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Analyzing Chemotherapy-Induced Resistance Dynamics
in Cancer Cell Populations

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1 Abstract

Chemotherapy is a common treatment for cancer, whose effectiveness depends on the development of resistance. We want to investigate the influence of the concentration of the chemotherapeutic drug on the long-term behavior of the distribution of resistance levels of the cancer cells and the resulting total tumor mass. We analyze two mechanisms of development of resistance, cell plasticity and mutation-selection. We use a discretization of the resistance levels to obtain a finite number of compartments and analyze the resulting n -dimensional system of nonlinear differential equations.

Discussing the case of two compartments (fully sensitive and fully resistant to treatment), using Dulac functions and Poincaré-Bendixson arguments we completely describe the global behavior of solutions for any parameter settings. We prove that in the case of cell plasticity, the global attractor is a triangle formed by three steady states and heteroclinic orbits. On the other hand, in the mutation-selection case the global attractor is a single heteroclinic orbit connecting zero to a positive steady state.

In the n -dimensional plasticity case, in the absence of chemotherapy there are $n + 1$ equilibria, which disappear one by one from the positive cone through a sequence of transcritical bifurcations as we increase the drug concentration. We describe how the distribution of resistance in the tumor is shifted as a response to more intense treatment.

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2 Introduction

Modern approaches to cancer research are shaped by the availability of vast amounts of data [16]. Mathematical models are a common tool to evaluate this data, particularly in order to develop individualized treatment plans [3], which is particularly important due to the heterogeneity among different tumors [7]. Clinical data is needed to calibrate a personal model for the individual patients [2, 19], estimating key parameters, allowing for individually tailored predictions or screening strategies [9, 10]. However, most cancer drugs perform poorly, which could imply that the currently used cancer models may be flawed or need refinements [7]. This causes the need to improve the modeling process, for example by using approaches that model different scales of the biological process [13] or take into account the heterogeneity between the cancer cells within a single tumor.

Drug resistance is one of the main reasons for failure of cytotoxic agents in cancer treatment [5, 6, 8]. Even though there is a variety of other treatment options including surgery, radiation, and stem cell therapies, chemotherapy is a widely applied and effective treatment option for many cancer types [1]. One possible way of preventing resistance causing treatment failure is the use of a combination of different drugs [4], requiring an in-depth understanding of the development of tumors and how drug resistance will influence this process. Modeling and simulating the development of tumors under chemotherapy is one tool to provide useful insights.

There are many approaches to modeling the tumor growth, making use of a variety of different fields, for example computer science, control theory [17] or game theory [12]. Mathematical approaches might be deterministic or stochastic, where the latter is mainly of interest if the total number of cancer cells is relatively small [15]. Deterministic models generally rely on differential equations and can mainly be separated by whether they use ordinary or partial differential equations. In ordinary differential equation models, the cancer cell population is divided into a finite number of compartments, that are homogeneous with respect to a certain characteristic structuring the population. For partial differential equation models, the population will be structured by a continuous variable [5]. Possible choices for structuring properties might be the level of resistance or sensitivity to the applied treatment, or the location of cells in space [17].

In the following thesis, we aim towards a qualitative analysis of the tumor dynamics under the influence of a constant concentration of a chemotherapeutic drug, as simulations show this to be generally more effective than applying doses periodically [17]. We do not intend to replicate the behavior of a certain type of cancer or to fit a model to a specific set of experimental data, but rather aim towards a general model, that can be applied in many cases. We will use a logistic growth model as intrinsic tumor growth model, which is a good choice especially for breast cancer, liver cancer, and lung cancer [11]. Appropriate parameter values depend on the specific tumor, reasonable ranges for different types of cancer

are provided in [11].

In order to take into account the heterogeneity of the cancer with respect to its resistance to the chemotherapeutic drug, we will structure the cancer cells by discretizing the generally continuous level of sensitivity to the drug [18] to obtain a finite number of compartments and respectively a system of nonlinear ordinary differential equations. We will model the interaction between the compartments by separately assuming two mechanisms for resistance emerging in cancer cells, cell plasticity and mutation-selection.

Cell plasticity generally refers to directed state transitions, triggered by changes of the environment, allowing cancer cells to gain a selective advantage through genetic and epigenetic modifications [5, 17, 18]. Specifically, some cancer cells can adapt to the hostile environment induced by the chemotherapeutic drug, which can be described as an increasing level of resistance [14]. This rate of change will highly depend on the concentration of the drug that is applied to the cancer cells. Experimental findings provide evidence suggesting the occurrence of this process [8].

The mechanism of mutation and selection involves an undirected change of phenotype during cell proliferation, leading to a heterogeneity of phenotypes within the tumor. It might increase or decrease the resistance level of the cell. The cells with an increased resistance level might be able to prevail due to the selection pressure that is imposed by the chemotherapeutic drug, as the increased level of resistance lowers the drug induced death rate, increasing the fitness of the respective phenotype.

This shows that both mechanisms differ in several key aspects, especially the direction in which cells can manipulate their phenotype, the trigger that is needed for that to happen, as well as the cells which might be affected by the respective process. While cell plasticity can apply to any cell at any time, mutations are confined to cell division and are hence more closely linked to the proliferation rate. The observation of these differences of the resistance mechanisms raise the question of how the differences will change the asymptotic behavior in the respective systems.

3 Two compartments

In the following section, we will look at the case of only two possible resistance values for the cancer cells: they are either fully sensitive or fully resistant to the constant chemotherapy treatment $c > 0$. We will obtain a two dimensional dynamical system with the system variables $x(t)$ being the amount of sensitive cancer cells, and $z(t)$ being the amount of resistant cancer cells. Due to the biological interpretation of these variables, we are only interested in solutions that are nonnegative at all times. For the respective proliferation rates $b_x, b_z > 0$,

it is natural to assume that there is a trade-off between resistance and proliferation rate, hence $b_x > b_z$, implying a positive fitness cost $b_x - b_z$ for the resistant variant. The dynamics of the two compartments depend on each other in different ways. On the one hand, there is competition for nutrients between both kinds of cells, which we want to model by logistic growth, scaled by a constant $d > 0$. On the other hand, there are different mechanisms of how the cancer cells might change their resistance level. We want to discuss the dynamic behavior of the system assuming two different mechanisms of change of phenotype.

3.1 Cell Plasticity

In this section, we want to analyze the behavior of the dynamical system assuming that the resistance level of the cells changes due to cell plasticity. This process allows the cancer cells to adjust to changes in the environment to gain an advantage in comparison to the less resistant cells [18]. In our case, the resistance level of the cells might increase due to the selection pressure imposed by the concentration of the chemotherapeutic drug. Since we discretize the generally continuous resistance level to a two element set, we will model this process using a single parameter p , which describes the part of the sensitive cells that are changing into resistant cells. This parameter will depend on the concentration c , and to be monotonously increasing in c with $p(0) = 0$, since a higher concentration of chemotherapy raises the pressure on the sensitive cells to increase their resistance level. Notice that this model does not allow for resistant cells to change back into sensitive cells. We will obtain the two dimensional system

$$\begin{aligned} x'(t) &= b_x x(t) - d(x(t) + z(t))x(t) - cx(t) - px(t) = f(x, z) \\ z'(t) &= b_z z(t) - d(x(t) + z(t))z(t) + px(t) = g(x, z). \end{aligned}$$

We can calculate the singular points and analyze their stability, using the Jacobian of the system:

$$J(x, z) = \begin{pmatrix} b_x - c - p - d(2x + z) & -dx \\ p - dz & b_z - d(x + 2z) \end{pmatrix}.$$

The trivial equilibrium at the origin has eigenvalues $\sigma_0 = \{b_z, b_x - c - p\}$ and is therefore unstable if $b_x > c + p$ and a saddle point otherwise. In case of a saddle point, we can determine the stable subspace of the linearization by calculating an eigenvector for the eigenvalue $b_x - c - p$. The eigenvector $(b_z + c + p - b_x, -p)^T$ will always have exactly one negative component, since the first component will always be positive in the relevant case of $b_x \leq c + p$. Hence, the intersection of the stable subspace and the first quadrant is trivial.

The equilibrium at $E_1 = (0, \frac{b_z}{d})$ has eigenvalues $\sigma_1 = \{-b_z, b_x - c - p - b_z\}$. Therefore, it is a saddle point if $b_x - b_z > c + p$, and is stable for larger values of $c + p$. The location of this equilibrium point does not depend on the concentration of chemotherapy c , because there are only resistant cells in the stable state, which

are not affected by changes in c .

In case $c + p < b_x - b_z$, we obtain another equilibrium point

$$E_2 = (x_2, z_2) = \left(\frac{(b_x - c - p)(b_x - b_z - c - p)}{d(b_x - b_z - c)}, \frac{p(b_x - c - p)}{d(b_x - b_z - c)} \right).$$

The spectrum is $\sigma_2 = \{-b_x + c + p, -b_x + c + p + b_z\}$, both eigenvalues are negative whenever the equilibrium point exists, it is always stable. This is the only possible further equilibrium point, since if we assume $x \neq 0$, we obtain a unique solution. Dividing the first equation by x yields $x + z = \frac{b_x - p - c}{d}$, and therefore $(b_x - b_z - p - c)z = px = \frac{p(b_x - p - c)}{d} - pz$. This can only be solved by $x = x_2$ and $z = z_2$.

