

# Modeling of drug resistance: comparison of two hypotheses on the example of LGGs

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## Abstract

Acquired drug resistance syndrom (ADR) is one of the most important features associated with tumor treatment and it is therefore a topic of intensive studies. We present two simple mathematical models reflecting different mechanisms of ADR with some Darwinian effects included. These effects allow resistant cells to become sensitive again. Basing on this mathematical approach we conclude that for constant continuous treatment, if no Darwinian effects are present then once resistant cells appear, sensitive cells are eliminated after a long time, independently of the mechanism of acquiring the resistance. However, with Darwinian effects the situation is a little better as the sensitive cells are not completely eliminated but they are still outcompeted by the resistant ones. Moreover, if the therapy is stopped resistant cells become dominated by sensitive cells and the situation changes completely in comparison to the case without Darwinian effects. We discuss these mechanisms on the example of gliomas.

## 1 Introduction

Tumors are still among the most frequent diseases in developed countries. In general, three main types of treatment are usually applied – surgery, chemotherapy and radiotherapy. Two factors are main limitations for chemotherapy. The first one is related to the therapy toxicity, which usually forces to stop therapy after some number of cycles and then a long brake is necessary. The second factor is drug resistance acquired by tumor cells, which causes that subsequent cycles of therapy become less and less efficient and could fail [6, 8, 16]. This is the reason that acquired drug resistance syndrom (ADR) is one of the most important features associated with tumor treatment and is therefore a topic of intensive studies from different perspectives. In this paper we focus on ADR associated with temozolomide (TMZ) treatment of gliomas.

Gliomas are brain tumors that account for about 80% of all brain tumors. The term “glioma” refers to tumors which originate from glial cell precursors. According to the World Health Organisation (WHO) gliomas are divided into four grades, according to their morphologic features. Grade I gliomas are very rare, non-infiltrating and usually curable. Grade II gliomas are usually referred to as low-grade gliomas (LGGs) while grade III and IV – as high-grade gliomas (HGGs); cf. [12]. In general, treating gliomas is difficult due to their location. Clinicians have lately focused their attention on chemotherapy which was shown by phase II trials to be

effective against both previously irradiated and unirradiated LGGs [9, 15]. Response of glioma cells to chemotherapy is a subject of many clinical and biological studies.

In [4] we considered two mathematical models describing different mechanisms of acquiring the drug resistance – one proposed by Ollier *et al.* [13] and the other based on the ideas of Pérez-García *et al.* [14]. The paper of Ollier *et al.* [13] is focused on analyzing which type of resistance, primary or acquired, plays more important role in the case of temozolomide (TMZ) treatment of LGGs. We are interested in analyzing acquired resistance, and therefore we omitted the influence of primary resistance onto the model dynamics. The second considered model is based on the ideas presented in [14]. However, we again took into account the role of acquired drug resistance. Hence, both models have similar structure but the mechanism of acquiring the drug resistance is different. Moreover, we did not assumed any specific tumor growth function (like logistic or Gompertz). Instead, we included a general function having logistic-type properties. We showed that the dynamics of both models, in the case of constant continuous chemotherapy, is similar: all solutions converge to a steady state in which the sub-population of sensitive cells becomes extinct. However, in the second model there is a whole spectrum of steady states lying in the invariant surface to which the solution can be attracted depending on the initial data. It could be suspected that this result is related to the lack of apoptotic death term not associated to the resistance which is present in the first model. Clearly, including such term (cf. [5]) in the model of Pérez-García *et al.* we obtain existence of unique steady state reflecting complete resistance like in the model of Ollier *et al.*

In this paper both models are complemented with genetic instability, sometimes considered as a main driver of ADR (cf. [6]), that is we include the mechanism of regaining drug sensitivity, assuming that due to some mutations a part of resistant cells can become sensitive again. This mechanism has not been included in the original model of Ollier *et al.* [13] and also in the models considered by us in [4].

## 1.1 Presentation of the models

Let us divide the whole population of LGG cells into three sub-populations: proliferating cells that are sensitive to chemotherapy (with concentration denoted by  $P$ ), damaged cells ( $D$ ) and cells with ADR ( $R$ ). Moreover, let  $C$  denote the drug concentration. Due to their biological meaning, all the concentrations are non-negative, that is  $P, D, R, C \in \mathbb{R}_+ = [0, +\infty)$ .

In the models we assume general law of the tumor growth described by some function  $f: \mathbb{R}_+ \rightarrow \mathbb{R}$  having logistic-type properties – we state precise assumptions on  $f$  later – with carrying capacity ( $K$ ) common for the whole population of LGG cells, that is  $V(t) = P(t) + D(t) + R(t)$ . However, proliferating cells and cells with ADR have different growth rates ( $\rho_P$  and  $\rho_R$ , respectively). Application of the drug leads to the decrease of the sub-population of sensitive cells (proportionally to the drug amount and the sub-population size, with a rate  $\alpha_P$ ), and moreover it results in the appearance of damaged and resistant cells.

Ollier *et al.* [13] assumed that damaged cells can either die (with a rate  $\mu_D$ ) or become resistant (with a rate  $\beta_D$ ). In [4] we considered more general form of the model in which the logistic function is replaced by the function  $f$ . Below we also include the process of sensitivity regaining (with a rate  $\gamma_1$ ). Hence, the first model of ADR syndrom we consider reads

$$\dot{P} = \rho_P P f \left( \frac{P + D + R}{K} \right) - \alpha_P C(t) P + \gamma_1 R, \quad (1a)$$

$$\dot{D} = \alpha_P C(t) P - (\beta_D + \mu_D) D, \quad (1b)$$

$$\dot{R} = \rho_R R f \left( \frac{P + D + R}{K} \right) + \beta_D D - \gamma_1 R. \quad (1c)$$

Basing on the ideas presented in [14] we also consider another model that reads

$$\dot{P} = \rho_P P f\left(\frac{P+D+R}{K}\right) - \alpha_P C(t)P + \gamma_1 R, \quad (2a)$$

$$\dot{D} = (1-\varepsilon)\alpha_P C(t)P - \frac{\rho_P}{k} D f\left(\frac{P+D+R}{K}\right), \quad (2b)$$

$$\dot{R} = \rho_R R f\left(\frac{P+D+R}{K}\right) + \varepsilon\alpha_P C(t)P - \gamma_1 R. \quad (2c)$$

In the model above, as in [14], it is assumed that the drug trigger a damage of DNA and during the division a cell either enters an apoptotic pathway or make an attempt to repair the damage and tries to divide. However, the damage cannot be repaired and the cell eventually dies. The parameter  $k$  is a mean number of division attempts before the cell death. Because of this assumption, the death rate of damaged cells is the same as the proliferation rate of undamaged cells divided by the parameter  $k$ . It is also assumed that damaged cells have some probability ( $\varepsilon$ ) to mutate and become resistant.

On the basis of biological interpretation and mathematical requirements we propose the following assumptions regarding the function  $f$  describing the tumor growth:

(H1)  $f: (0, +\infty) \rightarrow \mathbb{R}$  is of class  $C^1$ ,

(H2)  $f$  is strictly decreasing with  $f(1) = 0$ ,

(H3) (a) either  $f(0) = 1$  and it has a continuous derivative at 0,

(b) or  $\lim_{s \rightarrow 0^+} f(s) = +\infty$  and the function  $sf(s)$  is continuous on  $[0, \infty)$  with  $\lim_{s \rightarrow 0^+} sf(s) = 0$ .

Notice that for (H3a) we obtain the logistic-type growth while (H3b) reflects the Gompertz-type growth.

It should be marked that in [14] no apoptotic death for damaged cells was considered. However, including additional term  $-\sigma D$ ,  $\sigma > 0$ , into Equation (2b) does not change the structure of this equation. Clearly, if we consider the following change of the parameters appearing in Equation (2b):

$$\rho_P \rightarrow \tilde{\rho}_P = \sigma k + \rho_P, \quad K \rightarrow \tilde{K} = \frac{K}{\sigma + \frac{\rho_P}{k}},$$

then we obtain exactly the same equation with parameters  $\tilde{\rho}_P$ ,  $\tilde{K}$  instead of  $\rho_P$ ,  $K$ . On the other hand, in this case the parameters  $K$  and  $\tilde{K}$  are different in Equations (2b) and (2a), (2c). In [5] we showed that some of the model properties are different for  $\sigma > 0$  comparing to the original model with  $\sigma = 0$ . We proposed a Lyapunov function proving global stability of the steady state reflecting complete resistance. Here, we would like to focus on the original models and check the influence of mutations toward sensitivity on the models dynamics.

Following the ideas presented in [4] we consider the following change of variables

$$x = P/K, \quad y = D/K, \quad z = R/K, \quad \tilde{t} = \rho_P t, \quad (3)$$

and denote

$$\alpha = \alpha_P C / \rho_P, \quad \beta = \beta_D / \rho_P, \quad \mu = \mu_D / \rho_P, \quad \rho = \rho_R / \rho_P, \quad \gamma = \gamma_1 / \rho_P, \quad \kappa = 1/k, \quad (4)$$

obtaining dimensionless systems

$$\dot{x} = xf(x + y + z) - \alpha x + \gamma z, \quad (5a)$$

$$\dot{y} = \alpha x - (\beta + \mu)y, \quad (5b)$$

$$\dot{z} = \rho zf(x + y + z) + \beta y - \gamma z, \quad (5c)$$

and

$$\dot{x} = xf(x + y + z) - \alpha x + \gamma z, \quad (6a)$$

$$\dot{y} = (1 - \varepsilon)\alpha x - \kappa y f(x + y + z), \quad (6b)$$

$$\dot{z} = \rho zf(x + y + z) + \varepsilon \alpha x - \gamma z, \quad (6c)$$

where all parameters except  $\gamma \geq 0$  are positive and  $x(0) = x_0 \geq 0$ ,  $y(0) = y_0 \geq 0$ ,  $z(0) = z_0 \geq 0$ . Notice that as we consider ADR being the result of the treatment, it is necessary to assume  $\alpha > 0$ , and in the case  $\alpha = 0$  the models properties could be different. We discuss the models dynamics in this case in the last subsection of this article. The most important parameter from the point of view of the analysis presented in this paper is  $\gamma$ , that is the coefficient of back conversion of resistant cells into sensitive ones. Due to biological meaning it seems reasonable to assume that  $\gamma$  is small, such that  $\gamma < \rho$ . Moreover, as  $k$  is the number of divisions, the parameter  $\kappa = \frac{1}{k} \leq 1$ . However, when we include additional apoptotic death, as mentioned before models rescaling, then  $\kappa = \frac{1}{k} + \frac{\sigma}{\rho P}$ , which means that in general it makes sense to consider arbitrary positive values of this parameter.

