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Some remarks on modelling of drug resistance for low grade gliomas

Abstract In this paper we present a version of a simple mathematical model of acquiring drug resistance which was proposed in Bodnar and Foryś (2017). We based the original model on the idea coming from Pérez-García *et* al. (2015). Now, we include the explicit death term into the system and show that the dynamics of the new version of the model is the same as the dynamics of the second model considered by us and based on the idea of Ollier *et* al. (2017). We discuss the model dynamics and its dependence on the model parameters on the example of gliomas.

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1. Introduction In this paper we focus on tumour treatment and the so-called acquired chemotherapy resistance which is associated with longer usage of the same drug and causes problems when we observe relapse of the disease. Our main aim is to model the process of mutation from sensitive to resistant subpopulation of tumour cells as well as the growth of tumour consisting of both types of cells. In our previous work [2] we have compared two simple models of drug resistance, one based on the ideas proposed by Ollier *et al.* [7], and the other by Pérez-García *et al.* [8]. Both models were proposed to describe the dynamics of gliomas. However, they differ in the mechanism of acquiring resistance. Moreover, in the first model there is an explicit death term of cells, while such term is absent in the second model. In [2] we showed that the dynamics of both models, in the case of constant continuous indefinite chemotherapy, is very similar, that is all solutions tend to a steady state in which the subpopulation of sensitive cells goes extinct. However, the lack of an explicit death term in the model proposed by Pérez-García *et al.* could be considered as oversimplification and causes that the model has worst mathematical properties. Namely, there are infinitely many steady states and the

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asymptotic dynamics depends on the initial data. Therefore, we decided to add this term and compare the dynamics of the model considered before and the model with the additional death term.

We illustrate analytic results using parameters fitted to gliomas. Gliomas are brain tumours originating from glial cell precursors, accounting for about 80% of all brain tumours. In general, for glioma patients, three types of therapy are applied: resection, radiotherapy and chemotherapy. Clinicians have lately focused on chemotherapy, for which phase II trials [6, 9] showed effectiveness against both previously irradiated and unirradiated tumours. Response of glioma cells to chemotherapy is a topic of various studies, also from mathematical point of view; cf. [3, 4, 5, 10].

In [2] we considered two mathematical models describing two different mechanisms of acquiring drug resistance. The first model is based on the ideas of Ollier *et al.* [7] exploiting the so-called log-kill mechanism. However, Ollier *et al.* proposed their model to decide which type of resistance, primary or acquired, dominates in the case of temozolomide (TMZ) treatment of gliomas, while we focused on acquired drug resistance (ADR) and this is the reason that primary resistant cells were not included into our model. The second model we studied was based on both the ideas presented by Ollier *et al.* [7] and Pérez-García *et al.* [8]. Moreover, we did not assume the specific logistic type of the growth considered in [7] but included a general function having logistic-type properties. It should be noted that this generalization allows for the usage of the Gompertzian low of the tumour growth which is probably more common for tumour models than the logistic growth (cf. [1] for comparison of these models and the discussion on that topic).

In this paper we study the influence of the additional (i.e. explicit) death term on the dynamics of the second model considered by us in [2]. We show that this death term has regularizing properties, that is it causes that non-trivial steady state is unique.

2. Mathematical model Proposing the model of ADR effect we follow the ideas presented in [2]. We divide the population of tumour cells into three subpopulations:

- proliferating cells that are sensitive to chemotherapy with a concentration $P\colon \mathbb{R}_+ \to \mathbb{R}_+$;
- damaged cells with a concentration $D\colon \mathbb{R}_+ \to \mathbb{R}_+$;
- cells having ADR with a concentration $R\colon \mathbb{R}_+ \to \mathbb{R}_+$;

where $\mathbb{R}_+ = [0, +\infty)$. Additionally, $C\colon \mathbb{R}_+ \to \mathbb{R}_+$ denotes a drug concentration.

In the original Ollier *et al.* and Pérez-García *et al.* models the exact logistic function with carrying capacity K common for the whole population $V(t) =$

$P(t) + D(t) + R(t)$ is assumed as the underlying law of the growth. In the models proposed by us the underlying law is more general, described by a function $f : \mathbb{R}_+ \to \mathbb{R}$ that could be either Gompertzian or of logistic type.