Theorem 3.1. *All solutions with initial value in $[0, \infty)^2 \setminus \{(0, a) : a \geq 0\}$ converge to E_2 , if it exists, and to E_1 otherwise. The solutions starting in $\{(0, a) : a > 0\}$ always converge to E_1 .*

Proof. First, we want to show that the set $[0, \infty)^2$ is forward invariant. For this, we observe that in a state of purely resistant cells, $x = 0$ and $z > 0$, the amount of sensitive cells x cannot decrease further. This is obvious, since $x'(t) = 0$. This shows that even the positive z -axis is a forward invariant set. Additionally, we need to insure that in the case of purely sensitive cells, $x > 0$ and $z = 0$, the amount of resistant cells z cannot decrease further. This is implied by $z'(t) = px > 0$. Hence, no trajectory can leave the set $[0, \infty)^2$, and it is a forward invariant set.

Next, we will show that a solution starting in $[0, \infty)^2$ will remain bounded. The amount of sensitive cancer cells cannot grow unbounded, since for $x(t) > \frac{b_x}{d}$, we obtain $x'(t) = (b_x - c - p)x(t) - d(x(t) + z(t))x(t) \leq b_x x(t) - d \frac{b_x}{d} x(t) = 0$, using the invariance property. Similarly, the number of resistant cancer cells cannot grow unbounded, since $z(t) > \max(\frac{b_z}{d}, \frac{p}{d})$ implies

$$z'(t) = b_z z(t) - d(x(t) + z(t))z(t) + px(t) < b_z z(t) - dz(t) \frac{b_z}{d} + px(t) - dx(t) \frac{p}{d} = 0.$$

We can use the Poincaré-Bendixson theorem for every trajectory starting in $[0, \infty)^2$. Every trajectory starting in the first quadrant will either converge towards an equilibrium point, a limit cycle or a cycle of heteroclinic orbits.

It is not possible for a cycle of heteroclinic orbits to exist, since for any set of parameter values, there exists at most one saddle point. We now want to exclude periodic orbits by showing the existence of a Dulac function for the two dimensional system. We choose $\phi(x, z) = \frac{1}{xz}$. This is a Dulac function for the system, since for every $x, z > 0$ we obtain

$$\frac{\partial(\phi f)}{\partial x} + \frac{\partial(\phi g)}{\partial z} = \frac{-1}{xz} \left(dz + \frac{px}{z} - dx \right) = - \left(\frac{d}{x} + \frac{d}{z} + \frac{p}{z^2} \right) < 0,$$

the sign does not change in the open first quadrant. This shows that there cannot be any closed orbit in the open quadrant, hence no closed orbit can exist in the closed first quadrant either, due to the behavior on the axis. On the x -axis, we know that $z'(t) > 0$, which shows that there cannot be a closed trajectory starting in the open first quadrant intersecting this axis. On the other hand, the z -axis is consisting of two orbits and an equilibrium point, there cannot be another orbit intersecting with this axis.

Therefore, every trajectory will converge towards one of the equilibrium points. We now want to determine the basins of attraction of the equilibrium points. Assume that there is a trajectory starting in the first quadrant converging towards the origin. Due to the forward invariance of the first quadrant, the tangent space of the stable manifold would have to intersect the first quadrant. Since we have seen that this is not the case for any parameter values, the basin of attraction of the origin is just the equilibrium point itself. This shows that in the case of $c + p > b_x - b_z$, all points except the origin must converge towards E_1 , as there is no other equilibrium point in the closed forward invariant set.

Let now $c + p < b_x - b_z$ so that E_2 exists and E_1 is a saddle point. The basin of attraction of E_1 is therefore its stable manifold. Since the z -axis is invariant and the origin is not stable in this direction, the trajectories starting on the z -axis must be converging towards E_1 . Every other point does not converge to either the origin or E_1 , and must therefore be converging towards E_2 . $\square$

We notice that for $b_x - b_z < c + p$, the global attractor of the system is given by the two equilibrium points and their unique connecting heteroclinic orbit, that is contained in the z -axis, $\{0\} \times [0, \frac{b_z}{d}]$. In case of $b_x - b_z > c + p$, the global attractor is given by the three equilibrium points and their three connecting heteroclinic orbits, as well as the points in the bounded connected component determined by the three heteroclinic orbits.

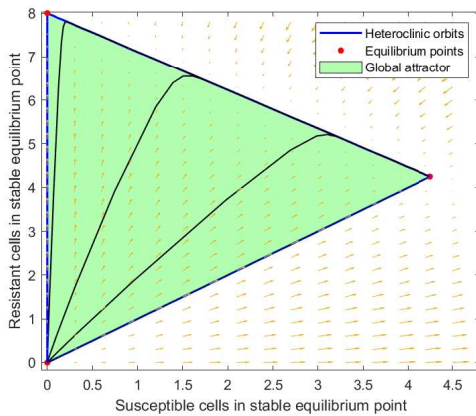


Figure 1: Global attractor of the system for $p = 0.05$, $c = 0.1$, $d = 0.1$, $b_x = 1$ and $b_z = 0.8$.

We notice that the heteroclinic orbit connecting the origin and E_1 is $\{0\} \times [0, \frac{b_z}{d}]$. Also, the unique heteroclinic orbit that is tangential to the eigenspace of the linearization in the origin, connecting the origin and E_2 , is a straight line, since by choosing an arbitrary point on the straight line connecting the origin and E_2 , given by $(x, z) = a(b_x - b_z - c - p, p)$, where $a \in (0, 1)$, we obtain $\frac{x'}{z'} = \frac{x}{z}$, since

$$\begin{aligned} x' &= (b_x - c - p - da(b_x - b_z - c))x \\ z' &= apb_z - da(b_x - b_z - c)ap + px \\ &= (b_x - c - p - da(b_x - b_z - c))z. \end{aligned}$$

Notice that there cannot be any more heteroclinic orbits connecting the origin and E_2 whose tangent in the origin encloses a smaller angle with the x -axis, since the eigenvector $(0, 1)^T$ of the linearization in the origin has a strictly smaller eigenvalue, $b_z < b_x - c - p$, due to the condition for the existence of E_2 . If we consider the linearized system in backwards time, the eigenspace that is the z -axis will have a strictly larger eigenvalue, hence the convergence in this direction is slower than in the direction of the connecting line to E_2 . This causes any other trajectory that approaches the origin in backwards time to be tangential to the z -axis, and therefore trajectories that start below the connecting line between the origin and E_2 will leave the first quadrant in backward time and are not relevant for our application.

The orbit that is tangential to the unstable subspace of the linearization in E_1 and connects E_1 and E_2 is also given by the straight line connecting the two equilibrium points. Let again $a \in (0, 1)$ and look at the behavior of the system at the respective convex combination of the two equilibrium points,

$$(x, z) = \left((1-a) \frac{(b_x - c - p)(b_x - b_z - c - p)}{d(b_x - b_z - p)}, a \frac{b_z}{d} + (1-a) \frac{p(b_x - c - p)}{d(b_x - b_z - p)} \right).$$

Then we will obtain

$$\begin{aligned} x' &= (b_x - c - p - (1-a)(b_x - c - p) - ab_z)x = a(x - E_{1,1})(b_x - b_z - c - p) \\ z' &= (b_z - (1-a)(b_x - c - p) - ab_z)z + px \\ &= (a-1)(b_x - b_z - c - p)z + px = a \left(z - \frac{b_z}{d} \right) (b_x - b_z - c - p) \\ &= a(z - E_{1,2})(b_x - b_z - c - p), \end{aligned}$$

where $E_{1,1}$ and $E_{1,2}$ denote the respective coordinates of the equilibrium point E_1 .

This shows that the system leaves the straight line between the two equilibrium points invariant, hence this is the unique connecting heteroclinic orbit. One example for the global attractor is the triangle shown in figure 1.

We can analytically determine the limits of the amount of sensitive and resistant cancer cells in the stable equilibrium point for $c = 0$ and $c \rightarrow \infty$. For $c \rightarrow 0$, the stable equilibrium point E_2 will tend towards $(\frac{b_x}{d}, 0)$, an equilibrium of purely sensitive cells. For $c \rightarrow \infty$, we obtain $E_1 = (0, \frac{b_z}{d})$, an equilibrium of purely resistant cells. The behavior of the location of the stable equilibrium point and the total tumor amount $T(c)$ depends on the parameter values and the function $p(c)$. One example of the dynamics is shown in figure 2.