## 1.2 Properties of the models without mutations

In [4] we studied Systems (5) and (6) without mutations, that is for  $\gamma = 0$ . Notice that in Alvarez-Arenas *et al.* [1] almost the same model as described by (5) with  $\gamma = 0$  was considered. However, the authors of [1] assumed that the coefficient  $\beta_D$  of transition of damaged cells into resistant once is not constant but also depends on the amount  $C(t)$  of delivered drugs. In mathematical analysis they also assumed that all coefficients are constant, so there is no difference between these two models from that point of view. They noticed, that construction of this simplified model is based on the assumption the ADR effect can be triggered only in the presence of therapy. This could be associated with Lamarckian hypotheses and no Darwinian effects are taken into account.

Below we summarize the results proved in [4] (cf. also [1]). Note, that due to Assumption (H3b), if  $f(s) \rightarrow +\infty$  as  $s \rightarrow 0^+$ , then the right-hand sides of Equations (5a) and (6a) are well defined at the origin and continuous in the positive neighborhood of it.

- Both systems have unique solutions for any non-negative initial data. Moreover, it occurs that the systems have the same invariant set, that is

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

- System (5) with  $\gamma = 0$  has two non-negative steady states:
  - trivial state  $A = (0, 0, 0)$  which is locally unstable,
  - semi-trivial state  $B = (0, 0, 1)$  which is locally stable.
- System (6) with  $\gamma = 0$  have the following steady states:
  - trivial state  $A = (0, 0, 0)$  which is unstable,

in the invariant surface  $x + y + z = 1$  the system reduces to

$$\begin{aligned}\dot{x} &= -\alpha x, \\ \dot{y} &= (1 - \varepsilon)\alpha x,\end{aligned}\tag{7}$$

with  $z = 1 - x - y$ . Therefore, all points of the form  $(0, \tilde{y}, 1 - \tilde{y})$  are steady states.

- The theorem below describes global dynamics of both systems (for a proper Lyapunov function see [5]).

**Theorem 1.** *In the invariant set  $\mathcal{P}$  the following statements hold.*

- (i) *All solutions of System (5) with  $\gamma = 0$  converges to  $(0, 0, 1)$ .*
- (ii) *All solutions of System (6) with  $\gamma = 0$  converges to  $(0, 1 - \bar{z}, \bar{z})$ , where  $\bar{z}$  depends on  $x_0, y_0, z_0$ .*

## 2 Analysis of the models with $\gamma > 0$

Note that for  $\gamma > 0$  the basic properties (like existence, uniqueness and non-negativity of solutions) of both models remain the same as for  $\gamma = 0$ . Moreover, invariant sets are also the same because any invariant set depends on the sum of all variables  $x + y + z$ , and this sum does not change for  $\gamma > 0$ . Therefore, we are able to prove the same result as in [4].

**Lemma 2.** *If  $0 \leq x_0 + y_0 + z_0 \leq 1$  then solutions of both Systems (5) and (6) fulfill*

$$0 \leq x(t) + y(t) + z(t) \leq 1, \quad \text{for } t > 0.$$

*Proof.* Non-negativity of the solutions is obvious due to the form of the right-hand side of both Systems. Adding up Equations (5a)–(5c) one gets

$$(x + y + z)' = (x + \rho z)f(x + y + z) - \mu y.$$

Hence, if there exists  $\bar{t} > 0$  such that  $x(\bar{t}) + y(\bar{t}) + z(\bar{t}) = 1$  then  $(x(\bar{t}) + y(\bar{t}) + z(\bar{t}))' = -\mu y \leq 0$ . Gronwall's Lemma and the uniqueness of solutions of System (5) imply  $x(t) + y(t) + z(t) \leq 1$ .

Adding up Equations (6a)–(6c) we obtain

$$(x + y + z)' = (x - \kappa y + \rho z) f(x + y + z).$$

Therefore, the surface  $x + y + z = 1$  is invariant, and uniqueness of solutions implies that for  $x_0 + y_0 + z_0 < 1$  there is  $x(t) + y(t) + z(t) < 1$ , for all  $t > 0$ , and Lemma is proved.  $\square$

Hence, in the following we study the dynamics of Systems (5) and (6) in the invariant set  $\mathcal{P}$ . Moreover, hereafter we assume

$$(H\gamma) \quad 0 < \gamma < \rho.$$

### Reference values of the parameters

In general, we are mainly interested in the models dynamics for biologically relevant values of the parameters. As these reference values we choose parameters estimated in [13] and we rescale them according to (4) obtaining  $\alpha = 0.414$ ,  $\beta = 1.413$ ,  $\mu = 5.688$  and  $\rho = 12$ . We also take an arbitrary value of  $\varepsilon = 0.1$  and  $\kappa = 0.714$  which reflects that a mean number of division tries is equal to 1.4. Therefore, we obtain the following set of reference parameters:

$$\alpha = 0.414, \quad \beta = 1.413, \quad \mu = 5.688, \quad \rho = 12, \quad \varepsilon = 0.1, \quad \kappa = 0.714.\tag{8}$$

On the other hand, many researchers assume that the growth rate of resistant cells  $\rho_R$  is not greater than the growth rate of sensitive ones  $\rho_P$  implying  $\rho \leq 1$ ; c.f. e.g. [2, 10] in the context of optimal control for heterogeneous tumors. Therefore, we shall also consider small values of  $\rho$  as well.

## 2.1 Analysis of System (5)

Let us first consider System (5) and denote  $\eta = \beta + \mu$ .

Looking for steady states we easily see that  $\bar{y} = \frac{\alpha}{\eta}\bar{x}$  for any steady state  $(\bar{x}, \bar{y}, \bar{z})$ . This means that if  $\bar{x} = 0$ , then  $\bar{y} = 0$  as well. However, if  $\bar{x} = 0$ , then from Equation (5a) we immediately obtain  $\bar{z} = 0$ . Hence, there is always the trivial steady state  $S_0 = (0, 0, 0)$ .

Assume now that  $\bar{x} \neq 0$ . This yields  $\bar{y} \neq 0$  and from Equation (5c) we obtain  $\bar{z} \neq 0$ . Hence, we can multiply Equation (5a) by  $\rho z$  and Equation (5c) by  $x$  and subtract them obtaining

$$\gamma\rho(\bar{z})^2 - (\alpha\rho - \gamma)\bar{x}\bar{z} - \beta\bar{x}\bar{y} = 0, \quad (9)$$

from which we get the quadratic equation for  $\frac{\bar{z}}{\bar{x}}$ :

$$\gamma\rho\left(\frac{\bar{z}}{\bar{x}}\right)^2 + (\gamma - \alpha\rho)\frac{\bar{z}}{\bar{x}} - \frac{\alpha\beta}{\eta} = 0.$$

This yields

$$\frac{\bar{z}}{\bar{x}} = \frac{\alpha\rho - \gamma + \sqrt{(\alpha\rho - \gamma)^2 + 4\frac{\alpha\beta\gamma\rho}{\eta}}}{2\gamma\rho} =: A, \quad (10)$$

and therefore  $\bar{z} = A\bar{x}$ . From this relation we can calculate the value of  $\bar{x}$  using Equation (5a):

$$f\left(\bar{x} + \frac{\alpha}{\eta}\bar{x} + A\bar{x}\right) = \alpha - \gamma A \implies \bar{x} = \frac{f^{-1}(\alpha - \gamma A)}{1 + \frac{\alpha}{\eta} + A}. \quad (11)$$

Note that the positive steady state  $S_+ = \left(\bar{x}, \frac{\alpha}{\eta}\bar{x}, A\bar{x}\right)$  bifurcates from the semi-trivial steady state  $(0, 0, 1)$  existing for  $\gamma = 0$  analyzed in [4]. Moreover, existence of the positive steady state requires  $\alpha - \gamma A > 0$ , because the steady state must be located in the invariant set  $\mathcal{P}$ . On the other hand, for the logistic type of  $f$  fulfilling (H3a) the other inequality should be also satisfied, namely

$$\alpha - \gamma A < 1,$$

while for the Gompertz type of  $f$  fulfilling (H3b) this is not a restriction.

**Proposition 3.** *The positive steady state  $S_+ = \left(\bar{x}, \frac{\alpha}{\eta}\bar{x}, A\bar{x}\right)$  of System (5) exists independently of the model parameters.*

*Proof.* We need to check the inequalities  $0 < \alpha - \gamma A < 1$ .

The first inequality, that is  $0 < \alpha - \gamma A$ , is equivalent to  $\eta > \beta$ , which is always satisfied for positive parameters.

The second inequality, that is  $\alpha - \gamma A < 1$ , is equivalent to

$$\alpha\rho + \gamma - 2\rho < \sqrt{(\alpha\rho - \gamma)^2 + 4\frac{\alpha\beta\gamma\rho}{\eta}}. \quad (12)$$

It is easy to see that if  $\alpha \leq 2 - \frac{\gamma}{\rho}$  then the left-hand side of Inequality (12) is non-positive, and therefore this inequality is satisfied. On the other hand, if  $\alpha > 2 - \frac{\gamma}{\rho}$  then both sides of Inequality (12) are positive, and squaring them we obtain the following equivalent inequality

$$(\rho - \gamma)(1 - \alpha) < \frac{\alpha\beta\gamma}{\eta}.$$

Note that we have  $\alpha > 2 - \frac{\gamma}{\rho} > 1$ , and therefore the left-hand side of the inequality above is negative due to (H $\gamma$ ) while the right-hand side is positive, which means that this inequality is always satisfied. Hence, Inequality (12) is always satisfied under Assumption (H $\gamma$ ).  $\square$

## Local stability of the steady states

Let us now consider local stability of the steady states of System (5). To shorten the notation, in the following we mean local stability whenever we refer to as stability. Let  $S = (\bar{x}, \bar{y}, \bar{z})$  denote a steady state,  $\bar{s} = \bar{x} + \bar{y} + \bar{z}$  and  $d = -f'(\bar{s})$ . Looking for the Jacobian matrix of System (5) we obtain

$$J(S) = \begin{pmatrix} f(\bar{s}) - \bar{x}d - \alpha & -\bar{x}d & -\bar{x}d + \gamma \\ \alpha & -\eta & 0 \\ -\rho\bar{z}d & -\rho\bar{z}d + \beta & \rho f(\bar{s}) - \rho\bar{z}d - \gamma \end{pmatrix}. \quad (13)$$

**Proposition 4.** *The trivial steady state  $S_0$  of System (5) is unstable.*

*Proof.* Let us first consider the Gompertz type of  $f$  that fulfills (H3b). In this case Equation (5a) can be estimated from below in the following way

$$\dot{x} \geq x \left( f(x + y + z) - \alpha \right).$$

If  $(x, y, z) \rightarrow (0, 0, 0)$  then  $f(x + y + z) > \alpha + c$ , for some constant  $c > 0$ , for sufficiently small  $x, y, z$ . Thus  $\dot{x} > cx$  for all  $x, y, z$  sufficiently small, and therefore  $x$  is repelled from 0 which contradicts the assumption.