Following the ideas presented in [8] and then in [2] we have assumed that the drug triggers a DNA damage and during the division a cell either enters an apoptotic pathway or makes an attempt to repair the damage and tries to divide. Moreover, the damage cannot be repaired and the cell eventually dies. This is modelled by a logistic type term with a minus sign in the equation for damaged cells. In this paper, we introduce an additional term expressing explicit death of damaged cells. Adding this term we assume that damaged cells dies not only when trying to divide but they may also undergo apoptosis. Hence, the model we consider here reads

$$\dot{P} = \rho_P P f\left(\frac{P+D+R}{K}\right) - \alpha_P C(t) P, \tag{1a}$$

$$\dot{D} = (1-\varepsilon)\alpha_P C(t) P - \frac{\rho_P}{k} D f\left(\frac{P+D+R}{K}\right) - \mu_D D, \tag{1b}$$

$$\dot{R} = \rho_R R f\left(\frac{P+D+R}{K}\right) + \varepsilon \alpha_P C(t) P, \tag{1c}$$

where:

- ρ_P is a proliferation rate of proliferating tumour cells;
- $f\colon \mathbb{R}_+ \to \mathbb{R}$ is Lipschitz continuous in $(0, +\infty)$ and strictly decreasing, $f(1) = 0$ and either $f(0) = 1$ or $\lim\limits_{x\to 0^+} f(x) = +\infty$, while $x \mapsto xf(x)$ is Lipchitz continuous in the right neighbourhood of 0 and $\lim\limits_{x\to 0^+} xf(x) = 0$;
- α_P is a rate at which the drug destroys tumour cells, however a small part of such cells mutate and acquire drug resistance with probability ε;
- k is a mean number of division attempts before the cell death, and due to the assumption, the death rate of damaged cells is the same as the proliferation rate of undamaged cells divided by k;
- ρ_R is a proliferation rate of resistant cells.

Notice that $f(x) = 1 - x$ reflects the logistic growth, while $f(x) = -\ln x$ reflects the Gompertzian one.

For simplification, in the analysis presented below we assume continuous indefinite drug dosage, that is $C(t) = \text{const} = C$. Let us now make the following change of variables

$$x = P/K, \quad y = D/K, \quad z = R/K, \quad \tilde{t} = \rho_p t, \tag{2}$$

and denote

$$\alpha = \alpha_P C/\rho_P, \quad \mu = \mu_D/\rho_P, \quad \rho = \rho_R/\rho_P, \quad \kappa = 1/k, \tag{3}$$

obtaining the dimensionless system

$$\dot{x} = xf\big(x+y+z\big) - \alpha x, \tag{4a}$$
$$\dot{y} = (1-\varepsilon)\alpha x - \kappa y f\big(x+y+z\big) - \mu y, \tag{4b}$$
$$\dot{z} = \rho z f\big(x+y+z\big) + \varepsilon\alpha x, \tag{4c}$$

where all parameters are positive and $x(0) = x_0 \geq 0$, $y(0) = y_0 \geq 0$, $z(0) = z_0 \geq 0$. Note that in this system the parameter α reflects the influence of treatment. In the following Section we analyze System (4) and compare its dynamics with the dynamics for $\mu = 0$ described in [2].

3. Analysis of the model Basic properties of System (4) are similar to those presented in [2] for $\mu = 0$. Namely, unique solutions exist for all nonnegative initial data, are nonnegative, and the set $x+y+z \leq 1$ is invariant.

LEMMA 3.1 If $0 \leq x_0 + y_0 + z_0 \leq 1$, then solutions of System (4) satisfy $0 \leq x(t) + y(t) + z(t) \leq 1$ for $t > 0$. Moreover, if $x_0 + y_0 + z_0 < 1$, then $x(t) + y(t) + z(t) < 1$.

PROOF Equation (4a) implies that if $x_0 = 0$, then $x(t) = 0$ for every t. Hence, $x(t) > 0$ for $x_0 > 0$. Moreover, if we assume that there exists $\bar{t} \geq 0$ such that $y(\bar{t}) = 0$, then $\dot{y}(\bar{t}) = (1-\varepsilon)\alpha x(\bar{t}) > 0$ for $x(t) > 0$. This means that $y(t)$ is nonnegative for any nonnegative initial data. The same argument implies nonnegativity of z.