Remark 3.2. *In the case of the sensitive cells not being fully sensitive, we obtain a chemotherapy induced death rate $c_x(c)$, and the same analysis will hold for any value of c_x . The possibly nonlinear rescaling of c will not change the qualitative dynamic behavior.*

However, if the resistant cells are not fully resistant, we will see a change of

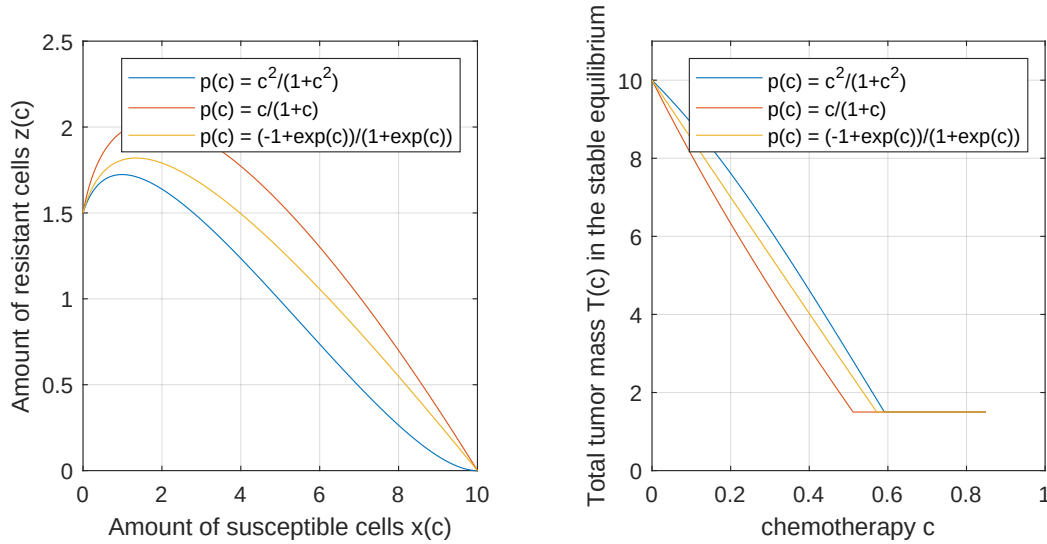


Figure 2: Behavior of the unique stable equilibrium point of the system for different choices of $p(c)$ and $b_x = 1$, $b_z = 0.15$ and $d = 0.1$.

the dynamic behavior. In this case, we can choose c sufficiently large that the growth rates b_x and b_z of both compartments are strictly smaller than the respective chemotherapy induced death rates. In this case, it will be possible to stabilize the origin by applying a sufficiently high concentration of the chemotherapeutic drug.

3.2 Mutation and Selection

In the following section, we want to analyze the dynamics of the same model assuming a different mechanism of resistance building up. We assume that the daughter cells that form during the cell division process might have a different phenotype than the mother cell due to mutation. Since this process is not induced by the chemotherapy treatment, the respective rate of change is not depending on the concentration c of the drug, but only depends on the proliferation rates of the respective compartment. We assume that the part $0 < \varepsilon < 1$ of new daughter cells in the opposite compartment will be equal for both phenotypes. We will obtain the following two dimensional system

$$\begin{aligned} x'(t) &= b_x(1 - \varepsilon)x(t) + b_z\varepsilon z(t) - d(x(t) + z(t))x(t) - cx(t) = f(x, z) \\ z'(t) &= b_z(1 - \varepsilon)z(t) + b_x\varepsilon x(t) - d(x(t) + z(t))z(t) = g(x, z). \end{aligned}$$

In this model, we cannot expect the z -axis to be invariant, like it was in the previous model. This is due to mutation happening in both directions, so any amount of resistant cells will lead to a non-trivial growth rate of sensitive cells. We can still show the invariance of the entire first quadrant.

The set $[0, \infty)^2$ is forward invariant under the influence of the system, since for $x > 0$ and $z = 0$, we obtain $z'(t) = b_x\varepsilon x > 0$, and for $x = 0$ and $z > 0$ we similarly obtain $x'(t) = b_z\varepsilon z > 0$. Therefore, every trajectory starting in $[0, \infty)^2$

will remain in this set for all times.

We can calculate the singular points and analyze their stability using the Jacobian

$$J(x, z) = \begin{pmatrix} b_x(1 - \varepsilon) - d(2x + z) - c & b_z\varepsilon - dx \\ b_x\varepsilon - dz & b_z(1 - \varepsilon) - d(x + 2z) \end{pmatrix}.$$

We will obtain the trivial equilibrium $x = 0$ and $z = 0$ with the eigenvalues

$$\sigma = \left\{ \frac{(b_x + b_z)(1 - \varepsilon) - c}{2} \pm \sqrt{\left(\frac{(b_x + b_z)(1 - \varepsilon) - c}{2} \right)^2 - b_x b_z(1 - 2\varepsilon) + c b_z(1 - \varepsilon)} \right\}.$$

The stability of this singular point depends on the choice of the parameters.

Lemma 3.3. *The origin is unstable whenever $c < b_x \frac{1-2\varepsilon}{1-\varepsilon}$, and is a saddle point for larger values of c . The tangent space of the stable manifold in the origin does not intersect the first quadrant for any parameter values.*

Proof. Let $\lambda_{\pm} = w \pm \sqrt{w^2 + a}$ be the previously calculated eigenvalues of the origin, where $w = \frac{1}{2}((b_x + b_z)(1 - \varepsilon) - c)$ and $a = -b_x b_z(1 - 2\varepsilon) + c b_z(1 - \varepsilon)$. These eigenvalues are real, since there cannot be a focus in the origin, since that would cause the trajectories to spiral close to the origin, which contradicts the forward invariance of the first quadrant. We first want to show that $\lambda_- > 0$ for $c < b_x \frac{1-2\varepsilon}{1-\varepsilon}$. We notice that the condition on c implies that $b_x b_z(1 - 2\varepsilon) > b_z c(1 - \varepsilon)$, and therefore $a < 0$. This yields $|w| > \sqrt{w^2 + a}$, and the sign of λ_- will be determined by the sign of w . We use the condition on c again to find the sign of w .

$$\begin{aligned} 2w &= (b_x + b_z)(1 - \varepsilon) - c \geq (b_x + b_z)(1 - \varepsilon) - b_x \frac{1 - 2\varepsilon}{1 - \varepsilon} \\ &\geq b_x \left(1 - \varepsilon - \frac{1 - 2\varepsilon}{1 - \varepsilon} \right) > 0, \end{aligned}$$

where the last step follows from $(1 - \varepsilon)^2 - 1 + 2\varepsilon = \varepsilon^2 > 0$.

In the case of $c > b_x \frac{1-2\varepsilon}{1-\varepsilon}$, the same calculation shows that $|w| < \sqrt{w^2 + a}$. Hence, $\lambda_+ > 0$ and $\lambda_- < 0$, and the origin is a saddle point. In this case, we will obtain a one dimensional tangent space for the stable manifold. One eigenvector characterizing this subspace is $\left(\frac{-1}{2b_x\varepsilon}(q + \sqrt{r}), 1 \right)^T$, where $q = (b_z - b_x)(1 - \varepsilon) + c$ and $r = b_x^2(1 - \varepsilon)^2 + (b_z(1 - \varepsilon) + c)^2 + 2b_x(b_z(-1 + 2\varepsilon + \varepsilon^2) - c(1 - \varepsilon))$. We now want to show that $q + \sqrt{r} > 0$ in order to determine the sign of the first component of the eigenvector. We notice that

$$r - q^2 = 2b_z(1 - \varepsilon)c + 4b_x b_z \varepsilon^2 - 2b_z(1 - \varepsilon)c = 4b_x b_z \varepsilon^2 > 0.$$

This implies $|\sqrt{r}| > |q|$, and the sign of the first component of the eigenvector is negative. This subspace does not intersect the first quadrant. $\square$

Remark 3.4. *The stable manifold of the origin cannot have a nontrivial intersection with the open first quadrant, because the first quadrant is invariant. If one of its points was on the stable manifold, then its trajectory would have to leave the first quadrant, since the stable manifold approaches the origin in the direction of the second and fourth quadrant. This is not possible, due to the invariance property. Hence, no trajectory starting in the first quadrant can converge to the origin.*

We notice that we did not use any of the constraints on the parameters in order to show that the eigenspace for the eigenvalue λ_- of the linearization does not intersect the first quadrant. This shows that in the case of the origin being an unstable equilibrium point, we will still have one eigenspace that is not intersecting the first quadrant.

Theorem 3.5. *There is exactly one more equilibrium point in the first quadrant.*

Proof. We first want to discuss the case $c = b_x - b_z$. In this case, the addition of both equations yields $0 = b_z(x + z) - d(x + z)^2$. Since we are interested in solutions in the first quadrant that are not located at the origin, we can assume that $x + z \neq 0$ holds. Therefore, the only solution is $x + z = \frac{b_z}{d}$. Using the second equation,

$$0 = b_z(1 - \varepsilon)z - d\frac{b_z}{d}z + b_x\varepsilon x = \varepsilon(-b_zz + b_x x),$$

we obtain the unique solution $x = \frac{b_z^2}{d(b_x + b_z)}$ and $z = \frac{b_x b_z}{d(b_x + b_z)}$.

We can now assume $b_x - b_z - c \neq 0$. We will aim to solve for the sum $T := x + z$ first, and determine the distribution between the two phenotypes by solving for $a := \frac{x}{x+z}$.