Next, we focus on the logistic type of  $f$  that fulfills (H3a). Then Matrix (13) reads

$$J(S_0) = \begin{pmatrix} 1 - \alpha & 0 & \gamma \\ \alpha & -\eta & 0 \\ 0 & \beta & \rho - \gamma \end{pmatrix},$$

which gives the characteristic polynomial

$$W_1(\lambda) = \lambda^3 + a_2\lambda^2 + a_1\lambda + a_0$$

with

$$a_2 = \eta + \alpha - 1 - \rho + \gamma, \quad a_1 = \eta(\alpha - 1) - (\rho - \gamma)(\eta + \alpha - 1), \quad a_0 = \eta(\rho - \gamma)(1 - \alpha) - \gamma\alpha\beta.$$

According to the Routh-Hurwitz Criterion if at least one of the parameters  $a_i$ ,  $i = 0, 1, 2$ , is negative then the steady state  $S_0$  is unstable.

We consider two mutually exclusive cases.

- Let  $\alpha \geq 1$ . Then  $a_0 < 0$ , obviously.
- Let  $\alpha < 1$  and define

$$\gamma_0 = \frac{\rho\eta(1 - \alpha)}{\alpha\beta + \eta(1 - \alpha)}.$$

If  $\gamma > \gamma_0$  then  $a_0 < 0$ .

If  $\gamma \leq \gamma_0$  then  $a_0 \geq 0$ . Suppose that  $a_i \geq 0$  for  $i = 0, 1, 2$ . We show that this leads to a contradiction.

The inequality  $a_2 \geq 0$  is equivalent to  $\gamma \geq \rho - (\alpha - 1 + \eta)$ . To have both  $a_2$  and  $a_0$  non-negative, one requires

$$\rho - (\alpha - 1 + \eta) \leq \frac{\rho\eta(1 - \alpha)}{\alpha\beta + \eta(1 - \alpha)},$$

which under our assumption is equivalent to

$$\rho \leq \frac{(\alpha - 1 + \eta)(\alpha\beta + \eta(1 - \alpha))}{\alpha\beta}.$$

As  $\rho > 0$ , this implies that  $\alpha + \eta > 1$ . Next, for  $\alpha + \eta > 1$ , the inequality  $a_1 \geq 0$  is equivalent to

$$\gamma \geq \rho + \frac{\eta(1 - \alpha)}{\eta + \alpha - 1}. \quad (14)$$

Note that  $\rho + \frac{\eta(1 - \alpha)}{\eta + \alpha - 1} > \rho$ , and therefore Inequality (14) contradicts Assumption (H $\gamma$ ). This means that at least one  $a_i$  is negative which implies instability of the steady state, and the proof is completed. □

Now, we turn to the positive steady state  $S_+$ . For this state we have

$$f(\bar{s}) - \alpha + \gamma \frac{\bar{z}}{\bar{x}} = 0 \quad \text{and} \quad \rho f(\bar{s}) - \gamma + \beta \frac{\bar{y}}{\bar{z}} = 0,$$

which yields  $f(\bar{s}) - \alpha = -\gamma A$  and  $\rho f(\bar{s}) - \gamma = -\frac{\alpha\beta}{\eta A}$ , and therefore

$$J(S_+) = \begin{pmatrix} -\gamma A - \bar{x}d & -\bar{x}d & -\bar{x}d + \gamma \\ \alpha & -\eta & 0 \\ -\rho A \bar{x}d & -\rho A \bar{x}d + \beta & -\rho A \bar{x}d - \frac{\alpha\beta}{\eta A} \end{pmatrix}.$$

From this Jacobian matrix we obtain the characteristic polynomial

$$W_2(\lambda) = \lambda^3 + b_2\lambda^2 + b_1\lambda + b_0$$

with

$$b_2 = \bar{x}d(\rho A + 1) + \eta + \gamma A + \frac{\alpha\beta}{\eta A} > 0,$$

$$b_1 = \bar{x}d \left( \gamma \rho A^2 + (\eta + \gamma)\rho A + \alpha + \eta + \frac{\alpha\beta}{\eta A} \right) + \eta \gamma A + \frac{\alpha\beta\gamma}{\eta} + \frac{\alpha\beta}{A} > 0,$$

$$b_0 = \bar{x}d \left( \eta \gamma \rho A^2 + (\alpha + \eta)\gamma \rho A + \alpha\beta + \frac{\alpha\beta}{A} + \frac{\alpha^2\beta}{\eta A} \right) > 0.$$

Using the Routh-Hurwitz Criterion one needs to check the sign of  $b_2b_1 - b_0$ . We have

$$b_2b_1 - b_0 = c_2(\bar{x}d)^2 + c_1\bar{x}d + c_0,$$

where

$$c_2 = (\rho A + 1) \left( \gamma \rho A^2 + (\eta + \gamma)\rho A + \alpha + \eta + \frac{\alpha\beta}{\eta A} \right) > 0,$$

$$c_1 = \gamma^2 \rho A^3 + \gamma \rho (\eta + \gamma) A^2 + \left( \frac{2\alpha\beta\gamma\rho}{\eta} + \eta^2\rho + \eta\gamma + \alpha\gamma - \alpha\gamma\rho + \alpha\rho\eta \right) A \\ + 2\alpha\beta\rho + \eta(\alpha + \eta) + \frac{\alpha\beta\gamma(2 + \rho)}{\eta} + \frac{2\alpha\beta}{A} + \frac{\alpha^2\beta^2}{\eta^2 A^2},$$

$$c_0 = \gamma^2 \eta A^2 + \frac{\alpha\beta\gamma + \eta^3}{\eta} \gamma A + 3\alpha\beta\gamma + \frac{(\alpha\beta\gamma + \eta^3)\alpha\beta}{\eta^2 A} + \frac{\alpha^2\beta^2}{\eta A^2} > 0.$$

Let us define

$$\rho_{\text{crit}} = 1 + \frac{2\beta}{\mu - \beta} + \frac{(\mu + \beta)^2}{\alpha(\mu - \beta)}.$$

**Proposition 5.** *If  $\mu \leq \beta$  or  $\mu > \beta$  and  $\rho \leq \rho_{\text{crit}}$  then the positive steady state  $S_+$  of System (5) is stable independently of the magnitude of  $\gamma$ .*

*If  $\mu > \beta$  and  $\rho > \rho_{\text{crit}}$  then  $S_+$  state is stable for  $\gamma < \frac{\rho(\mu+\beta)^2(\alpha+\mu+\beta)}{\alpha\rho(\mu-\beta)-(\mu+\beta)(\alpha+\mu+\beta)}$ .*

*Proof.* Note that if the coefficient of  $A$  in  $c_1$  is positive then  $c_1 > 0$  as well, and the steady state is stable. Positivity of the coefficient of  $A$  is equivalent to the following inequality

$$\eta^2\rho(\eta + \alpha) > -\gamma\left(\alpha((1 - \rho)\eta + 2\beta\rho) + \eta^2\right) = -\gamma\left(\alpha(\rho(\beta - \mu) + \beta + \mu) + (\beta + \mu)^2\right).$$

It is easy to see that the assumptions imply that the inequality above holds.  $\square$

**Corollary 6.** *If  $\gamma$  is small enough then the positive steady state  $S_+$  of System (5) is stable.*

**Corollary 7.** *If  $\rho \leq 1$  then the positive steady state  $S_+$  of System (5) is stable independently of the magnitude of  $\gamma$ .*

For reference parameters (8) we have  $\mu = 5.688 > \beta = 1.413$  and  $\rho = 12 < \rho_{\text{crit}} \approx 30.15$ , so Proposition 5 yields stability of  $S_+$ . On the other hand, as we noted before, the assumption  $\rho \leq 1$  is rather typical and made by many researchers in various context; c.f. e.g. [2, 10] in the context of optimal control for heterogeneous tumors. Therefore, we can conclude that also in such cases the positive steady state  $S_+$  is stable.

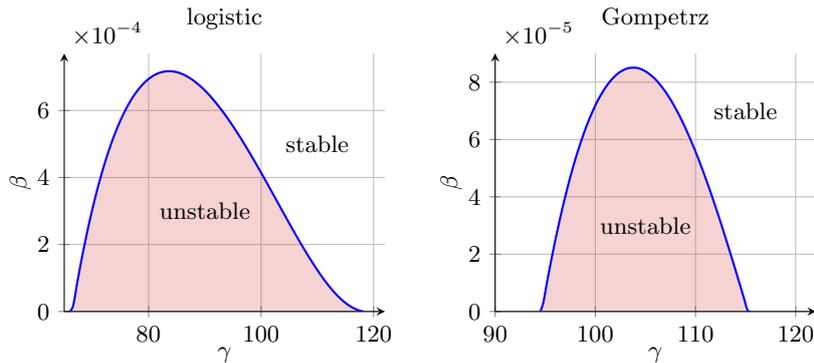


Figure 1: Regions of stability and instability for the positive steady state  $S_+$  of System (5) for  $\alpha = 1$  and  $\rho = 122$  with the logistic function  $f(s) = 1 - s$  (left) and Gompertz function  $f(s) = -\ln s$  (right). Blue curve represents the border between the regions.

At the end of this subsection we would like to illustrate the possible instability of the positive steady state  $S_+$  of System (5). We would like to mark that this is only mathematical illustration as the values of the model parameters, especially  $\rho$ , are rather unrealistic. In Figure 1 regions of stability/instability for the logistic function (left panel) and the Gompertz function (right panel) in the space  $(\gamma, \beta)$  are depicted. We see that the instability regions are very small, as the unimodal function reflecting the border of this region has its maximal value of the order  $6 \cdot 10^{-4}$  for the logistic function and  $8 \cdot 10^{-5}$  for the Gompertz one.

Next presented figures illustrate the model behavior for some parameter values from the unstable region. In Figure 2 we see two exemplary solutions for the logistic and Gompertz function. Graphs presented in Fig. 3 confirm that the solutions are attracted by limit cycles, although the amplitude of oscillations in the case of the Gompertz function is very small.