Let us denote $w(t) = x(t) + y(t) + z(t)$. From System (4) we obtain the following equation for w:

$$\dot{w} = \big(x - \kappa y + \rho z\big) f(w) - \mu y.$$

Properties of f imply $f(1) = 0$. Hence, if there exists $\bar{t} > 0$ such that $w(\bar{t}) = 1$, then $\dot{w} = -\mu y \leq 0$. Uniqueness of solutions of System (4) yield $w(t) \leq 1$. Moreover, as y is positive for any positive x, we can change this inequality to be strict. On the other hand, if $x = 0$, then we have the system of equations

$$\begin{aligned} \dot{y} &= -\kappa y f\big(y+z\big) - \mu y, \\ \dot{z} &= \rho z f\big(y+z\big), \end{aligned} \tag{5}$$

for which we also obtain positivity of y for positive y_0 and the same argument yields the desired inequality. ∎

Lemma 3.1 above allows to consider System (4) in the invariant subspace of the positive octant

$$\mathcal{P} = \{(x,y,z) \in \mathbb{R}^3_+ : \ x+y+z \leq 1\}.$$

Note that in $\mathcal{P}$ solutions of System (4) exist for all $t \geq 0$. This property is obvious for the logistic type of f. On the other hand, if $f(x) \to +\infty$ as $x \to 0^+$, then we define the right-hand side of Eq. (4a) for $x = 0$ to be equal to 0 in a continuous manner. Moreover, in $\mathcal{P}$ we have $f(w) \geq 0$, which will be important in the model analysis.

3.1. Steady states Looking for steady states we easily see that from Eq. (4c) there must be $x = 0$ and $zf(w) = 0$. Hence, at the steady state either $x = z = 0$ or $x = 0$ and $w = 1$. In both cases from the second equation we get $y\big(\kappa f(w) + \mu\big) = 0$, and therefore $y = 0$. Hence, we have exactly two steady states of System (4):

1. Trivial steady state $T = (0, 0, 0)$;
2. Semitrivial steady state $S = (0, 0, 1)$.

Calculating Jacobian matrix we obtain

$$J(x, y, z) = \begin{pmatrix} f(w) + xf'(w) - \alpha & xf'(w) & xf'(w) \\ (1-\varepsilon)\alpha - \kappa y f'(w) & -\kappa f(w) - \kappa y f'(w) - \mu & -\kappa y f'(w) \\ \varepsilon\alpha + \rho z f'(w) & \rho z f'(w) & \rho f(w) + \rho z f'(w) \end{pmatrix}.$$

For the logistic type of f we can use this matrix to check local stability of both steady states. On the other hand, for the Gompertzian type of this function the derivative $f'(0)$ could not be defined.

Lemma 3.2 The trivial steady state T is unstable, while the semitrival state S is a stable node, independently of the type of f.

Proof First notice that the last variable z is strictly increasing inside $\mathcal{P}$. Hence, the state T repels solutions at least in z-direction, and therefore it is unstable.

Let $d = -f'(1) > 0$. Then,

$$J(0, 0, 1) = \begin{pmatrix} -\alpha & 0 & 0 \\ (1-\varepsilon)\alpha & -\mu & 0 \\ \varepsilon\alpha - \rho d & -\rho d & -\rho d \end{pmatrix}.$$

It is easy to see that all eigenvalues are real negative, so S is an unstable node. ∎

Note that Lemma 3.2 yields that the death term $-\mu y$ in the second equation Eq. (4b) acts as a regularization of System (4). Clearly, from [2] we know that for System (4) with $\mu = 0$ all points of the form $(0, \tilde{y}, 1 - \tilde{y})$, $\tilde{y} \in [0, 1]$ are steady states. Hence, in that case steady states are not isolated and standard

tools do not work. If $\mu > 0$, then the semitrivial steady state S is isolated and attracts all solutions in $\mathcal{P}$.

3.2. Global dynamics

THEOREM 3.3 In the invariant set $\mathcal{P}$ all solutions of System (4) converges to $(0, 0, 1)$.