In this case, summing both equations shows that $0 = (b_x - b_z - c)x + b_z T - dT^2$, and since $T \neq 0$, we obtain

$$(b_x - b_z - c)a + b_z = dT. \tag{1}$$

Using $T \neq 0$ again, the second equation becomes

$$\begin{aligned} b_x \varepsilon x + b_z(1 - \varepsilon)z &= zdT = z(b_z + (b_x - b_z - c)a) \\ b_x \varepsilon a + b_z(1 - \varepsilon)(1 - a) &= (1 - a)(b_z + (b_x - b_z - c)a). \end{aligned}$$

Solving the quadratic equation, we obtain

$$a_{\pm} = \frac{-\varepsilon(b_x + b_z) + b_x - b_z - c}{2(b_x - b_z - c)} \pm \sqrt{\left(\frac{-\varepsilon(b_x + b_z) + b_x - b_z - c}{2(b_x - b_z - c)}\right)^2 + \frac{\varepsilon b_z}{b_x - b_z - c}}.$$

In order to show that the equilibrium point $(Ta, T(1 - a))$ is in the first quadrant, we need to check that $T > 0$ and $a \in [0, 1]$. We notice that the solutions can

be represented as $a_{\pm} = w \pm \sqrt{w^2 + v}$, where $w = \frac{-\varepsilon(b_x + b_z) + b_x - b_z - c}{2(b_x - b_z - c)}$ and $v = \frac{\varepsilon b_z}{b_x - b_z - c}$.

We first want to discuss the case of $b_x - b_z - c > 0$. We notice that $v > 0$, therefore $a_- < 0$ and $a_+ > 0$. Using (1), we notice that $T(a_+) > 0$. All that is left to show is therefore $a_+ \leq 1$. This follows from

$$\begin{aligned} 2qa_+ &= q - \varepsilon(b_x + b_z) + \sqrt{(q - \varepsilon(b_x + b_z))^2 + 4\varepsilon b_z q} \\ (2a_+ - 1)q &= -\varepsilon(b_x + b_z) + \sqrt{(q + \varepsilon(b_x + b_z))^2 - 4\varepsilon q b_x} \\ 2(a_+ - 1)(b_x - b_z - c) &= -(q + \varepsilon(b_x + b_z)) + \sqrt{(q + \varepsilon(b_x + b_z))^2 - 4\varepsilon q b_x}, \end{aligned}$$

since the right hand side will be negative using $q := b_x - b_z - c > 0$, and with the same condition, $a_+ - 1 < 0$.

We have seen that in the case of $b_x - b_z - c > 0$, there exists a unique equilibrium point in the first quadrant. We now want to discuss the case of $q = b_x - b_z - c < 0$.

First, we want to check whether $a_{\pm} \leq 1$ holds. The same calculation as before shows that

$$(a_{\pm} - 1)q = -(q + \varepsilon(b_x + b_z)) \pm \sqrt{(q + \varepsilon(b_x + b_z))^2 - 4\varepsilon q b_x}.$$

In this case, $-4\varepsilon q b_x > 0$, and therefore the sign of the right hand side will be the same as the sign that we choose for the square root. Hence, $a_+ - 1 < 0$ and $a_- - 1 > 0$, we will not need to take a_- into account any further. The equation

$$2(b_x - b_z - c)a_+ = w + \sqrt{w^2 + 4\varepsilon b_z(b_x - b_z - c)},$$

where $w = b_x - b_z - c - \varepsilon(b_x + b_z)$, shows that $a_+ > 0$, since the right hand side is negative due to $b_x - b_z - c < 0$. All that is left to show is that $T(a_+) > 0$.

Observe that it is not possible that $(b_x + b_z)(1 - \varepsilon) < \frac{1-2\varepsilon}{1-\varepsilon}b_x$ holds for any parameter values, since this would imply that $b_x(1 - \varepsilon)^2 < (1 - 2\varepsilon)b_x$ and therefore $\varepsilon^2 b_x < 0$. By plugging a_+ into (1), we get

$$\begin{aligned} 2dT &= b_x + b_z - c - \varepsilon(b_x + b_z) + \sqrt{(b_x - b_z - c - \varepsilon(b_x + b_z))^2 + 4\varepsilon b_z(b_x - b_z - c)} \\ &= b_x + b_z - c - \varepsilon(b_x + b_z) + \sqrt{(b_x + b_z - c - \varepsilon(b_x + b_z))^2 - 4b_z w}, \end{aligned}$$

where $w = c(1 - \varepsilon) - b_x(1 - 2\varepsilon)$. Observe that in case of $c > \frac{1-2\varepsilon}{1-\varepsilon}b_x$, the absolute value of the square root is larger than the absolute value of $b_x + b_z - c - \varepsilon(b_x + b_z)$, and in case of $c < \frac{1-2\varepsilon}{1-\varepsilon}b_x$, the summand $b_x + b_z - c - \varepsilon(b_x + b_z)$ will be positive. Since at least one of both cases has to be true for any possible combination of parameter values, this yields $T(a_+) > 0$.

Therefore, we obtain the unique equilibrium point in the open first quadrant at $E_1 := (Ta, T(1 - a))$. $\square$

We can show that all solutions starting in the first quadrant will remain bounded. If we assume $z > \frac{b_z + b_x \varepsilon}{d}$, then $z'(t) < (b_z - dz)z + (b_x \varepsilon - dz)x < 0$, and similarly for $x > \frac{b_x + b_z \varepsilon}{d}$, then $x'(t) < (b_x - c - dx)x + (b_z \varepsilon - dx)z < 0$.

Therefore, by Poincaré-Bendixson theorem, we know that every trajectory converges to either an equilibrium point, a limit cycle or a cycle of heteroclinic orbits.

The function $\phi : (0, \infty)^2 \rightarrow (0, \infty)$, where $\phi(x, z) = \frac{1}{xz}$, is a Dulac function for this model, since for any $x, z > 0$, the relevant sign will be negative:

$$\begin{aligned} \frac{\partial(\phi f)}{\partial x} + \frac{\partial(\phi g)}{\partial z} &= \frac{b_x(1 - \varepsilon) - d(2x + z) - c + b_z(1 - \varepsilon) - d(x + 2z) - \frac{f(x, z)}{x} - \frac{g(x, z)}{z}}{xz} \\ &= \frac{-d(x + z)}{xz} - \frac{b_z \varepsilon}{x^2} - \frac{b_x \varepsilon}{z^2} < 0. \end{aligned}$$

Due to the existence of a Dulac function, we can now exclude that a closed orbit exists, therefore every trajectory will converge to an equilibrium point in $[0, \infty)^2$ or to a cycle of heteroclinic orbits. There cannot be a cycle of heteroclinic orbit in the first quadrant, since there are only two equilibrium points. Therefore, we would need at least one trajectory starting in the first quadrant and converging to the origin, which is a contradiction to remark 3.4.

This shows that the equilibrium point E_2 must be asymptotically stable, and that the basin of attraction contains $[0, \infty)^2 \setminus \{(0, 0)\}$. The global attractor of the system consists of both equilibrium points and their unique connecting heteroclinic orbit. This heteroclinic orbit is obviously unique when the origin is a saddle. If the origin is unstable, the components of the eigenvector of the linearization that belongs to the smaller eigenvalue have different signs, as we have concluded from the proof of lemma 3.3. Every trajectory that is not converging towards the origin in the direction of the eigenspace corresponding to the larger eigenvalue will therefore approach the origin tangential to the other eigenspace and hence leave the first quadrant in backwards time. Since these trajectories are not relevant for our application, we obtain the uniqueness of the heteroclinic orbit.

In order to determine the global attractor of the system, we are using the eigenvector of the linearization in the origin, $\phi = \left(w - \frac{(1-\varepsilon)(b_z - b_x) + c}{2}, b_x \varepsilon \right) \in (0, \infty)^2$, where we set $w = \sqrt{\left(\frac{(b_x + b_z)(1-\varepsilon) - c}{2} \right)^2 + b_z(c(1 - \varepsilon) - b_x(1 - 2\varepsilon))}$. We notice that the heteroclinic orbit will be a straight line, since for any point on the connecting line $(x, z) = a\phi$, parametrized by $a \in (0, 1)$, we will obtain

$$\begin{aligned} x' &= (b_x(1 - \varepsilon) - c - d(x + z))x + a\varepsilon^2 b_x b_z \\ &= \left(b_z(1 - \varepsilon) - d(x + z) + \frac{x}{a} \right) x \\ z' &= (b_z(1 - \varepsilon) - d(x + z))z + \varepsilon b_x x \\ &= \left(b_z(1 - \varepsilon) - d(x + z) + \frac{x}{a} \right) z \end{aligned}$$

using that $\varepsilon^2 b_x b_z = w^2 - \left(\frac{(1-\varepsilon)(b_z - b_x) + c}{2} \right)^2$. Therefore, the global attractor of the system does only consist of the two equilibrium points and their unique connecting heteroclinic orbit, which is a straight line.

We can analytically determine the limits for the stable equilibrium point as $c = 0$ and $c \rightarrow \infty$. For $c = 0$, we obtain

$$E_1 = \frac{1}{2d(b_x - b_z)} \left(b_x^2(1 - \varepsilon)^2 - \varepsilon(1 - \varepsilon)b_z^2 + b_x b_z(-1 + \varepsilon + 2\varepsilon^2) + ((1 - \varepsilon)b_x - \varepsilon b_z)w \right),$$

$$\text{where } w = \sqrt{(b_x - b_z - \varepsilon(b_x + b_z))^2 + 4\varepsilon b_z(b_x - b_z)}.$$

Now discussing the limit for $c \rightarrow \infty$, our first observation is that the function $w(c) = \sqrt{(b_x - b_z - c - \varepsilon(b_x + b_z))^2 + 4\varepsilon b_z(b_x - b_z - c)}$ fulfills $\frac{w(c)}{c} \xrightarrow{c \rightarrow \infty} 1$. This yields

$$c - w(c) = \frac{(c - w(c))(c + w(c))}{c + w(c)} = \frac{2c(1 - \varepsilon)(b_x - b_z) + k}{c + w(c)} \xrightarrow{c \rightarrow \infty} (1 - \varepsilon)(b_x - b_z),$$

where k does not depend on c . Therefore, $T(c) \rightarrow \frac{(1 - \varepsilon)b_z}{d}$.