## 2.2 Analysis of System (6)

Let us look for steady states  $S = (\bar{x}, \bar{y}, \bar{z})$  of System (6) and assume that  $\bar{x} = 0$ . From Equation (6a) we obtain  $\bar{z} = 0$  while Equation (6b) yields  $\bar{y}f(\bar{s}) = 0$ , where  $\bar{s} = \bar{x} + \bar{y} + \bar{z}$  as

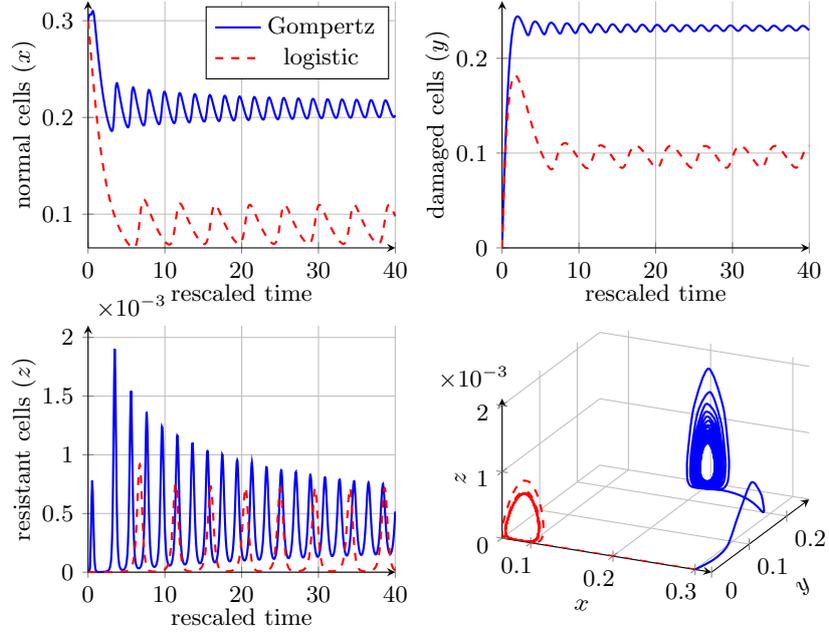


Figure 2: Exemplary solutions of System (5) in unstable case for both the logistic and Gompertz function. Parameter values:  $\alpha = 1$ ,  $\beta = 0.00001$ ,  $\gamma = 100$  and  $\rho = 122$ .

before. Hence, either  $\bar{y} = 0$  or  $\bar{s} = 1$  which means that the trivial steady state  $S_0 = (0, 0, 0)$  and the semi-trivial state  $S_1 = (0, 1, 0)$  exist independently of the magnitude of  $\gamma$ .

Assuming  $\bar{x} \neq 0$ , from Equations (6a) and (6c) we see that  $\bar{z} \neq 0$ . Clearly, if  $\bar{z} = 0$  and  $\bar{x} \neq 0$  then from Equation (6a) there is  $f(s) = \alpha$ , but then from (6c)  $\rho\alpha\bar{x} + \varepsilon\alpha\bar{x} - \gamma\bar{z} = 0$  and if  $\bar{z} = 0$  then  $\bar{x} = 0$ , which contradicts the assumption. Hence, we can multiply Equation (6c) by  $\bar{x}$  and subtract it from Equation (6a) multiplied by  $\rho\bar{z}$ . This implies that if there is a positive steady state then it satisfies

$$\gamma\rho\bar{z}^2 + (\gamma - \alpha\rho)\bar{x}\bar{z} - \varepsilon\alpha\bar{x}^2 = 0 \implies \frac{\bar{z}}{\bar{x}} = \frac{\alpha\rho - \gamma + \sqrt{(\alpha\rho - \gamma)^2 + 4\varepsilon\alpha\rho\gamma}}{2\gamma\rho} := B. \quad (15)$$

This means that the coordinates of the positive steady state satisfy  $\bar{z} = \bar{x}B$ .

Next, adding all three equations of System (6) we obtain either  $f(\bar{s}) = 0$  or  $\bar{x} - \kappa\bar{y} + \rho\bar{z} = 0$ . The first possibility contradicts the assumption  $\bar{x} \neq 0$ , which is easily seen after adding Equations (6a) and (6c). The second possibility implies

$$\bar{y} = \frac{1 + \rho B}{\kappa}\bar{x} \quad \text{and} \quad \bar{z} = B\bar{x}. \quad (16)$$

Using Relations (16) in Equation (6a) one gets

$$f\left(\bar{x} + \frac{1 + \rho B}{\kappa}\bar{x} + \bar{x}B\right) = \alpha - \gamma B, \quad (17)$$

and if  $\alpha - \gamma B > 0$ , and  $\alpha - \gamma B < 1$  for the logistic type of  $f$  fulfilling (H3a), then we can calculate

$$\bar{x} = \frac{f^{-1}(\alpha - \gamma B)}{1 + B + \frac{1 + \rho B}{\kappa}}. \quad (18)$$

Hence, we obtain the positive steady state  $S_+ = (\bar{x}, \frac{1 + \rho B}{\kappa}\bar{x}, B\bar{x})$  with  $\bar{x}$  defined by (18). Note that this state bifurcates from the semi-trivial steady state  $(0, \frac{\rho}{\kappa + \rho}, \frac{\kappa}{\kappa + \rho})$  existing for  $\gamma = 0$ . Clearly, if  $\gamma \rightarrow 0$  then Equation (15) implies  $\bar{x} \rightarrow 0$ , and from Equations (6b) and (6c) we

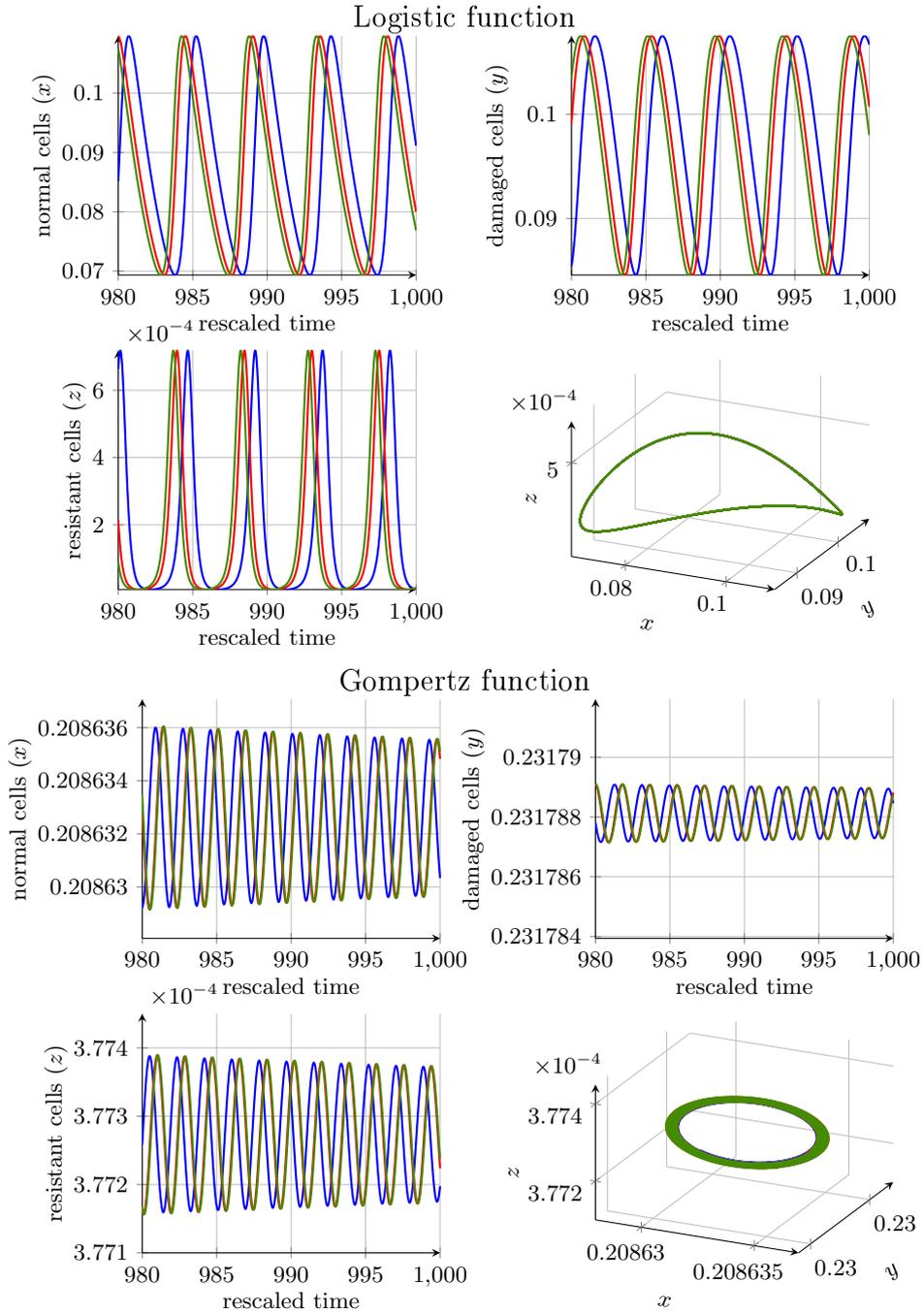


Figure 3: Asymptotic dynamics of the solutions presented in Fig. 2.

obtain either  $\bar{y} = 0$  and  $\bar{z} = 0$  or  $f(\bar{s}) \rightarrow 0$ , that is  $\bar{y} + \bar{z} \rightarrow 1$ . In the first case we have the trivial steady state while in the second one Equation (16) gives  $-\kappa\bar{y} + \rho\bar{z} \rightarrow 0$  which together with the relation  $\bar{y} + \bar{z} \rightarrow 1$  yields  $\bar{y} \rightarrow \frac{\rho}{\kappa+\rho}$  and  $\bar{z} \rightarrow \frac{\kappa}{\kappa+\rho}$ .

**Proposition 8.** *Assume  $\varepsilon < 1$ . The positive steady state  $S_+$  of System (6) exists independently of the model parameters.*

*Proof.* One need to check the inequality  $\alpha - \gamma B > 0$ , as well as the inequality  $\alpha - \gamma B < 1$  for the logistic type of  $f$ . However, the first inequality is equivalent to

$$\alpha\rho + \gamma > \sqrt{(\alpha\rho - \gamma)^2 + 4\varepsilon\alpha\rho\gamma},$$

and squaring both sides one gets the equivalent inequality  $\varepsilon < 1$ , which we assume.

On the other hand, for  $\alpha \leq 1$  the second inequality is always satisfied. Now, assume that  $\alpha > 1$ . Then the inequality  $\alpha - \gamma B < 1$  is equivalent to

$$\alpha\rho - 2\rho + \gamma < \sqrt{(\alpha\rho - \gamma)^2 + 4\varepsilon\alpha\rho\gamma},$$

which is obviously satisfied for  $\alpha \leq 2 - \frac{\gamma}{\rho}$ . For  $\alpha > 2 - \frac{\gamma}{\rho}$  we obtain the following equivalent inequality

$$(\rho - \gamma)(1 - \alpha) < \alpha\gamma\varepsilon,$$

but now  $\alpha > 1$  and this inequality is satisfied due to Assumption (H $\gamma$ ). This completes the proof.  $\square$

### Local stability of the steady states

Now, we turn to the analysis of stability of the steady states of System (6). Calculating the Jacobian matrix for a state  $S = (\bar{x}, \bar{y}, \bar{z})$  we obtain

$$J(S) = \begin{pmatrix} f(\bar{s}) - \bar{x}d - \alpha & -\bar{x}d & -\bar{x}d + \gamma \\ (1 - \varepsilon)\alpha + \kappa\bar{y}d & -\kappa(f(\bar{s}) - \bar{y}d) & \kappa\bar{y}d \\ \varepsilon\alpha - \rho\bar{z}d & -\rho\bar{z}d & \rho f(\bar{s}) - \rho\bar{z}d - \gamma \end{pmatrix}, \quad (19)$$

where  $d = -f'(\bar{s})$  as for System (5).