PROOF Recall that in $\mathcal{P}$ there is $f(w) \geq 0$, and $w \in [0, 1]$, obviously. Let us define

$$L(x, y, z) = Ax + y + B(1 - x - y - z), \quad \text{where} \quad A = 1 - \varepsilon/2, \ B = 1 - \varepsilon/4.$$

We show that L is a Lyapunov function. It is obvious that $L(x, y, z) \geq 0$ in $\mathcal{P}$ and $L(x, y, z) = 0$ iff $x = 0$, $y = 0$ and $w = 1$. Calculating the derivative of L along trajectories of System (4) we obtain

$$\begin{aligned}
\dot{L}(x, y, z) &= A\big(xf(w) - \alpha x\big) + (1 - \varepsilon)\alpha x - \kappa y f(w) - \mu y \\
&\quad - B\big(xf(w) - \kappa y f(w) - \mu y + \rho z f(w)\big) \\
&= (A - B)xf(w) + \big((1 - \varepsilon) - A\big)\alpha x + (B - 1)\big(\kappa f(w)y + \mu y\big) \\
&\quad - B\rho z f(w) \\
&= -\frac{\varepsilon}{4}xf(w) - \frac{\varepsilon}{2}\alpha x - \frac{\varepsilon}{4}\big(\kappa f(w)y + \mu y\big) - \Big(1 - \frac{\varepsilon}{4}\Big)\rho z f(w).
\end{aligned}$$

We see that $\dot{L}(x, y, z) \leq 0$ and $\dot{L}(x, y, z) = 0$ iff $x = 0$, $y = 0$ and $z = 0$ or $w = 1$. Moreover, L is of class $\mathbf{C}^1$, so from the Lyapunov-LaSalle Invariance Principle we obtain that all solutions are attracted by the invariant subset $\{x = 0 \ \wedge \ y = 0 \ \wedge \ (z = 0 \ \vee \ w = 1)\} \subset \mathcal{P}$. However, the coordinate z is increasing and the state $(0, 0, 0)$ is repelling, so the solution must be attracted by the semitrivial state S. ∎

Note that the same function L could be also used to check global dynamics of System (4) for $\mu = 0$. Clearly, again from the Lyapunov-LaSalle Invariance Principle we obtain that all solutions are attracted by the invariant subset $\{x = 0, \ f(w) = 1\} \subset \mathcal{P}$.

4. Numerical simulations In this section we present results of numerical simulations. Taking parameters as estimated in [7] and [8], after rescaling (2) we get the following nominal values

$$\alpha = 0.414, \quad \rho = 12, \quad \mu = 5.688, \quad \kappa = 0.714, \quad \varepsilon = 0.1, \tag{6}$$

where the value of ε was taken arbitrarily. In the simulations presented below values of the parameters are fixed at nominal levels, except for the parameter which is examined.

In our simulations we focus on two issues:

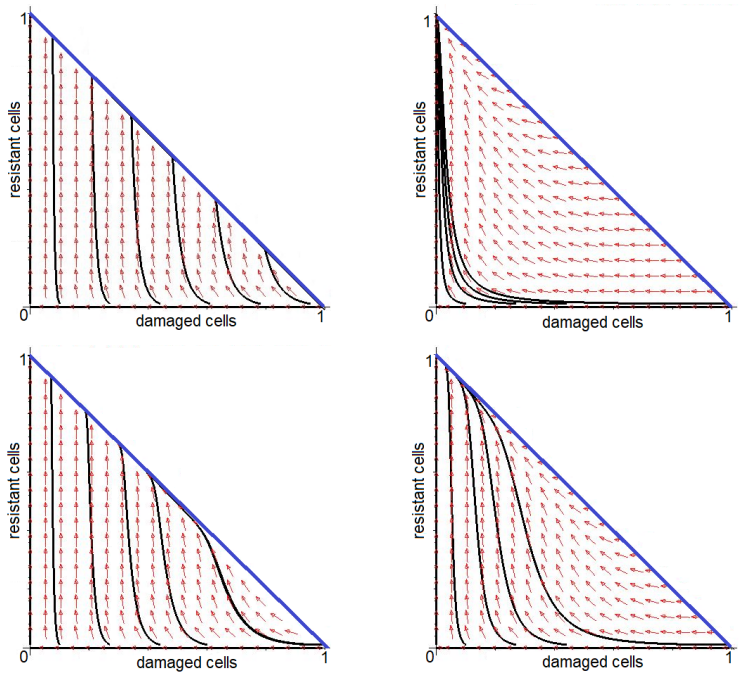

Figure 1: Phase portraits for System (5) with $\mu = 0$ (left top graph), μ nominal (right top graph), $\mu = 0.1$ (left bottom graph) and $\mu = 1$ (right bottom graph).