Similarly, we obtain $a_+ = \frac{1}{2} + \frac{k}{c} - \frac{w(c)}{2c} \rightarrow 0$. The stable equilibrium point will converge towards $(0, \frac{(1 - \varepsilon)b_z}{d})$. This shows that, while there will always be non-zero amounts of both phenotypes in the stable equilibrium point, the increasing concentration of the chemotherapeutic drug will lead to an arbitrarily small amount of sensitive cells.

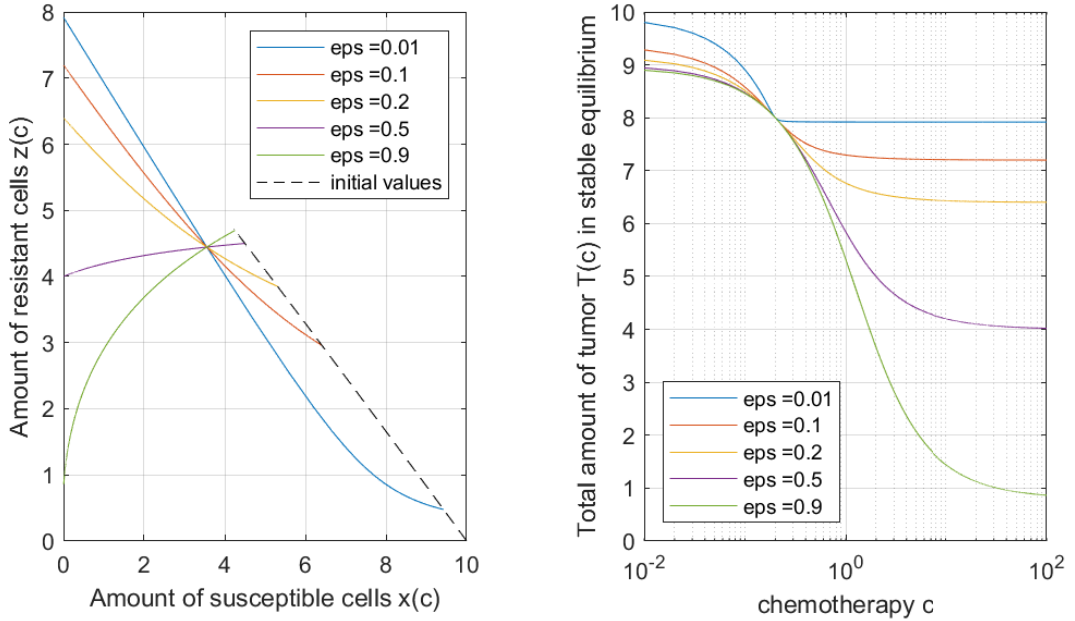


Figure 3: Behavior of the stable equilibrium point of the system for different choices of ε and $b_x = 1$, $b_z = 0.8$ and $d = 0.1$. The dashed line marks the initial values for $c = 0$ and $\varepsilon \in [0, 1]$.

The location of the stable equilibrium depends on the parameter values, one example is shown in figure 3. Observe that all lines in the plot meet in a single point at $\left(\frac{b_z^2}{d(b_x + b_z)}, \frac{b_x b_z}{d(b_x + b_z)} \right)$, since this value is taken for $b_z = b_x - c$, independently

of the choice of ε . Notice that for this choice of parameters, the fitnesses of both compartments are equal, hence it makes no difference at what rate the cells mutate to the other compartment.

Remark 3.6. *If we choose $\varepsilon = \frac{b_z}{b_x + b_z}$, the amount of resistant cancer cells $z(c)$ in the stable equilibrium point is not affected by a change in the chemotherapy c .*

Proof. Let $\varepsilon = \frac{b_z + \delta}{b_x + b_z}$. Then we obtain

$$\begin{aligned} z(c) &= T(1 - a) = \frac{(b_x - c + w - \delta)(b_x - c - w + \delta)}{4d(b_x - b_z - c)} \\ &= \frac{(b_x - c)^2 - (w - \delta)^2}{4d(b_x - b_z - c)} \\ &= \frac{4b_z(b_x - b_z - c - \varepsilon(b_x - b_z - c)) + 2\delta w - \delta^2}{4d(b_x - b_z - c)} \\ &= \frac{(1 - \varepsilon)b_z}{d} + \delta \frac{2w - \delta}{4d(b_x - b_z - c)} \end{aligned}$$

where $w = \sqrt{(b_x - b_z - c - \varepsilon(b_x + b_z))^2 + 4\varepsilon b_z(b_x - b_z - c)}$. This shows that $z(c)$ is constant for $\delta = 0$. $\square$

We notice that the choice $\varepsilon = \frac{b_z}{b_x + b_z}$ yields $b_x \varepsilon = (1 - \varepsilon)b_z$. The influx into the second compartment is consisting of proliferation of resistant cells and mutation of sensitive cells with the same factor, hence only depending on the total tumor mass T . The condition from the second differential equation for an equilibrium point becomes $0 = (b_x \varepsilon T - dTz) = T(b_x \varepsilon - dz)$, the solution does not depend on x .

Remark 3.7. *Similar to the case of cell plasticity, the assumption of the sensitive compartment being not fully sensitive does not change the qualitative dynamic behavior, while the assumption of the resistant compartment being not fully resistant would allow to stabilize the origin for sufficiently high concentrations of the chemotherapeutic drug.*

3.3 Comparison of the results

We have shown that for both mechanisms and any set of parameter values, there exists a unique stable equilibrium point in the first quadrant, while the origin is not stable. The mechanisms differ in the location of the stable equilibrium point. In the case of mutation-selection, the stable equilibrium will always be located in the open first quadrant, and it will be the only equilibrium point besides the origin. In contrast, under cell plasticity, the resistant component might become extinct when the concentration of the chemotherapeutic drug is 0, and the sensitive component might become extinct as $c + p \geq b_x - b_z$. For any $c + p < b_x - b_z$, there exists another equilibrium point consisting purely of resistant cancer cells, which will become the unique stable equilibrium point due to a transcritical bifurcation at $b_z = b_x - c - p$, where the fitnesses of the phenotypes coincide.

The global attractor in the mutation-selection case consists of two equilibrium points and their connecting heteroclinic orbit, while for cell plasticity, the global attractor consists of a triangle of three equilibrium points and their connecting heteroclinic orbits prior to the transcritical bifurcation, and consists of a single heteroclinic orbit and the two remaining equilibrium points after the bifurcation. In all cases, the connecting heteroclinic orbits are straight lines. We can interpret our observation of the heteroclinic orbits between the origin and the stable equilibrium point being straight lines as a stable balance between the phenotypes that does not depend on the absolute tumor mass. For both mechanisms and fixed parameter values, there exists a stable equilibrium for the distribution of the total cancer mass onto both phenotypes.

We can conclude that for both mechanisms, it is not possible to stabilize the origin for any concentration of the chemotherapeutic drug. However, both the stable total tumor mass and the proportion of resistant cells depend on this concentration. Notably, the resistant share might reach 1 in the case of cell plasticity, but always strictly less than 1 for the mutation-selection case.

4 Multiple compartments

We now want to refine the discretization and extend the model to take into account differing levels of resistance. For this, we will use n compartments with monotonously increasing resistance, the influence of the chemotherapy for compartment k will be described by $c_k(c)$, which is monotonously increasing in c , and fulfills $c_1 > \dots > c_{n-1} > c_n = 0$ for any fixed c . The growth rates b_i of the phenotypes are decreasing in i , $b_1 > \dots > b_n > 0$, due to the natural assumption of a fitness cost for the increase in resistance.

4.1 Cell Plasticity

We assume that cell plasticity only allows cells to change into neighboring compartments, and that the rate of change $p(c)$ is the same for any pair of adjacent compartments. We obtain the n -dimensional system of nonlinear differential equations

$$\begin{aligned} x_1'(t) &= b_1 x_1 - dT x_1 - c_1 x_1 - p x_1 \\ x_k'(t) &= b_k x_k - dT x_k - c_k x_k - p x_k + p x_{k-1} \\ x_n'(t) &= b_n x_n - dT x_n + p x_{n-1}, \end{aligned}$$

where $T = \sum_{i=1}^n x_i$ describes the total cancer mass, and $2 \leq k \leq n-1$. Introducing the fitness coefficients $f_i = b_i - c_i - p$, for every $1 \leq i \leq n-1$, and $f_n = b_n$, the system equations will simplify to

$$x_k' = (f_k - dT)x_k + p x_{k-1}, \tag{2}$$

where $x_0 = 0$.

The Jacobian of the system is given by

$$J(x) = \begin{pmatrix} f_1 & 0 & \dots & 0 \\ p & f_2 & \dots & 0 \\ \vdots & \ddots & \ddots & \vdots \\ 0 & \dots & p & f_n \end{pmatrix} - dT I_n - d(x_1, \dots, x_n)^T (1, \dots, 1),$$

therefore the origin is not stable, since $f_n = b_n > 0$ is a positive eigenvalue of $J(0)$ for any parameter values.