**Proposition 9.** *The trivial steady state  $S_0$  of System (6) is unstable.*

*Proof.* For the Gompertz type of  $f$  fulfilling (H3a) the proof is analogous to the proof of the same result for System (5).

For the logistic type of  $f$  fulfilling (H3b) we have

$$J(S_0) = \begin{pmatrix} 1 - \alpha & 0 & \gamma \\ (1 - \varepsilon)\alpha & -\kappa & 0 \\ \varepsilon\alpha & 0 & \rho - \gamma \end{pmatrix},$$

and it is obvious that  $\lambda_1 = -\kappa$  is an eigenvalue, and therefore the stability depends on the reduced matrix

$$J_2(S_0) = \begin{pmatrix} 1 - \alpha & \gamma \\ \varepsilon\alpha & \rho - \gamma \end{pmatrix}.$$

We need to check the signs of trace and determinant of the matrix  $J_2(S_0)$ . We easily see that

$$\text{tr } J_2(S_0) = \rho - \gamma + 1 - \alpha, \quad \det J_2(S_0) = \rho(1 - \alpha) - \gamma(1 - \alpha(1 - \varepsilon)).$$

The determinant  $\det J_2(S_0)$  is positive in two cases:

- (i)  $1 - \alpha(1 - \varepsilon) > 0$  and  $\gamma < \frac{\rho(1 - \alpha)}{1 - \alpha(1 - \varepsilon)}$ ,
- (ii)  $1 - \alpha(1 - \varepsilon) < 0$  and  $\gamma > \frac{\rho(\alpha - 1)}{\alpha(1 - \varepsilon) - 1}$ .

Consider case (i). Notice, that  $\alpha$  must be smaller than 1 as  $\gamma$  is positive, and therefore the right-hand side of the second inequality is smaller than  $\rho$ . This gives  $\gamma < \rho$ , that is (H $\gamma$ ). However, in such a case  $\text{tr } J_2(S_0) > 0$ , as  $\alpha < 1$ , so the steady state is unstable.

Consider case (ii). Then  $\alpha > \frac{1}{1 - \varepsilon} > 1$  and the second inequality means that  $\gamma > \rho \left(1 + \frac{\alpha\varepsilon}{\alpha - 1 - \alpha\varepsilon}\right) > \rho$ , which contradicts (H $\gamma$ ), and thus the assertion of the proposition holds.  $\square$

Let us study stability of  $S_1$ . For this state we have  $f(\bar{s}) = 0$  and we obtain the Jacobian matrix of the form

$$J(S_1) = \begin{pmatrix} -\alpha & 0 & \gamma \\ (1-\varepsilon)\alpha + \kappa d & \kappa d & \kappa d \\ \varepsilon\alpha & 0 & -\gamma \end{pmatrix}.$$

For this matrix  $\lambda = \kappa d > 0$  is an eigenvalue, yielding instability of  $S_1$  independently of the model parameters. Note however, that in the invariant surface  $x + y + z = 1$  System (6) reduces to

$$\begin{aligned} \dot{x} &= \gamma - (\alpha + \gamma)x - \gamma y, \\ \dot{y} &= (1 - \varepsilon)\alpha x, \end{aligned}$$

and it is easy to see that this system has exactly one steady state  $(0, 1)$  and  $y$  is strictly increasing, so it must tend to 1, yielding  $x \rightarrow 0$ . Hence, in the invariant surface the projection of the state  $S_1$  is globally stable.

**Corollary 10.** *The semi-trivial steady state  $S_1$  of System (6) is unstable independently of the model parameters, while the projection of this point onto the invariant surface  $x + y + z = 1$  is globally stable within this surface.*

For the positive steady state  $S_+$  there are the following relations:

$$f(\bar{s}) = \alpha - \gamma B, \quad \rho f(\bar{s}) - \gamma = -\alpha\varepsilon \frac{\bar{x}}{\bar{z}} = -\frac{\alpha\varepsilon}{B},$$

yielding the following form of the Jacobian matrix

$$J(S_+) = \begin{pmatrix} -\gamma B - \bar{x}d & -\bar{x}d & -\bar{x}d + \gamma \\ (1-\varepsilon)\alpha + \bar{x}d(1 + \rho B) & -\kappa(\alpha - \gamma B) + \bar{x}d(1 + \rho B) & \bar{x}d(1 + \rho B) \\ \varepsilon\alpha - \bar{x}d\rho B & -\bar{x}d\rho B & -\frac{\alpha\varepsilon}{B} - \bar{x}d\rho B \end{pmatrix}.$$

Now, calculating the characteristic polynomial for  $S_+$  one gets

$$W(\lambda) = \lambda^3 + a_2\lambda^2 + a_1\lambda + a_0,$$

with

$$\begin{aligned} a_2 &= \gamma B + \kappa(\alpha - \gamma B) + \frac{\alpha\varepsilon}{B}, \\ a_1 &= \bar{x}d \left( (\alpha - \gamma B)(\kappa(1 + \rho B) + \rho^2 B + 1) \right) + \kappa(\alpha - \gamma B) \left( \gamma B + \frac{\alpha\varepsilon}{B} \right), \\ a_0 &= \bar{x}d \left( \kappa(\alpha - \gamma B)(B + 1) \left( \gamma\rho B + \frac{\alpha\varepsilon}{B} \right) + \alpha(1 - \varepsilon) \left( \gamma\rho B + \frac{\alpha\varepsilon}{B} \right) \right). \end{aligned}$$

Recall that  $\alpha > \gamma B$  and  $\varepsilon < 1$ , hence all  $a_i > 0$ ,  $i = 0, 1, 2$ . Denoting  $U = \alpha - \gamma B > 0$ , according to the Routh-Hurwitz Criterion, one needs to check the sign of

$$\begin{aligned} C_{RH} := a_2 a_1 - a_0 &= \kappa U \left( \gamma B + \kappa U + \frac{\alpha\varepsilon}{B} \right) \left( \gamma B + \frac{\alpha\varepsilon}{B} \right) \\ &\quad + \bar{x}d \left( (1 - \rho)\gamma(1 + \kappa)BU \right. \\ &\quad \left. + \left( \kappa(\rho + \kappa)\rho U^2 + \alpha\gamma\varepsilon(\kappa(1 - \rho) - \rho^2) \right) B \right. \\ &\quad \left. + \kappa(1 + \kappa)U^2 + \alpha\varepsilon(\alpha\rho^2 - \gamma) - (1 - \rho)\alpha^2\kappa\varepsilon + \frac{\alpha^2\varepsilon^2}{B} \right). \end{aligned}$$

As in general it is difficult to attribute a sign to the  $C_{RH}$  expression, let us consider a special case  $\varepsilon \rightarrow 0$ . Then we have

$$B \rightarrow \frac{\alpha\rho - \gamma}{\gamma\rho}, \quad \alpha - \gamma B \rightarrow \frac{\gamma}{\rho}.$$

Note that in this case there should be  $\alpha\rho - \gamma > 0$  as we want to have the positive steady state, and we obtain

$$\begin{aligned} a_2 &\rightarrow \frac{\alpha\rho - \gamma + \gamma\kappa}{\rho}, \\ a_1 &\rightarrow \bar{x}d \frac{\rho(\alpha\rho - \gamma + \alpha\kappa) + \gamma}{\rho} + \frac{\gamma\kappa(\alpha\rho - \gamma)}{\rho^2}, \\ a_0 &\rightarrow \bar{x}d(\alpha\rho - \gamma) \frac{\kappa(\alpha\rho - \gamma + \gamma\rho) + \alpha\rho^2}{\rho^2}. \end{aligned}$$

Some algebraic calculations show that

$$C_{HR} \rightarrow C_{HR}^{\lim} := \frac{\gamma\kappa(\alpha\rho - \gamma)(\alpha\rho - \gamma + \gamma\kappa)}{\rho^3} - \frac{\alpha\gamma\bar{x}d}{\rho^2} \left( \rho^2 - \left( \frac{\gamma}{\alpha} + \kappa(\kappa + 1) + 1 \right) \rho + \frac{\gamma}{\alpha} \right). \quad (20)$$

It should be marked that in a general case the value  $\bar{x}d$  does not depend on the other model parameters. Clearly, we are always able to change the slope of the function  $f$  at  $\bar{x}$  to make the value  $d$  as large or as small as we want. Thus, if the sign of the second term of the limit  $C_{HR}^{\lim}$  defined by (20) is negative then the steady state is stable for any function  $f$ , and if this term is positive the steady state is unstable for at least some function  $f$ . The sign of this term depends on the sign of

$$P_\rho(\rho) = \rho^2 - \left( \frac{\gamma}{\alpha} + \kappa(\kappa + 1) + 1 \right) \rho + \frac{\gamma}{\alpha},$$

which is a quadratic polynomial in  $\rho$ . The determinant of it reads

$$\Delta_\rho = \left( \frac{\gamma}{\alpha} - 1 \right)^2 + 2\kappa(\kappa + 1) \left( \frac{\gamma}{\alpha} + 1 \right) + \kappa^2(\kappa + 1)^2 > 0.$$

Thus,  $P_\rho$  has two positive roots

$$\rho_1 = \frac{\frac{\gamma}{\alpha} + \kappa(\kappa + 1) + 1 - \sqrt{\Delta_\rho}}{2}, \quad \rho_2 = \frac{\frac{\gamma}{\alpha} + \kappa(\kappa + 1) + 1 + \sqrt{\Delta_\rho}}{2},$$

and  $P_\rho$  is non-positive for  $\rho \in [\rho_1, \rho_2]$  and positive otherwise. Let us recall that we need to have  $\rho > \frac{\gamma}{\alpha}$  and it is easy to check that  $\frac{\gamma}{\alpha} \in (\rho_1, \rho_2)$ . Hence, we are in a position to formulate the following corollary.