1. comparison between the dynamics of System (4) with $\mu = 0$ and the nominal $\mu = 5.688$;

2. comparison of the dynamics of System (4) for changing values of the parameters ρ, α and ε.

To compare the dynamics of System (4) for $\mu = 0$ and μ nominal, we first look at the phase portrait of reduced asymptotic System (5). Figure 1 shows that the dynamics of System (5) for nominal μ is very different when compared to $\mu = 0$. Although in both cases the coordinate y is decreasing, but for $\mu = 0$ it decreases not so much, keeping values not less than $y_0 - 0.2$, where $y_0 > 0$ is the initial value for this variable, while for nominal μ this coordinate decreases to 0 fast. For better illustration of the dependence of asymptotic dynamics on μ, in Fig. 1 we present also the phase portraits for $\mu = 0.1$ and $\mu = 1$. Although for positive μ all solutions converge to $(0, 1)$ in the phase space, with smaller μ the phase portrait is more similar to those for $\mu = 0$. Figure 2 shows the comparison between the dynamics of the full System (4) with nominal parameters (6) and $\mu = 0$.

The next three figures illustrate the dynamics of System (4) with changing ρ, α and ε, while other parameters are fixed at nominal values. We see that, independently of the magnitude of the parameters, solutions are quickly attracted by the steady state S. The only difference is visible for small α;

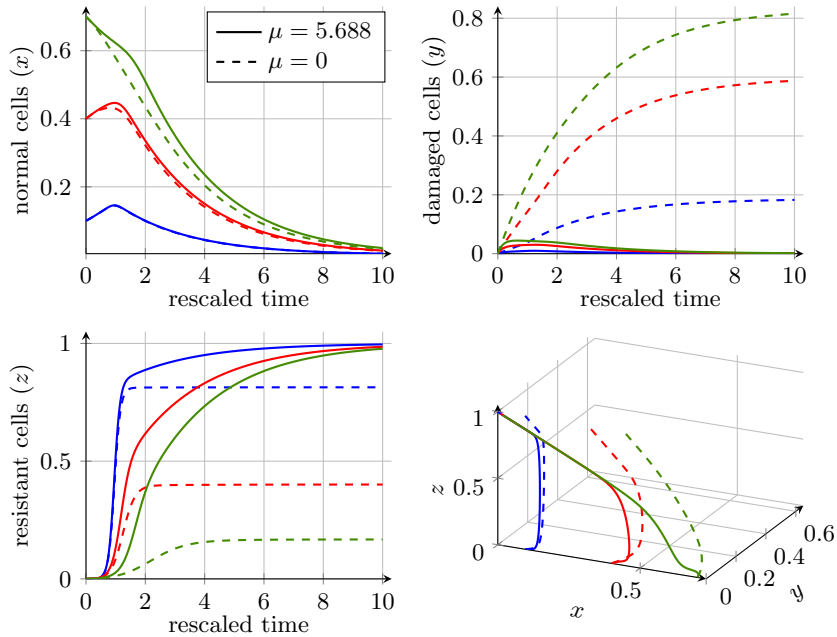

Figure 2: Comparison of solutions of System (4) with $\mu = 5.688$ and $\mu = 0$ for various initial portions of normal cells.