Observe that in equilibrium points, $x_k = 0$ implies $x_{k-1} = 0$. Inductively, this yields the following remark.

Remark 4.1. *If $x_k^* = 0$ for any component of the equilibrium point, then every previous component is also zero, $x_{k-j}^* = 0$ for every $1 \leq j \leq k - 1$.*

We now want to characterize all equilibrium points of the system.

Theorem 4.2. *For any $0 \leq k \leq n$, there exists an equilibrium point E_{k+1} with $x_k = 0$ and $x_{k+1} > 0$ in $[0, \infty)^n$ if and only if $f_{k+1} > f_i$, for every $i > k + 1$, and it is unique whenever it exists.*

Proof. Let E_{k+1} be such an equilibrium point. Remark 4.1 shows that all components with indices less than k are zero, but all components with indices $k + 1$ or larger are non-zero. Equation (2) shows that $dT = f_{k+1}$. Let $k + 2 \leq j \leq n$ be arbitrary, then $(f_j - f_{k+1})x_j = -px_{j-1} \leq 0$, and due to $x_j > 0$, we obtain $f_j \leq f_{k+1}$, which shows that this is a necessary condition for the existence of this equilibrium point.

Let now $f_{k+1} > f_i$ for any $i > k + 1$. We want to show the unique existence of E_{k+1} . For $k = n$, the origin is the unique solution. In every other case, we have a solution that fulfills $dT = f_{k+1} \geq f_n > 0$. Equation (2) shows that iteratively, the coordinates of the equilibrium point must fulfill $x_j = \frac{p}{f_{k+1} - f_j} x_{j-1}$, which are all positive due to $x_{k+1} > 0$ and $f_{k+1} - f_j > 0$ for any $j \geq k + 2$. We can solve

$$f_{k+1} = dT = dx_{k+1} \left(1 + \sum_{i=k+2}^n \prod_{j=i}^n \frac{p}{f_{k+1} - f_j} \right)$$

uniquely for x_{k+1} to obtain $E_{k+1} \in [0, \infty)^n$. $\square$

Observe that for the equilibrium point E_k , the Jacobian has the eigenvalues $f_i - dT$, where $1 \leq i \leq k - 1$. For an E_k to be stable, we need $f_k = dT > f_i$, for all $1 \leq i \leq k - 1$. Combining this fact with the condition for the existence for E_k , we notice that there is always at most one stable equilibrium point, which is given by E_k where $k = \arg \max_{1 \leq i \leq n} f_i$.

Lemma 4.3. *For every solution $(x_1, \dots, x_n)$ of the system of differential equations, the total cancer mass $T(t) = \sum_{i=1}^n x_i$ is bounded.*

Proof. We obtain $T' = \sum_{i=1}^n (b_i - c_i)x_i - dT^2 \leq b_1T - dT^2$ by adding all n differential equations, which will be negative for all $dT > b_1$. This shows that $\limsup_{t \rightarrow \infty} T \leq \frac{b_1}{d}$. $\square$

We now want to show that all phenotypes with a sufficient level of resistance will persist in the long-term behavior.

Lemma 4.4. *If $f_k > f_i$ for all $1 \leq i \leq n$ where $i \neq k$, then $\limsup_{t \rightarrow \infty} T(t) \geq \frac{f_k}{d}$, and therefore $\limsup_{t \rightarrow \infty} x_i(t) = 0$, for all $i < k$, and $\limsup_{t \rightarrow \infty} x_i(t) > 0$, for all $i \geq k$.*

Proof. Looking at the differential equation $x'_k = (f_k - dT)x_k + px_{k-1}$, we notice that x_k will grow exponentially, as long as $dT < f_k$, which shows the first claim, $\limsup_{t \rightarrow \infty} dT(t) \geq f_k$.

If $k > 1$, assume $\limsup_{t \rightarrow \infty} x_1 > 0$. Since $f_k > f_1$, it follows that $x'_k \geq (f_k - dT)x_k$ is leading to an exponentially increasing function x_k , that is not bounded. This contradicts lemma 4.3, and hence implies $\limsup_{t \rightarrow \infty} x_1(t) = 0$. Inductively, it follows that $x'_i = (f_i - dT)x_i + px_{i-1}$, where $x_{i-1} \rightarrow 0$, and therefore x_i is decaying exponentially for every $i < k$.

If we assumed that there is an $i \geq k$ such that $\limsup_{t \rightarrow \infty} x_i(t) = 0$, then

$$0 \leftarrow x'_i = (f_i - dT)x_i + px_{i-1},$$

hence $\lim_{t \rightarrow \infty} x_{i-1} = 0$. Inductively, we know that $\lim_{t \rightarrow \infty} x_k = 0$, which implies that the solution of $y' = (f_k - dT)y$ converges to 0. Since $f_j - f_k < 0$ for any $j \neq k$, all other differential equations will inductively have their solutions converging to 0, as $x'_{i+1} = (f_{i+1} - f_k)x_{i+1} + (f_k - dT)x_{i+1} + px_i$, where $x_i \rightarrow 0$.

This would show that all $x_i \rightarrow 0$, and hence their sum $T \rightarrow 0$. This contradicts the first claim that $\limsup_{t \rightarrow \infty} dT = f_k > 0$. This shows that all $\limsup_{t \rightarrow \infty} x_i(t) > 0$ for all $i \geq k$. $\square$

We will analyze the dynamics of the system for a specific configuration of the parameter values.

Example 4.5. *We can choose $c_i(c) = \frac{n-i}{n}c$, discretizing the resistance levels of the cells linearly. Due to this, index of the equilibrium point E_k associated with the fittest component, $f_k = \max_{1 \leq i \leq n} f_i$, is monotonously increasing, since all differences $c_i - c_j$ are monotonous in c .*

We assume that the loss in the growth rate b_i increases as i increases, since first the cheapest and then more expensive resources have to be used to keep increasing the level of resistance. For this example, we want to choose $b_i = e - e^{\frac{i-1}{n}}$.

Choose $p(c) = \frac{0.1c^2}{1+c^2}$, a monotonously increasing and bounded function.

For the given example, the equilibrium point E_k appears to be globally stable. We can check this hypothesis numerically. The behavior of the system for the initial distribution of only fully sensitive cells is shown in figure 4. For the choice $c = 1.5$, the fitness f_5 will be maximal. Due to lemma 4.4, we expect all phenotypes with less resistance to become extinct. This expectation is confirmed by the

numerical solution of the system. As time passes, the phenotype that is mainly represented in the distribution at a given point of time shifts to the next more resistant phenotypes one by one, while the cells that are less resistant than the fittest phenotype x_5 will vanish. In the long-term behavior, the system converges towards the equilibrium point E_5 .

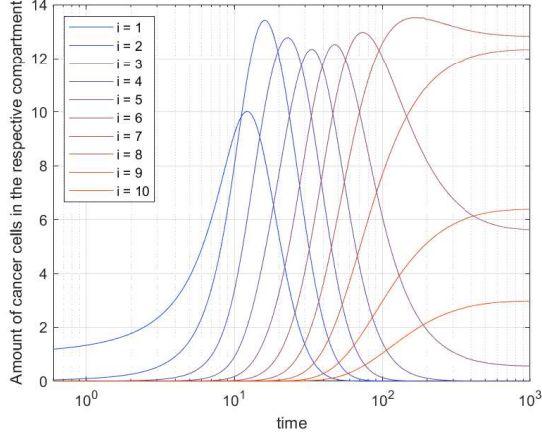


Figure 4: Solution for the parameters given in example 4.5 with initially only fully sensitive cells and $c = 1.5$.

We can analytically solve the set of equations for the distribution of cancer cells in the stable equilibrium point. The resulting distributions for some values for c are shown in figure 5. We notice that higher concentrations of chemotherapy c are decreasing the total amount of cancer cells. The amount of cells with phenotypes of higher resistance levels are taking up a larger part of the overall tumor for large values of c , while there are no cells of phenotypes with lower resistance levels for sufficiently large values of c .

We have seen that the possibly stable equilibrium point E_k depends on the choice of c , as well as the number of equilibrium points. As we increase c , the number of equilibrium points will

decrease from $n + 1$ to 2, assuming that $c_i(c)$ are not bounded.

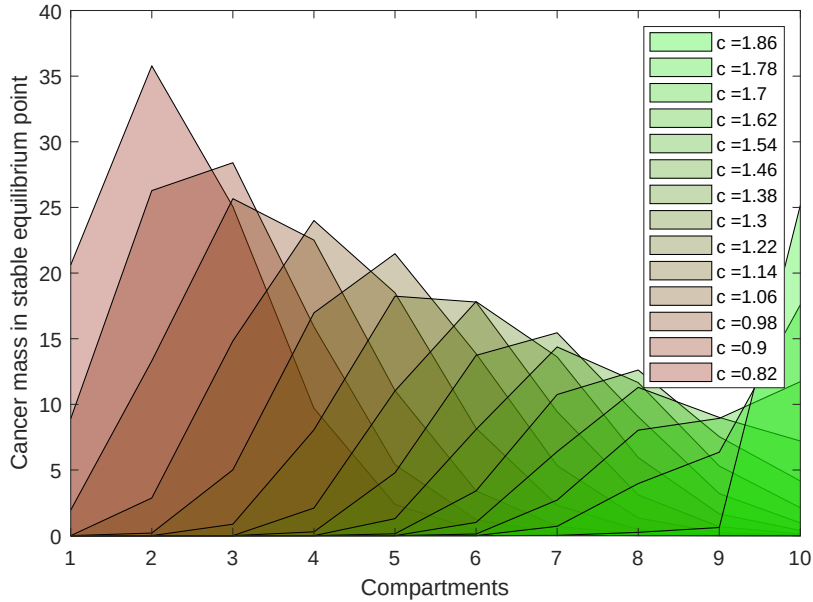


Figure 5: Distribution of the cancer cells between the phenotypes in the stable equilibrium point.

