b)). The reader will have noticed that in both cases we have not achieved complete eradication of the tumoral mass, but only its reduction. This is often the aim of medical doctors, if complete eradication of the tumor is not possible.

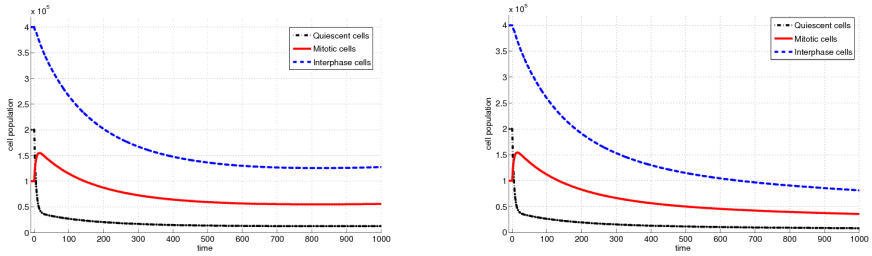


(a) Tumor growth for $T = 20$, $k = 2 \cdot 10^4$.

(b) Tumor growth for $T = 20$, $k = 4 \cdot 10^4$.

FIGURE 10. Inefficacy of periodic therapy θ_2 when the administration period is too large and the drugs concentration too low.

7. **Discussion.** Starting from a cell population structured by age, we have derived a delay differential equations system for proliferating tumor cells (8)-(10). This approach allowed us to simulate the effects of phase-specific drugs which target cells in the mitotic phase. The basic model was further extended by including immunotherapeutic treatments (11)-(15). The result is an improvement of the models in [26, 16], both from the mathematical and the biological point of view.



(a) Tumor reduction for $T = 7$, $k = 4 \cdot 10^4$. (b) Tumor reduction for $T = 15$, $k = 6 \cdot 10^4$.

FIGURE 11. Periodic immunotherapy $\theta_2(t)$: tumor size reduces by weekly or biweekly administrations.

Although being an oversimplification of the real-life phenomenon, a constant delay approach was our choice. Our aim was to give results for the dynamics of a solid tumor cured with mitosis-specific drugs and immunotherapy. As it was observed by Santiago et al. ([21]), the time between two consecutive mitoses (i.e. the length of the interphase) is affected by medicaments: if the drug concentration is high, tumor cells stay in the interphase longer. The next approach could be the inclusion of a state-dependent delay $\tau(D)$ into the model, where $D(t)$ is the drug concentration at time t. Our results suggest that, if we manage to extend the interphase duration to a certain time interval, the tumor can be defeated by drugs only or with the parallel support of immunotherapy (Section 4, Section 6).

From the mathematical point of view, we gave new insights for the stability analysis of a delay system for which the standard approach by Cooke ([7]) is not suitable (Section 4.2). Our results were inspired by [15]. Further, we gave conditions on the initial data for the positivity of solutions of the delay system (Section 3). Choosing the initial data from a proper set, solutions will not leave the positive cone. This is an important result, as in DDE systems the nonnegativity of solutions is not automatically given by nonnegative initial data ([24]).

For the moment we have focused on the qualitative dynamics of the system. As next, we would compare our simulations to medical data and estimate the parameters from the latter. This would allow for a better definition of criteria for tumor reduction or, in the best case, eradication.

REFERENCES

[1] J. Al-Omari and S. Gourley, *Dynamics of a stage-structured population model incorporating a state-dependent maturation delay*, Nonlinear Analysis: Real World Applications **6** (2005), 13–33.

[2] B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts and P. Walter, "Molecular Biology of the Cell," 5^{th} edition, Taylor & Francis Ltd., New York, 2007.

[3] A. Bellen and M. Zennaro, "Numerical Methods for Delay Differential Equations," Clarendon Press, New York, 2003.

[4] S. P. Blythe, R. M. Nisbet and W. S. C. Gurney, *The dynamics of population models with distributed maturation periods*, Theoretical Population Biology, **25** (1984), 289–311.

[5] G. Bocharov and K. P. Hadeler, *Structured population models, conservation laws, and delay equations*, Journal of Differential Equations, **168** (2000), 212–237.