**Corollary 11.** *If  $\rho \in (\frac{\gamma}{\alpha}, \rho_2]$  then the positive steady state  $S_3$  of System (6) is stable for sufficiently small  $\varepsilon$  and any arbitrary function  $f$ . If  $\rho > \rho_2$  then there exist such small  $\varepsilon$  and a function  $f$  that this steady state is unstable.*

Note that  $P_\rho(1) = -\kappa(\kappa + 1) < 1$ , hence another less specific corollary could be formulated.

**Corollary 12.** *If  $\gamma < \alpha$  and  $\rho \in (\frac{\gamma}{\alpha}, 1]$  then the positive steady state  $S_3$  of System (6) is stable for sufficiently small  $\varepsilon$  and any arbitrary function  $f$ .*

Now, let us illustrate the possible stability switches of the positive steady state  $S_+$  of System (6). In Figures 4 and 5 we see the regions of stability and instability of the positive steady state  $S_+$  of System (6) in the plane  $(\gamma, \varepsilon)$  for the logistic and Gompertz function  $f$ , respectively. Although both figures show that instability is possible for both functions, but we should mark that it appears only for small values of  $\varepsilon$ . Note, that the regions of stability

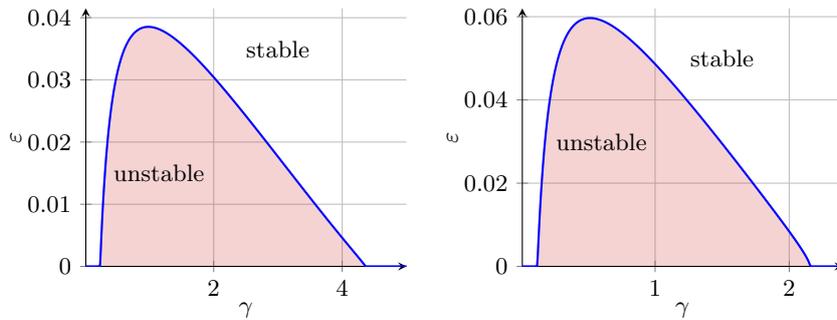


Figure 4: Regions of stability and instability for the positive steady state  $S_+$  of System (6) with the logistic function  $f(s) = 1 - s$ . Blue curve represents the border between these regions described by the relation  $C_{RH} = 0$ . For the left-hand side panel the reference parameter values (8), except  $\varepsilon$ , were used; for the right-hand side panel:  $\alpha = 0.3$ ,  $\kappa = 0.46$ ,  $\rho = 8$ .

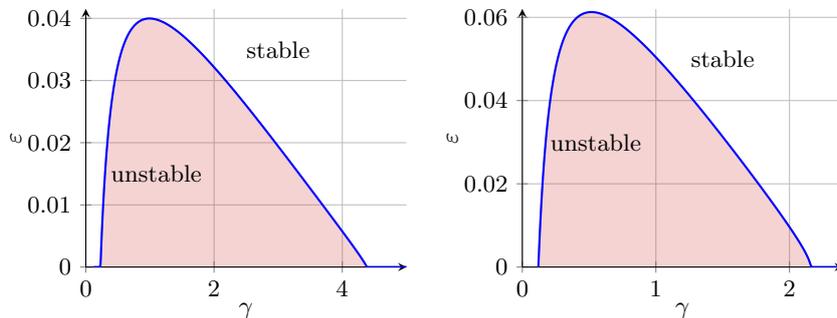


Figure 5: Regions of stability and instability for the positive steady state  $S_+$  of System (6) with the Gompertz function  $f(s) = -\ln s$ . Blue curve represents the border between these regions described by the relation  $C_{RH} = 0$ . For the left-hand side panel the reference parameter values (8), except  $\varepsilon$ , were used; for the right-hand side panel:  $\alpha = 0.3$ ,  $\kappa = 0.46$ ,  $\rho = 8$ .

and instability for the logistic and Gompertz functions are very similar. The curve  $C_{RH} = 0$  defining the border between these regions is a unimodal function with maximal value near 0.04 for reference parameters and 0.06 for  $\alpha = 0.3$ ,  $\kappa = 0.46$  and  $\rho = 8$ .

At the end of our analysis we would like to illustrate the behavior of System (6) in unstable case. This illustration for the logistic function  $f(s) = 1 - s$  is presented in Fig. 6, where we see oscillatory dynamics of the solutions with eventual periodic behavior. We would like to note that similar dynamics could be obtained for the Gompertz function  $f(s) = -\ln s$ , and therefore we do not include an additional figure here.

### 2.3 Positive steady state depending on $\gamma$

In this subsection we consider the positive steady state  $S_+$  as a function of  $\gamma$ , which is the parameter of our interest in the present study. We mainly focus on the logistic function  $f(s) = 1 - s$ , however some part of the analysis presented below is valid for a general function  $f$ .

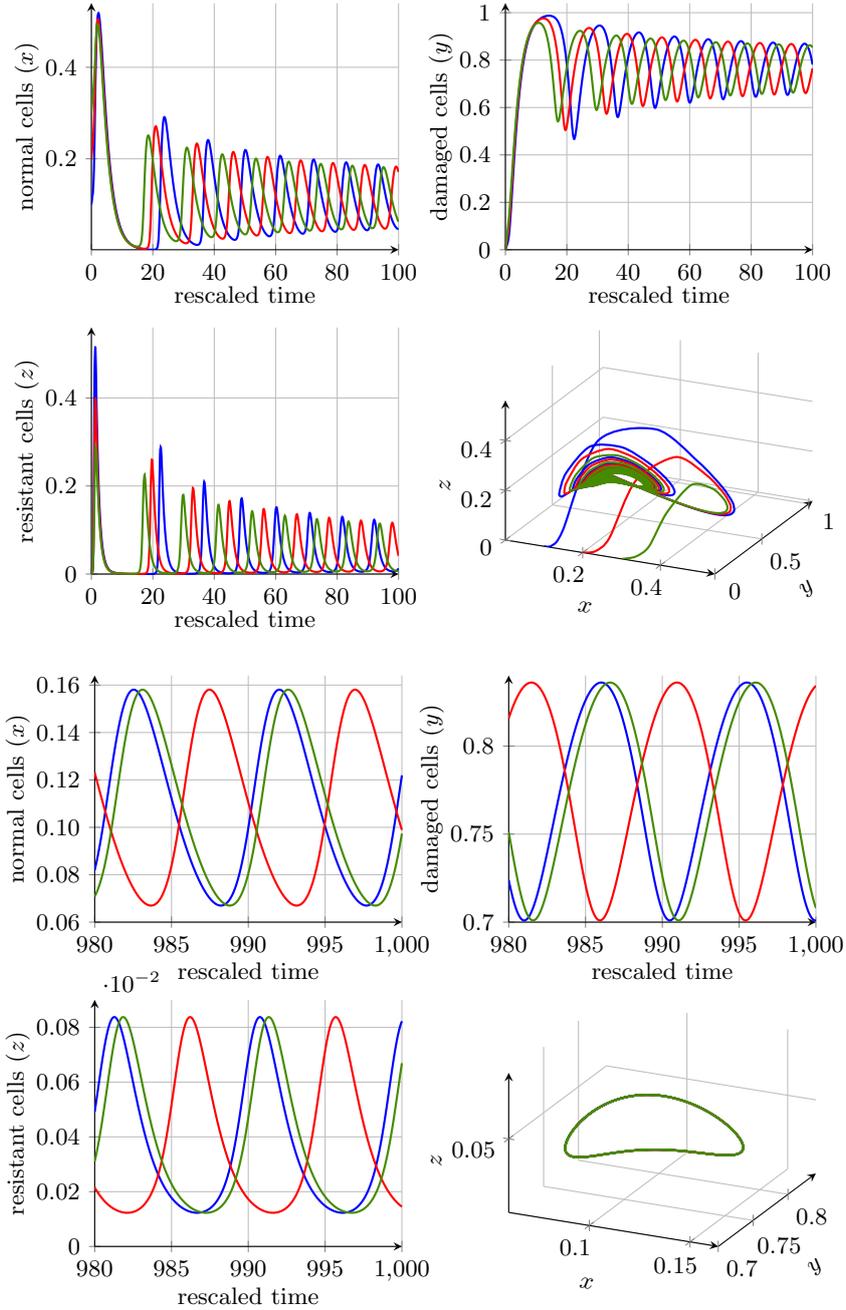


Figure 6: Exemplary solutions of System (6) with the logistic function  $f(s) = 1 - s$  illustrating unstable case. We took reference parameter values (8) except  $\gamma = 1$  and  $\varepsilon = 0.03$ . The top panel shows the solutions and phase space for the time interval  $[0, 100]$ , while the bottom panel shows eventual periodic behavior of these solutions, the time interval  $[980, 1,000]$ .

### 2.3.1 System (5)

We know that the positive steady state  $S_+$  bifurcates from the semi-trivial state  $(0, 0, 1)$  independently of the model parameters. Looking for the dependence on  $\gamma$  we calculate:

$$\frac{\partial A}{\partial \gamma} = -\alpha \frac{\sqrt{\Delta} + \alpha\rho - \gamma + 2\frac{\beta}{\eta}\gamma}{2\gamma^2\sqrt{\Delta}} < 0,$$

$$\frac{\partial(\gamma A)}{\partial \gamma} = -\frac{\sqrt{\Delta} + \alpha\rho - \gamma - 2\alpha\rho\frac{\beta}{\eta}}{2\rho\sqrt{\Delta}},$$

where  $\Delta = (\alpha\rho - \gamma)^2 + 4\alpha\gamma\rho\frac{\beta}{\eta}$ . Note that  $\frac{\partial(\gamma A)}{\partial\gamma} < 0$  as  $\sqrt{\Delta} > 2\alpha\rho\frac{\beta}{\eta} - (\alpha\rho - \gamma)$  due to the relation between the parameters  $\eta > \beta$ .

Moreover, if we treat  $\bar{x}$  as a function of  $\gamma$ , then we can differentiate Formula (17) obtaining

$$f'(\bar{s}) \left( \frac{\partial\bar{x}}{\partial\gamma} \left( 1 + \frac{\alpha}{\eta} + A \right) + \bar{x} \frac{\partial A}{\partial\gamma} \right) = -A - \gamma \frac{\partial A}{\partial\gamma},$$

and if  $f'(\bar{s}) = -d \neq 0$  we get

$$\frac{\partial\bar{x}}{\partial\gamma} = \frac{A - \frac{\partial A}{\partial\gamma} (\bar{x}d - \gamma)}{d \left( 1 + \frac{\alpha}{\eta} + A \right)},$$

which means that for sufficiently small  $\gamma$  the coordinate  $\bar{x}$  is an increasing function of  $\gamma$ . Moreover, as  $\bar{y} = \frac{\alpha}{\eta}\bar{x}$  then  $\bar{y}$  is increasing as well. Note that for the logistic function  $f(s) = 1 - s$  we have  $d = 1$  and  $\bar{x} = \frac{1 - \alpha + \gamma A}{1 + \frac{\alpha}{\eta} + A}$ , and therefore the sufficient condition for  $\bar{x}$  to be increasing as a function of  $\gamma$  reads

$$\gamma < \frac{1 - \alpha}{1 + \frac{\alpha}{\eta}},$$

which requires  $\alpha < 1$ . In this case we also have

$$\bar{z} = A\bar{x} = (1 - \alpha + \gamma A) \frac{1}{1 + \frac{\alpha + \eta}{\eta A}},$$

which is the product of two decreasing positive functions implying that  $\bar{z}$  is decreasing as a function of  $\gamma$  for the logistic function  $f$  independently of the model parameters.