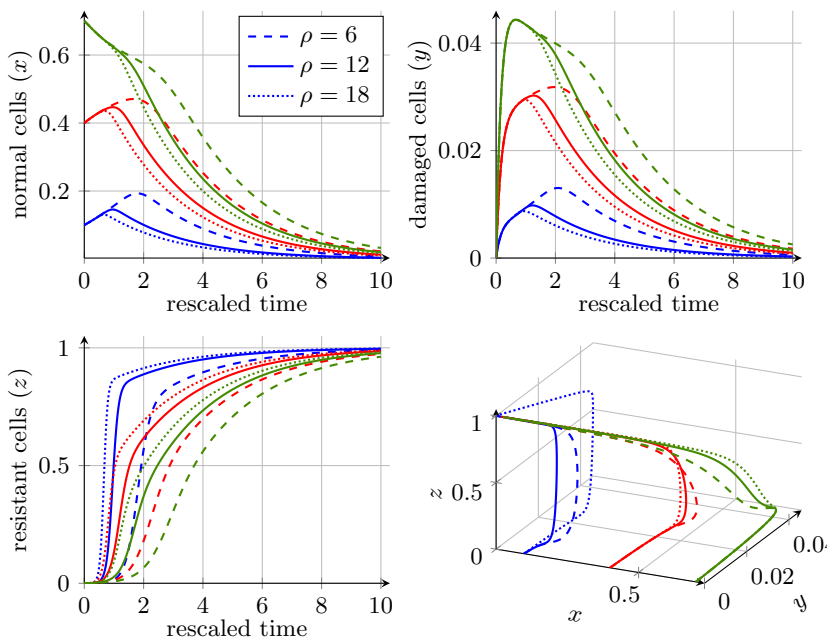

Figure 3: Solutions of System (4) with various initial portions of normal cells for various values of the parameter ρ with other parameters chosen as nominal.

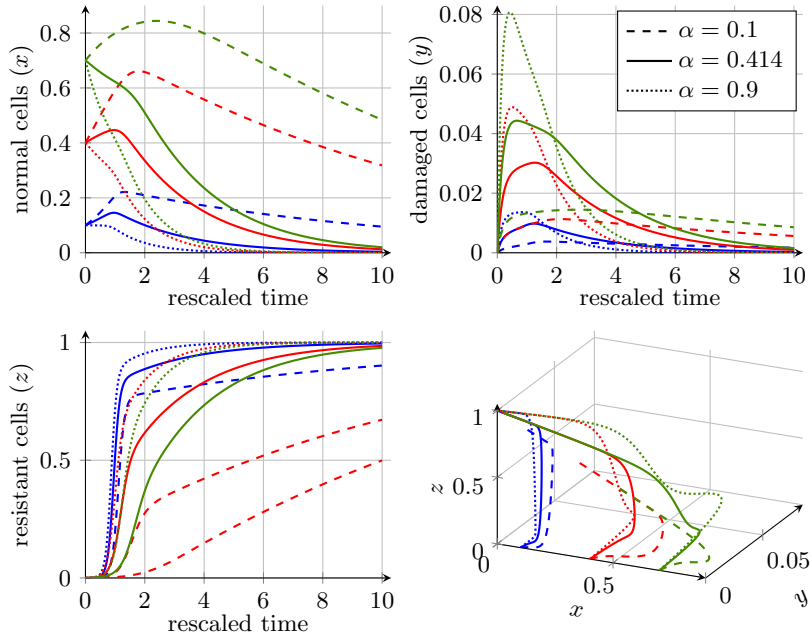

Figure 4: Comparison of solutions of System (4) with $\alpha = 0.1$, $\alpha = 0.414$ and $\alpha = 0.9$.