[6] M. Chaplain and A. Matzavinos, *Mathematical modeling of spatio-temporal phenomena in tumor immunology*, in "Tutorials in Mathematical Biosciences. III," Lecuture Notes in Math., **1872**, Berlin, (2006), 131–183.

[7] K. L. Cooke and P. van den Driessche, *On zeros of some transcendental equations*, Funkcialaj Ekvacioj, **29** (1986), 77–90.
[8] G. M. Cooper and R. E. Hausman, "The Cell: A Molecular Approach," ASM Press, Washington, 1997.
[9] A. d'Onofrio, *A general framework for modeling tumor-immune system competition and immunotherapy: Mathematical analysis and biomedical inferences*, Physica D, **208** (2005), 220–235.
[10] A. d'Onofrio, *Tumor-immune system interaction: Modelling the tumor-stimulated proliferation of effectors and immunotherapy*, Mathematical Models and Methods in Applied Science, **16** (2006), 1375–1401.
[11] A. d'Onofrio, F. Gatti, P. Cerrai and L. Freschi, *Delay-induced oscillatory dynamics of tumour-immune system interaction*, Mathematical and Computer Modelling, **51** (2010), 572–591.
[12] J. Dyson, R. Villella-Bressan and G. Webb, *Asynchronous exponential growth in an age structured population of proliferating and quiescent cells*, Deterministic and Stochastic Modeling of Biointeraction (West Lafayette, IN, 2000), Mathematical Biosciences, **177/178** (2002), 73–83.
[13] J. Dyson, R. Villella-Bressan and G. Webb, *A spatial model of tumor growth with cell age, cell size, and mutation of cell phenotypes*, Mathematical Modelling of Natural Phenomena, **2** (2007), 69–100.
[14] W. S. C. Gurney, S. P. Blythe and R. M. Nisbet, *Nicholson's blowflies revisited*, Nature, **287** (1980), 17–21.
[15] Y. Kuang, "Delay Differential Equations: With Applications in Population Dynamics," Academic Press, New York, 2003.
[16] W. Liu, T. Hillen and H. Freedman, *A mathematical model for M-phase specific chemotherapy including the G_0-phase and immunoresponse*, Mathematical Bioscience and Engineering, **4** (2007), 239–259.
[17] H. Lodish *et al.*, "Molecular Cell Biology," 3rd Ed. Scientific American Books , New York, 1995.
[18] N. MacDonald, "Biological Delay Systems: Linear Stability Theory," Cambridge University Press, 1989.
[19] R. Nisbet and W. Gurney, *The systematic formulation of population models for insects with dynamically varying instar duration*, Theoretical Population Biology, **23** (1983), 114–135.
[20] T. Roose, S. J. Chapman and P. K. Maini, *Mathematical models of avascular tumor growth*, SIAM Review, **49** (2007), 179–208.
[21] R. A. Santiago-Mozos, I. G. Khan and M. Madden, *Revealing the origin and nature of drug resistance of dynamic tumour systems*, International Journal of Knowledge Discovery in Bioinformatics, **1** (2010), 26–53.
[22] F. R. Sharpe and A. J. Lotka, *A problem in age distribution*, Philosophical Magazine Series 6, **21** (1911), 435–438.
[23] H. Smith, "Monotone Dynamical Systems: An Introduction to the Theory of Competitive and Cooperative Systems," Mathematical Surveys and Monographs, **41**, American Mathematical Society, Providence, Rhode Island, 1995.
[24] H. Smith, "An Introduction to Delay Differential Equations with Applications to the Life Sciences," Springer, New York, 2011.
[25] U. Veronesi and G. Quaranta, "Un Male Curabile," Mondadori Editore, Milano, 1986.
[26] M. Villasana and A. Radunskaya, *A delay differential equation model for tumor growth*, Journal of Mathematical Biology, **47** (2003), 270–294.
[27] G. Webb, "Theory of Nonlinear Age-Dependent Population Dynamics," Monographs and Textbooks in Pure and Applied Mathematics, 1985.

Received May 25, 2011; Accepted October 6, 2011.

E-mail address: barbarossa@ma.tum.de
E-mail address: kuttler@ma.tum.de
E-mail address: jonathanzinsl@aol.com