### 2.3.2 System (6)

For this system the positive steady state  $S_+$  bifurcates from the semi-trivial state  $\left( 0, \frac{\rho}{\kappa + \rho}, \frac{\kappa}{\kappa + \rho} \right)$  existing for  $\gamma = 0$ . For reference parameters (8) and the logistic function  $f$  this point is approximately  $(0, 0.9438, 0.05616)$ .

As before, we consider the dependence on  $\gamma$  and make some calculations. Note, that the calculations regarding  $A$  and  $B$  are almost the same. The only difference is that  $\varepsilon$  appears in the place of  $\frac{\beta}{\eta}$  present in System (5). Therefore, we have

$$\begin{aligned} \frac{\partial B}{\partial\gamma} &= -\alpha \frac{\sqrt{\Delta} + \alpha\rho - \gamma + 2\varepsilon\gamma}{2\gamma^2\sqrt{\Delta}} < 0, \\ \frac{\partial(\gamma B)}{\partial\gamma} &= -\frac{\sqrt{\Delta} + \alpha\rho - \gamma - 2\alpha\rho\varepsilon}{2\rho\sqrt{\Delta}}, \end{aligned}$$

where  $\Delta = (\alpha\rho - \gamma)^2 + 4\varepsilon\alpha\gamma\rho$ . Note that, like in the previous case,  $\frac{\partial(\gamma B)}{\partial\gamma} < 0$  as  $\sqrt{\Delta} > 2\alpha\rho\varepsilon - (\alpha\rho - \gamma)$  for any  $\varepsilon < 1$ .

As before, we can differentiate Formula (17) obtaining

$$f'(\bar{s}) \left( \frac{\partial\bar{x}}{\partial\gamma} \left( 1 + B + \frac{1 + \rho B}{\kappa} \right) + \bar{x} \frac{\partial B}{\partial\gamma} \left( 1 + \frac{\rho}{\kappa} \right) \right) = -B - \gamma \frac{\partial B}{\partial\gamma},$$

and if  $f'(\bar{s}) = -d \neq 0$  we get

$$\frac{\partial\bar{x}}{\partial\gamma} = \frac{B - \frac{\partial B}{\partial\gamma} (\bar{x}d (1 + \frac{\rho}{\kappa}) - \gamma)}{d \left( 1 + B + \frac{1 + \rho B}{\kappa} \right)}$$

which means that for sufficiently small  $\gamma$  the coordinate  $\bar{x}$  is an increasing function of  $\gamma$ . For the logistic function  $f(s) = 1 - s$  and  $\varepsilon \rightarrow 0$  it is enough that

$$\frac{\gamma\kappa(\rho - \gamma)}{\kappa(\alpha\rho + \gamma(\rho - 1)) + \alpha\rho^2} \left(1 + \frac{\rho}{\kappa}\right) > \gamma \iff \gamma < \frac{\kappa + \rho}{\kappa + 1}(1 - \alpha),$$

which requires  $\alpha < 1$ , as before. On the other hand, it is easy to see that for  $\alpha < \frac{\kappa + \rho}{\kappa(1 + \rho) + 2\rho}$  the inequality above is not restrictive, as we have

$$\gamma < \alpha\rho < \frac{\kappa + \rho}{\kappa + 1}(1 - \alpha).$$

Continuing our analysis of this specific case of the logistic function  $f$ , we see that

$$\bar{z} = B\bar{x} = (1 - \alpha + \gamma B) \frac{1}{1 + \frac{\rho}{\kappa} + \frac{1 + \kappa}{\kappa B}},$$

and  $\bar{z}$  as a function of  $\gamma$  is a product of two positive decreasing functions, implying that  $\bar{z}$  is decreasing as a function of  $\gamma$ . Similarly,

$$\bar{y} = \frac{1 + \rho B}{\kappa} \bar{x} = \frac{1 - \alpha + \gamma B}{1 + \kappa \frac{1 + B}{1 + \rho B}},$$

and therefore

$$\frac{\partial \bar{y}}{\partial \gamma} = \frac{\frac{\partial(\gamma B)}{\partial \gamma} \left(1 + \kappa \frac{1 + B}{1 + \rho B}\right) - (1 - \alpha + \gamma B) \frac{\partial B}{\partial \gamma} \frac{\kappa(1 - \rho)}{(1 + \rho B)^2}}{\left(1 + \kappa \frac{1 + B}{1 + \rho B}\right)^2},$$

implying that  $\bar{y}$  is decreasing for all  $\rho > 1$  due to two negative terms in the numerator, while for  $\rho < 1$  we have a sum of negative and positive terms, so  $\bar{y}$  may not be necessarily decreasing. Considering  $\varepsilon \rightarrow 0$  we obtain

$$\bar{y} \rightarrow \frac{\alpha\rho(\rho - \gamma)}{\gamma\kappa(\rho - 1) + \alpha\rho(\kappa + \rho)}.$$

Now, it is an easy to calculate the derivative of  $\bar{y}$  with respect to  $\gamma$  obtaining

$$\frac{\partial \bar{y}}{\partial \gamma} \rightarrow -\frac{\alpha\rho^2(\rho(\alpha + \kappa) - \kappa(1 - \alpha))}{(\gamma\kappa(\rho - 1) + \alpha\rho(\kappa + \rho))^2}.$$

Therefore, if

$$\rho < \frac{\kappa(1 - \alpha)}{\alpha + \kappa} \tag{21}$$

then  $\bar{y}$  is an increasing function of  $\gamma$  for sufficiently small  $\varepsilon$ . Of course, it again requires  $\alpha < 1$ . For reference parameter values (except  $\rho$ , of course) this threshold is equal to 0.371. In Fig. 7 we present dependence of coordinates of the positive steady state  $S_+$  on  $\gamma$  for several sets of the parameter values. We see that for  $\rho = 0.3$  the  $y$ -coordinate is increasing for both sets of chosen parameter values, which agrees with the estimation obtained above. Note that in presented graphs we have  $\varepsilon = 0.1$  while the estimation has been obtained for  $\varepsilon \rightarrow 0$ .

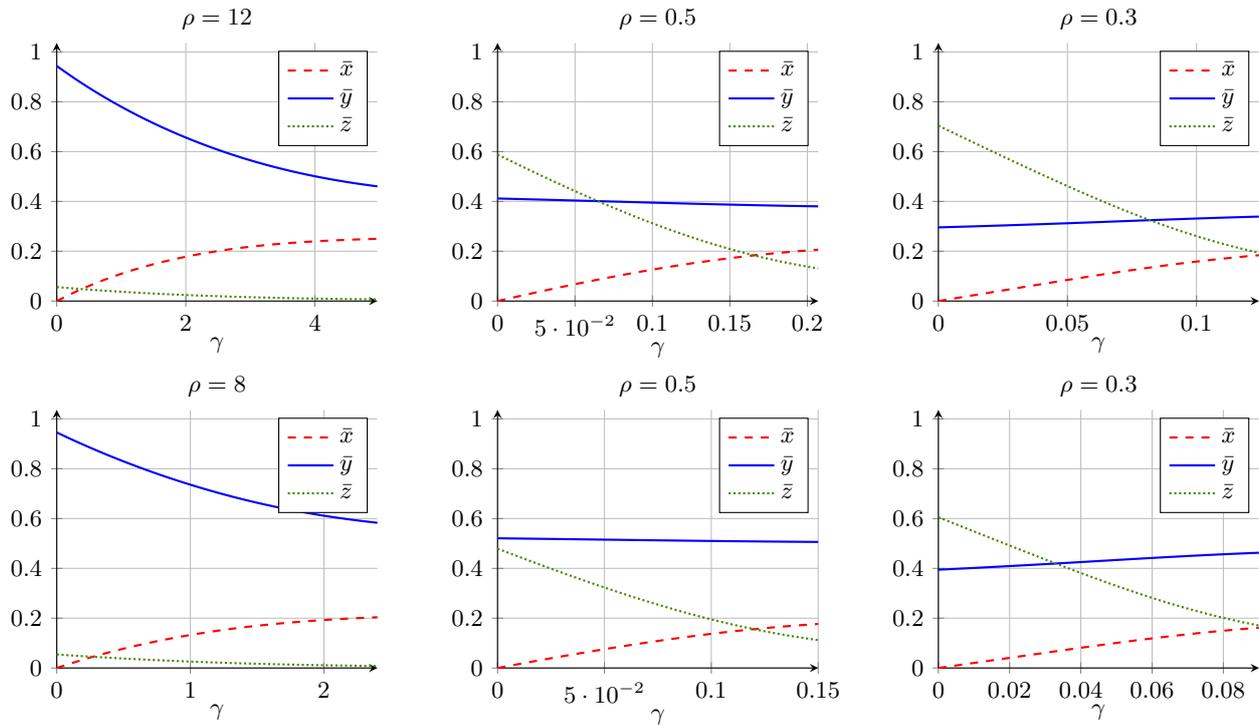


Figure 7: Dependence of the positive steady state  $S_+$  of System (6) on the magnitude of  $\gamma$  for the logistic function  $f$ :  $\bar{x}$ ,  $\bar{y}$  and  $\bar{z}$  are depicted in solid red, dashed blue and dotted green, respectively. Parameter values: in the top row reference values (8) with (from left)  $\rho = 12$ ,  $\rho = 0.5$  and  $\rho = 0.3$ ; in the bottom row  $\alpha = 0.3$ ,  $\kappa = 0.46$  and (from left)  $\rho = 8$ ,  $\rho = 0.5$ , and  $\rho = 0.3$ . The values of  $\gamma$  are restricted to those bounded above by  $\alpha\rho$ , like for  $\varepsilon \rightarrow 0$ , although  $\varepsilon = 0.1$  here.

## 2.4 Dynamics of the systems for $\alpha = 0$ .

Let us recall that the coefficient  $\alpha$  reflects chemotherapy. Thus, it is interesting to study what will happen if we stop the treatment, that is  $\alpha = 0$  starting from some time  $t_0 > 0$ . As the system is autonomous, we again can assume  $t_0 = 0$  without lack of generality. Clearly, in this case the  $y$ -coordinate of the solution of both Systems (5) and (6) is decreasing, while the  $x$ -coordinate is increasing.