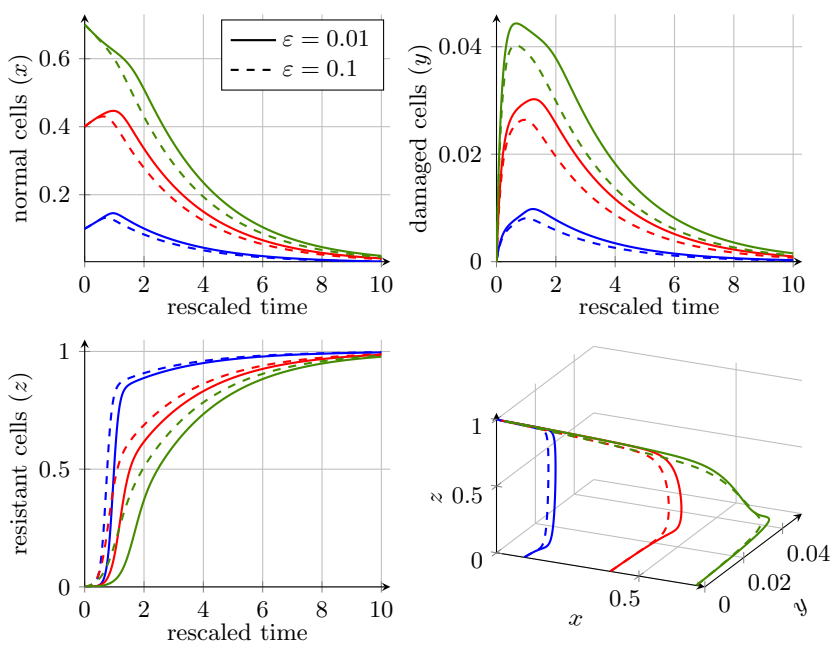

Figure 5: Comparison of solutions of System (4) with $\varepsilon = 0.01$ and $\varepsilon = 0.1$.

cf. Fig. 4. Figure 3 illustrates the dynamics of System (4) with changing ρ. Figures 4 and 5 show similar dynamics with changing α and ε, respectively. However, we see that the parameter α influences the model dynamics more than the others – recall that α reflects the influence of treatment. The smaller the value of α is, the larger maximal level of the normal cells is achieved and the longer time of convergence to the steady state is observed.

Although all solutions converge to the steady state $S = (0, 0, 1)$, as stated in Theorem 3.3, it is interesting to compare the model dynamics and, in particular, the rate of the convergence for various values of the model parameters. By the rate of convergence we mean the time at which the level of resistant cells reaches 0.8, that is the total level of both proliferating and dead cells does not exceed 0.2.

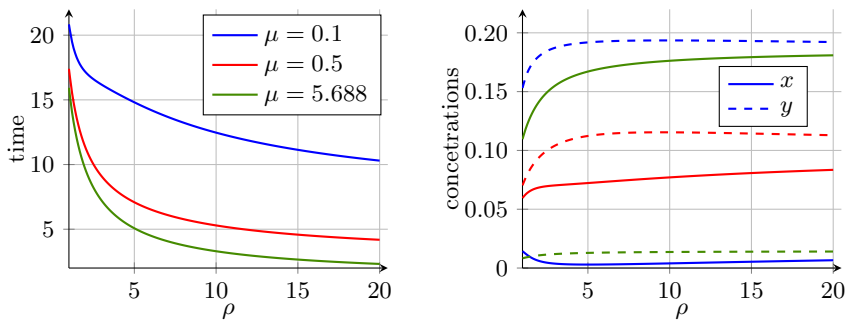

Figure 6: The dependence of time at which the level of resistant cells reaches 0.8 on the growth parameter ρ (left graph) for various values of μ. In the right graph we indicate the level of proliferating cells (solid lines, x), and damaged cells (dashed lines, y) at the time when the resistant cells reach the level 0.8.

First, we investigate the influence of the growth ratio of resistant cells ρ on the convergence rate. In order to do that we numerically find the solution of System (4) with initial values $(0.3, 0, 0)$ and calculate the time at which the resistant cells attain the level 0.8. The results are presented in the left graph of Fig. 6. It turns out that an increase in proliferation rate of resistant cells increases the ratio of the convergence of solutions to the steady state. On the other hand, the increase of the damaged cells parameter increases the rate of the convergence as well. For small μ (smaller than 1) this convergence ratio changes rapidly, while for $\mu > 1$ the change is much slower. For values greater than 5 the change in the convergence ratio is almost not noticeable, so we do include in the picture only the case for $\mu = 5.688$, which is the value used in [1].

On the right-hand side of Fig. 6 we illustrated the value of x (solid lines) and y (dashed lines) at time when the resistant cells reach the level 0.8. Note that this dependence does not need to be monotonic in ρ.