Let $f_k = f_j$ for some $k < j$ and some fixed c_0 . Assume that $c_k - c_j > 0$ is monotonously increasing in a neighborhood of c_0 . This insures that the difference of the fitnesses $(f_k - f_j)(c)$ changes its sign in c_0 . Looking at coordinate j of E_k , we observe that due to $dT = f_k$, we obtain

$$0 = x_j(f_j - f_k) + px_{j-1}.$$

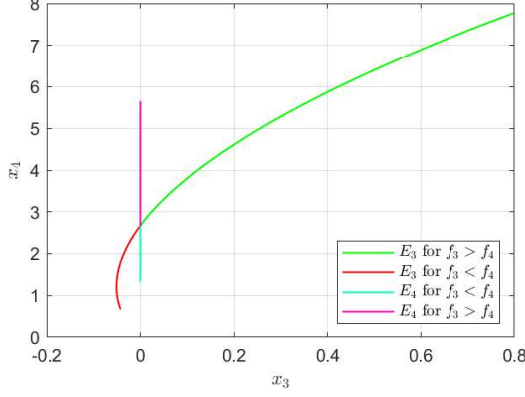


Figure 6: Projection of the equilibrium point E_3 and E_4 onto the $x_3 - x_4$ -plane in the neighborhood of the critical value where $f_3 = f_4$, using the parameter values from 4.5.

As $(f_j - f_k)(c)$ is nonnegative for any $c \geq c_0$ in a neighborhood of c_0 , there is a solution in the positive cone only for $f_j = f_k$, which implies $c = c_0$. The solution needs to fulfill $x_{j-1} = 0$, and using remark 4.1, this implies that $x_k = \dots = x_{j-1} = 0$. The uniqueness of solutions from theorem 4.2 shows that E_k coincides with E_{j+i} for some $i \geq 0$. We can exclude the origin E_{n+1} , since $dT = f_k \geq f_n > 0$. If we assume that E_k coincides with another E_{j+i} for $i > 0$, then $f_j = f_k = f_{j+i}$, and E_j will also fulfill $x_j = \dots = x_{j+i-1} = 0$. This shows that any set of equilibrium points E_i with equal maximal associated fitnesses f_i will coincide at the equilibrium point with the largest in-

dex.

As c is further increased, the equilibrium point E_k traverses through E_j , and is hence crossing the subspace $x_k = \dots = x_{j-1} = 0$ for $c = c_0$ and leaves the positive cone for $c > c_0$, since we assumed $(f_k - f_j)(c) < 0$.

This process is visualized in figure 6. The figure shows the movement of the equilibrium point E_3 in the $x_3 - x_4$ -plane. For the parameter value of c such that $f_3 = f_4$, the equilibrium point coincides with E_4 . Notice that all further components x_i where $i \geq 5$ do also coincide for this parameter value. Increasing c further will make the equilibrium point move out of the positive cone.

If the $c_i(c)$ are chosen such that $c_k - c_j$ are not necessarily monotonous, it is possible that equilibrium points move back into the positive cone as c increases further, but for $c \rightarrow \infty$, only the origin and E_n will exist.

The bifurcation diagram for one choice of parameter values is shown in figure 7. We notice that the number of equilibrium points is monotonously decreasing in c , as expected, since all $(c_j - c_k)(c)$ are linear and hence monotonous. The possibly stable equilibrium point is always the one with the largest total cancer mass T , which is always the one with the lowest index out of the equilibrium points existing for a certain value of c . We notice that the amount of resistance that a phenotype needs in order to persist in environments with a higher concentration

of chemotherapy c is monotonously increasing.

We notice that it is not possible for the tumor mass to converge towards 0, because there is a steady state E_n that consists of fully resistant cells. Since we assume $c_n = 0$, there is no influence of the concentration of the chemotherapeutic drug on this equilibrium point. If we were relaxing the assumption of the discretization and allowed for $c_n > 0$, this steady state will also vanish for a sufficiently large c , since $f_n = b_n - c_n(c)$ would be negative. In this case, the origin would be the only remaining equilibrium point, and would be stable, since all fitnesses and therefore all eigenvalues of the Jacobian will be negative. Relaxing this assumption would be a natural conclusion from the continuous system, since for a distribution of phenotypes on the interval $[0, 1]$, the fully resistant cells are a set of measure 0.

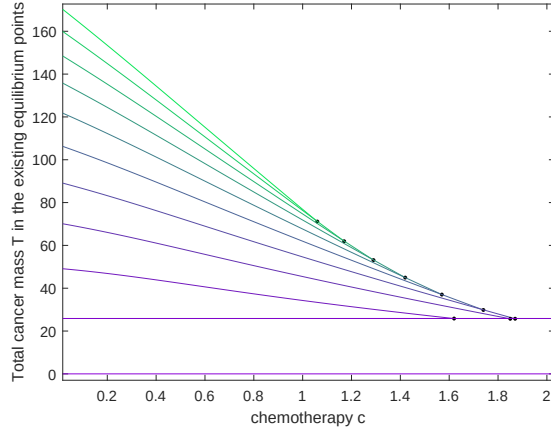


Figure 7: Bifurcation diagram for the parameters given in example 4.5.

4.2 Mutation and Selection

In the following section, we want analyze the dynamic behavior of the mutation-selection case for the refined discretization of the resistance levels. We assume that cells can only mutate into neighboring compartments, with the rates $\varepsilon_k^+, \varepsilon_k^-$ for the mutation of cells of phenotype k to the more resistant or to the more sensitive compartment respectively. We assume that all $\varepsilon_k^\pm < 0.5$. We obtain the n -dimensional system of nonlinear differential equations

$$\begin{aligned} x_1'(t) &= b_1(1 - \varepsilon_1^+)x_1 + b_2x_2\varepsilon_2^- - dTx_1 - c_1x_1 \\ x_k'(t) &= b_k(1 - \varepsilon_k^+ - \varepsilon_k^-)x_k + b_{k-1}x_{k-1}\varepsilon_{k-1}^+ + b_{k+1}x_{k+1}\varepsilon_{k+1}^- - dTx_k - c_kx_k \\ x_n'(t) &= b_n(1 - \varepsilon_n^-)x_n + b_{n-1}x_{n-1}\varepsilon_{n-1}^+ - dTx_n, \end{aligned}$$

where $T = \sum_{i=1}^n x_i$ again denotes the total tumor mass, and $2 \leq k \leq n-1$. By defining again the fitness coefficients $f_1 = b_1(1 - \varepsilon_1^+) - c_1$, $f_k = b_k(1 - \varepsilon_k^+ - \varepsilon_k^-) - c_k$ and $f_n = b_n(1 - \varepsilon_n^-)$, we can calculate the Jacobian of the system:

$$J(x) = \begin{pmatrix} f_1 - dT & b_2\varepsilon_2^- & \dots & 0 \\ b_1\varepsilon_1^+ & f_2 - dT & \dots & 0 \\ \vdots & \ddots & \ddots & \vdots \\ 0 & \dots & b_{n-1}\varepsilon_{n-1}^+ & f_n - dT \end{pmatrix} - d(x_1, \dots, x_n)^T(1, \dots, 1).$$

The origin is obviously an equilibrium point for the given system, and the Jacobian in this case is a tridiagonal matrix.

Lemma 4.6. *The origin is not stable, for every value of c .*

Proof. We need to show that the tridiagonal matrix

$$J(c) = \begin{pmatrix} f_1 & b_2 \varepsilon_2^- & \dots & 0 \\ b_1 \varepsilon_1^+ & f_2 & \dots & 0 \\ \vdots & \ddots & \ddots & \vdots \\ 0 & \dots & b_{n-1} \varepsilon_{n-1}^+ & f_n \end{pmatrix}$$

has an eigenvalue in the right half plane.

First, we look at the case of all $b_i < c_i$, for $1 \leq i \leq n-1$. This can certainly be accomplished by choosing a sufficiently large value $c = c^*$, as we can assume that all $c_i(c)$ grow unbounded as $c \rightarrow \infty$. We now use Gershgorin discs columnwise to locate the eigenvalues of $J(c^*)$. The last column will yield the disc

$$D_n = \{z \in \mathbb{C} : |z - b_n(1 - \varepsilon_n^-)| \leq b_n \varepsilon_n^-\}.$$

Since $\varepsilon_n^- < 0.5$, this is entirely contained in the positive half plane. All the other discs are contained in the negative half plane, since $\Re(z) \leq b_i - c_i < 0$, for every $z \in D_i$, where D_i denotes the disc for column i . We notice that $D_n \cap \bigcup_{i=1}^{n-1} D_i = \emptyset$, and therefore there is exactly one eigenvalue in the connected component that consists of D_n . Hence, there is exactly one eigenvalue with positive real part whenever $c \geq c^*$.