For System (5) the equation for  $y$  could be solved and we see that this coordinate decreases to 0 exponentially with the exponent  $\eta = \beta + \mu$ . Therefore, the only coordinate that is able to change its monotonicity is  $z$ .

Let us check the behavior of asymptotic equations for System (5), that is

$$\dot{x} = xf(x+z) + \gamma z, \quad (22a)$$

$$\dot{z} = \rho z f(x+z) - \gamma z. \quad (22b)$$

Studying the dynamics of System (22) we easily see that there exists the only steady state  $(1, 0)$ , and according to the Poincaré-Bendixson Theorem it is globally stable, due to monotonicity of the coordinate  $x$ . In Figure 8 we see that the dynamics of the full System (5) (top left) and asymptotic System (22) (bottom) are almost indistinguishable. We also see that the qualitative dynamics of the asymptotic System (22) does not depend on the model parameters. However, for smaller values of  $\rho$  the rate of convergence of solutions to the steady state is smaller than for larger values of  $\rho$ .

In fact, we can prove global stability of the steady state  $(1, 0, 0)$ .

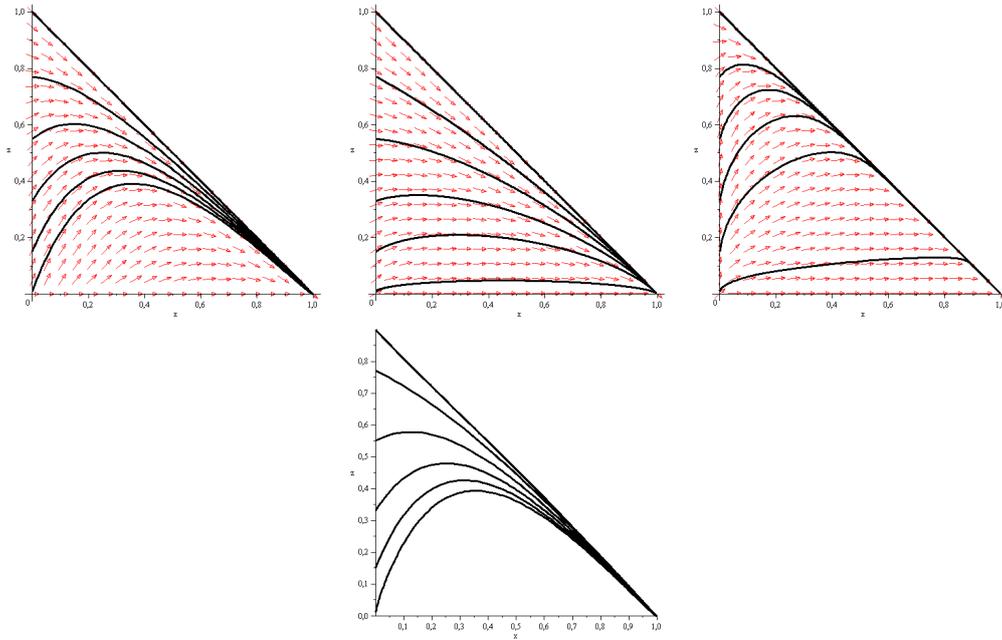


Figure 8: Top panel: Phase portraits of asymptotic System (22) with  $\rho = 12$  (reference),  $\gamma = 3$  (left) and  $\rho = 1$ ,  $\gamma = 0.5$  (middle), and  $\rho = 0.5$ ,  $\gamma = 0.05$  (right). Other parameter values are taken as reference. Bottom panel: The projection onto  $(x, z)$  of the solutions of the full System (5) with  $\alpha = 0$  and  $y_0 = 0.1$ . Parameter values are taken as reference and  $\gamma = 3$ .

**Proposition 13.** *The steady state  $(1, 0, 0)$  of System (5) with  $\alpha = 0$  is globally stable in  $\mathcal{P}$  except the trivial point.*

*Proof.* Let us define the following Lyapunov function  $L(x, y, z) = (1-x) + 2y$ . It is obvious that in  $\mathcal{P}$  the function  $L$  is non-negative and  $L(x, y, z) = 0$  only at the point  $(1, 0, 0)$ . Calculating the derivative of  $L$  along solutions of System (5) we obtain

$$\dot{L} = -xf(s) - \eta y - \gamma z \leq 0.$$

Moreover,  $\dot{L} = 0$  in  $\mathcal{P}$  iff  $x = y = z = 0$  or  $y = z = 0$  and  $f(s) = 1$ . However, the only invariant subset of the set  $\{(x, y, z) \in \mathcal{P} : \dot{L}(x, y, z) = 0\}$  that can attract other solutions is the steady state  $(1, 0, 0)$ , which completes the proof.  $\square$

For System (6) the situation is more complex, as we could expect, because there is no unique non-trivial steady state. At the steady state either  $\bar{y} = 0$  or  $f(\bar{s}) = 0$ . This yields the existence of the trivial steady state  $(0, 0, 0)$  as well as the whole family of states  $(\bar{x}, 1 - \bar{x}, 0)$  within the invariant surface  $x + y + z = 1$ . The same Lyapunov function as in the proof of Proposition 13 shows that any steady state from that family could attract other solutions. Figure 9 illustrates the dynamics of the system in such a case. We see that depending on parameter values as well as initial data the solutions are attracted by different steady states satisfying  $\bar{x} + \bar{y} = 1$ . Moreover, for each of the presented solutions the asymptotic ratio of the sensitive cells exceeds 60%.

Thus, independently of the model (that is System (5) or System (6)) if the chemotherapy is stopped after some time of treatment and that treatment is not continued any more then the subpopulation of resistant tumor cells will eventually go to extinction, which is related to the Darwinian effects allowing the cells to recover sensitivity. However, for System (5) we observe complete recovery of sensitivity, while for System (6) it is only partial, as there will be a portion of damaged cells remaining in the organism.

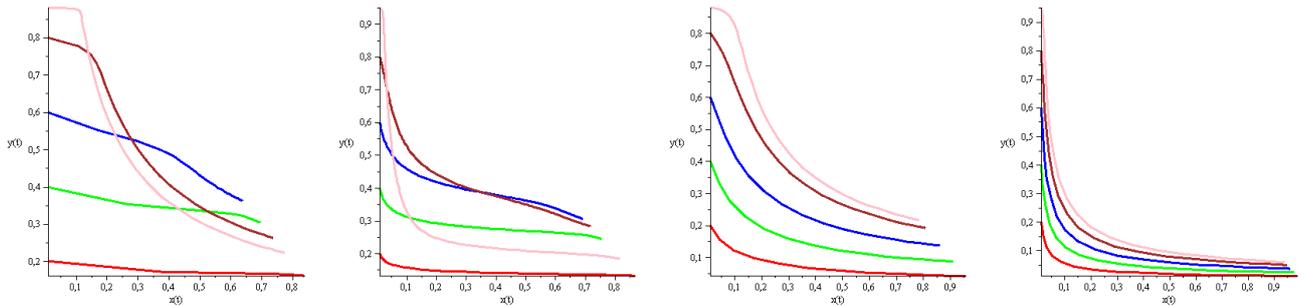


Figure 9: Projection of the solutions of System (6) with  $\alpha = 0$  into the space  $(x, y)$ . Initial conditions are:  $x(0) = 0.01$ ,  $z(0) = 0.1$  (left panels) and  $z(0) = 0.01$  (right panels), while  $y(0)$  changes. Parameter values are taken as reference, except  $\rho$  and  $\gamma$ , which are, from left:  $\rho = 12$  (reference) and  $\gamma = 3$ ,  $\rho = 1$  and  $\gamma = 0.5$ ;  $\rho = 12$  and  $\gamma = 3$ ;  $\rho = 1$  and  $\gamma = 0.5$ . As we see, the solutions tend to the invariant subspace  $x + y + z = 1$ . However, as  $z \rightarrow 0$ , we have the relation  $x + y \rightarrow 1$ , which is represented by “ends” of the curves localized within the line  $x + y = 1$ .

### 3 Discussion and conclusions

In the paper we have considered two models of possible mechanisms of acquired drug resistance based on the ideas presented in [13] and [14]. Within the whole population of tumor cells we distinguish three sub-populations of sensitive, damaged and resistant cells. We assumed continuous therapy reflected by a coefficient  $\alpha$ . Unlike in the original papers, we also included a spontaneous recovery of sensitivity by tumor cells related to Darwinian effects and described by a coefficient  $\gamma$ . It occurs that if even a small portion of resistant cells can regain sensitivity, it changes the whole picture dramatically. Clearly, if  $\gamma = 0$  (i.e. resistant cells cannot become sensitive again) then the only possible stable behavior of both considered systems is attraction by a state reflecting complete resistance; cf. [4] and the results summarized in Subsection 1.2. Even if therapy is stopped there is no chance for coming back to the complete sensitivity. On the other hand, whenever  $\gamma > 0$  then there is a positive steady state, stable in most parameter regimes for both models. However, for some parameters the positive steady state loses stability and oscillatory behavior appears. It should be marked that such a behavior for System (5) could be observed only for biologically unrealistic parameter values, but for System (6) this is not the case. This constitutes one of the main differences between the considered models. Note that the coordinates of the positive steady state as functions of  $\gamma$  are monotonic (either for all  $\gamma$  regarding  $\bar{z}$ , or at least for small  $\gamma$ ) such that with increasing  $\gamma$  more and more “good” sensitive cells is present while  $\bar{z}$  decreases. The coordinate  $\bar{y}$  decreases for System (5). On the other hand, for System (6) the coordinate  $\bar{y}$  usually decreases, but for small values of  $\varepsilon$  (that is small rate of acquiring drug resistance) and sufficiently small  $\rho$  it increases with increasing  $\gamma$ .

We have also compared the dynamics of the systems with prolonged constant therapy with the situation when the therapy is stopped. The latter case is qualitatively different from the case in which the therapy is prolonged for all  $t \geq 0$ . For both systems, when the therapy is stopped, the resistant subpopulation becomes extinct. This situation is also completely different from those obtained for  $\gamma = 0$ , where the subpopulation of sensitive cells becomes extinct as a result of prolonged ADR.

Of course we realize that both systems considered in this paper are extremely simplified, as tumors are highly heterogeneous and we are able to distinguish much more than two subpopulations of sensitive and resistant cells. The idea of multi-compartmental modeling in this area could be related to gene amplification (cf. e.g. [7]) and gave rise to simple but even infinite-dimensional models; cf. [17, 18] and the simplified version in [11]. However, even in the case we consider, as the models are non-linear, we see that the dynamics is complex, including oscilla-

tory behavior, while it could bring some insight as regards the dependence of this dynamics on the Darwinian effects.

## 4 Acknowledgments

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