The dependence of the convergence rate on the drug efficiency parameter α is very similar when compared to the left-hand side graph of Fig. 7. On the

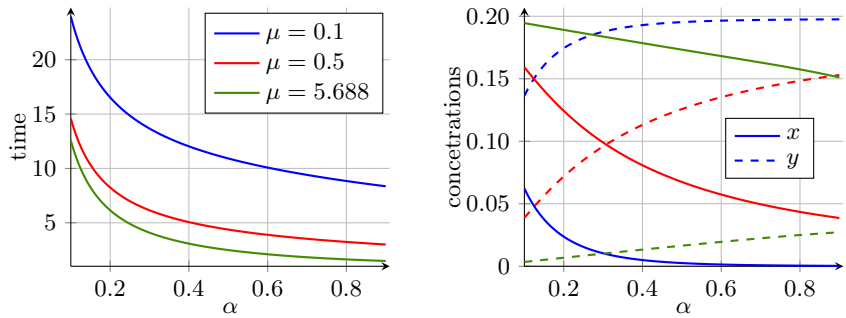

Figure 7: The dependence of time at which the level of resistant cells reaches 0.8 on the growth parameter α (left graph) for various values of μ. In the right graph we indicate the level of proliferating cells (solid lines, x), and damaged cells (dashed lines, y) at the time when the resistant cells reach the level 0.8.

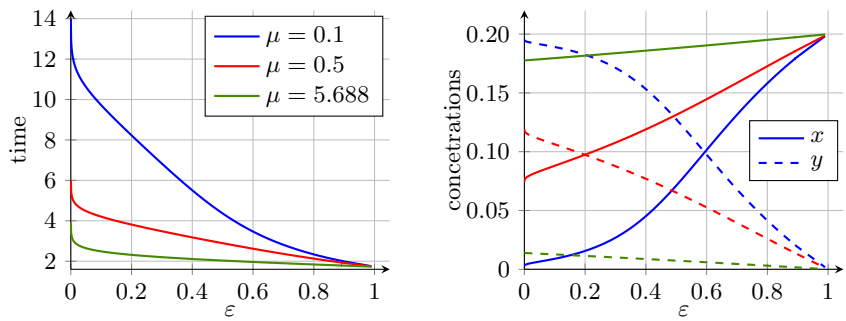

Figure 8: The dependence of time at which the level of resistant cells reaches 0.8 on the probability of acquiring of drug resistance ε (left graph) for various values of μ. In the right graph we indicate the level of proliferating cells (solid lines, x), and damaged cells (dashed lines, y) at the time when the resistant cells reach the level 0.8.

other hand, the level of proliferating cells decreases while the level of damaged cells increases with the increase of α.

The dependence on the probability of acquiring of drug resistance ε is not surprising. The time of acquiring drug resistance by 80% of cells decreases when the mutation parameter increases. The number of proliferating cells increases while the number of damaged cells decreases with an increase of the mutation parameter ε; cf. Fig. 8.

5. Conclusions In this paper we studied a mathematical model of acquiring drug resistance by low grade glioma cells. We combined the ideas presented in [7] and [8]. We complemented the model with a term reflecting additional death of damaged cells and studied the influence of it on the model dynamics. It turned out that in the considered case densities of normal (drug sensitive) and damaged cells converge to 0, while the density of drug resistant

cells converges to the carrying capacity. We proved that fact by constructing an appropriate Lyapunov functional. Numerical simulations revealed that the rate of the convergence to the steady state depends in a monotonic way on the growth rate of resistant cells, the death rate of damaged cells and on the drug efficiency.

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O modelowaniu lekooporności dla glejaków niskiego stopnia

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Streszczenie W artykule analizujemy nową wersję modelu opisującego efekt nabytej lekooporności, który zaproponowaliśmy w pracy Bodnar & Foryś (2017). Oryginalny model powstał w oparciu o idee przedstawione w artykule Pérez-García *i* in. (2015). W bieżącej pracy włączamy do modelu dodatkowy składnik opisujący bezpośrednią śmiertelność komórek uszkodzonych. Okazuje się, że dynamika tak zmienionego modelu jest analogiczna, jak w przypadku drugiego modelu rozważanego przez nas, który z kolei powstał w oparciu o idee Olliera *i* in. (2017). Dynamika modelu została przeanalizowana dla parametrów odzwierciedlających wzrost glejaka niskiego stopnia, przy czym analizowaliśmy wpływ zmian poszczególnych parametrów na tę dynamikę.

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