To show the same result for arbitrary values of c , we first want to transform the matrix to be symmetric. $J(c)$ is similar to and hence has the same eigenvalues as

$$M(c) = \begin{pmatrix} f_1 & \sqrt{b_1 b_2 \varepsilon_1^+ \varepsilon_2^-} & \dots & 0 \\ \sqrt{b_1 b_2 \varepsilon_1^+ \varepsilon_2^-} & f_2 & \dots & 0 \\ \vdots & \ddots & \ddots & \vdots \\ 0 & \dots & \sqrt{b_{n-1} b_n \varepsilon_{n-1}^+ \varepsilon_n^-} & f_n \end{pmatrix}.$$

Using the similarity of the matrices for $c = c^*$, the previous argument shows that $M(c^*)$ has an eigenvalue ρ in the right half plane. For arbitrary $c < c^*$, we can express

$$M(c) = M(c^*) + A(c),$$

where $A(c) = \text{diag}(c_i(c^*) - c_i(c))$ is positive semidefinite. Since both summands are real symmetric matrices, we can use Weyl's inequality to find bounds for the location of the eigenvalues. In particular, the largest eigenvalue λ of $M(c)$ fulfills

$$\lambda \geq \rho + \min_{1 \leq i \leq n} \{c_i(c^*) - c_i(c)\} = \rho > 0,$$

since all $c_i(c^*) \geq c_i(c)$, as we assume c_i to be monotonously increasing. This shows that $M(c)$ and hence also $J(c)$ has an eigenvalue in the right half plane. The origin is not stable. $\square$

Every other equilibrium point that might exist in the positive cone must have a non-zero amount of every phenotype. This can be shown inductively by assuming that there exists an equilibrium point with $x_k = 0$ for some $1 \leq k \leq n$. Then

$$0 = \varepsilon_{k-1}^+ b_{k-1} x_{k-1} + \varepsilon_{k+1}^- b_{k+1} x_{k+1},$$

where we set $x_0 = 0 = x_{n+1}$ for the case of $k = 1$ and $k = n$ respectively. Since all coordinates are assumed to be nonnegative, we obtain $x_{k-1} = 0 = x_{k+1}$. Inductively, all components are zero, and the origin is the only equilibrium point with any trivial components.

Remark 4.7. *All solutions of this system of differential equations are bounded, since the proof of lemma 4.3 still holds, because the summation of all differential equations does not depend on the choice of the resistance mechanism.*

We now want to discuss bounds on the location of the further equilibrium points that might exist.

Lemma 4.8. *For every nontrivial equilibrium point, $dT > f_i$ holds for every $1 \leq i \leq n$.*

Proof. Since all compartments are non-trivial, all mutation-induced growth rates are strictly positive, $\varepsilon_i^\pm b_i x_i > 0$. Hence, in order to obtain a solution for the homogeneous system of equations, all summands $(f_i - dT)x_i$ have to be strictly negative. $\square$

Lemma 4.9. *For any $T > 0$, there cannot be more than one equilibrium point with the same total tumor mass T .*

Proof. Define for every $1 \leq k \leq n - 1$ the ratio between the amounts of cells in neighboring compartments in the equilibrium point, $e_k = \frac{x_k}{x_{k+1}}$. This is well-defined, as all components are positive. Using the last differential equation, we notice that $e_{n-1} = \frac{dT - f_n}{b_{n-1} \varepsilon_{n-1}^+}$. This allows us to recursively express

$$e_k = \frac{1}{b_k \varepsilon_k^+} (dT - f_{k+1} - \varepsilon_{k+2}^- b_{k+2} e_{k+1}^{-1}) \quad (3)$$

for every $k \leq n - 2$, using the differential equation for x'_{k+1} . For a fixed set of parameter values, this allows us to express every x_i as a multiple of x_n . For a known total tumor mass T , we can hence first solve for x_n and obtain a unique distribution onto the phenotypes. $\square$

Let $a_k = \frac{x_k}{T}$ denote which part of the cancer cells are of phenotype k . Then in a nontrivial equilibrium point, dividing all conditions by T , we obtain

$$dx_k = f_k a_k + \varepsilon_{k-1}^+ b_{k-1} a_{k-1} + \varepsilon_{k+1}^- b_{k+1} a_{k+1},$$

for any $1 \leq k \leq n$, where $a_0 = 0 = a_{n+1}$. Summing up all those equations yields

$$dT = \sum_{i=1}^n (b_i - c_i) a_i,$$

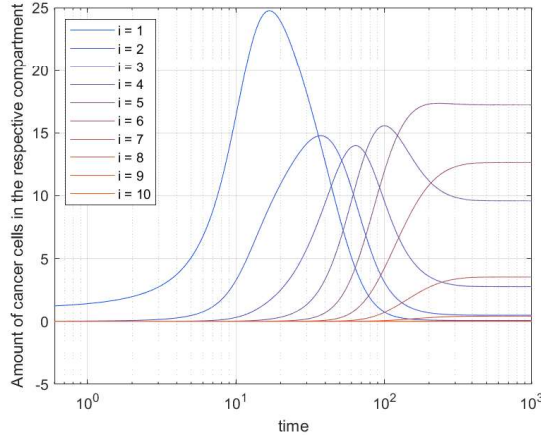


Figure 8: Solution for $c = 1.5$ and the parameters given in example 4.10.

the total tumor mass is expressed as a convex combination. This shows $\min b_i - c_i \leq dT \leq \max b_i - c_i$, imposing bounds on the possible tumor mass T . Notice that these bounds are monotonously decreasing. Similar to the plasticity case, we can look at the dynamic behavior for a certain choice of parameter values.

Example 4.10. We can again choose $c_i(c) = \frac{n-i}{n}c$, discretizing the resistance levels of the cells linearly and again assume that the fitness cost increases as the level of resistance increases. For this example, we choose $b_i = e - e^{\frac{i-1}{n}}$. Let all $\varepsilon_k^\pm = 0.01$.

A numerical solution of the amount of cells that are present for each phenotype as time passes are shown in figure 8. We notice that the distribution of cancer cells appears to converge to a steady state in which all phenotypes are present. We notice that the dominant phenotype is x_5 , which is the one with the largest fitness for this choice of c .

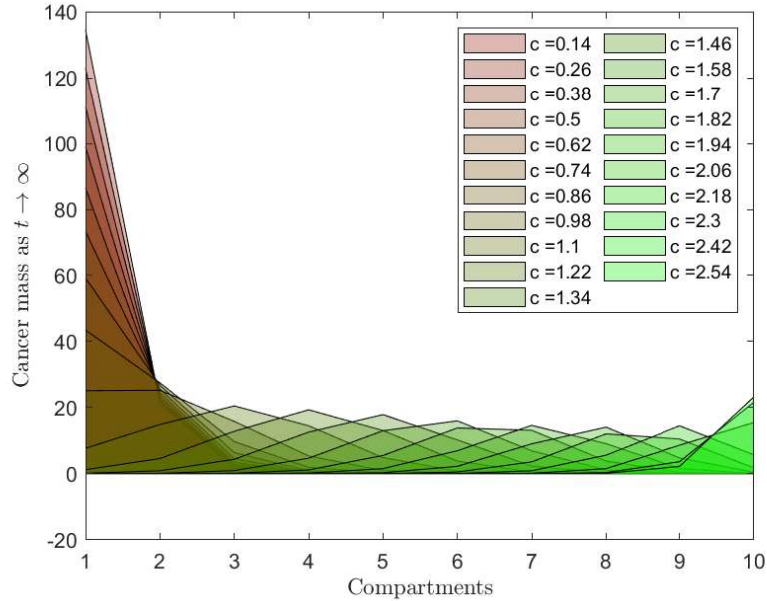


Figure 9: Distribution of the cancer cells between the phenotypes in the long-term behavior.

If we change the concentration c of the chemotherapeutic drug, we will observe convergence to other steady distributions. These numerical results are shown in figure 9. We notice that there is always a dominant phenotype, which shifts

towards the more resistant phenotypes as the concentration of the chemotherapeutic drug is increased. We also notice that every phenotype is present in the numerically estimated limit distribution for every value of c .

We can show analytically that all phenotypes will persist for all times.

Theorem 4.11. *For any nontrivial initial value, the solution of the system of differential equations will fulfill $\limsup_{t \rightarrow \infty} x_i(t) > 0$ for every $1 \leq i \leq n$.*

Proof. Assume that there is an $1 \leq i \leq n$ with $\limsup_{t \rightarrow \infty} x_i(t) = 0$. Then the respective differential equation

$$0 \leftarrow x'_i(t) = (f_i - dT)x_i + \varepsilon_{i-1}^+ b_{i-1} x_{i-1} + \varepsilon_{i+1}^- b_{i+1} x_{i+1},$$

where $x_0 = 0 = x_{n+1}$, shows that both neighboring phenotypes will go extinct, $x_{i-1}, x_{i+1} \rightarrow 0$. Inductively, all components will converge to 0, and also $T \rightarrow 0$, which implies that there is a $t^* > 0$ such that $T(t) < \frac{b_n(1-\varepsilon_n^-)}{2}$ for every $t \geq t^*$. Hence,

$$x'_n(t) = (f_n - dT)x_n + \varepsilon_{n-1}^+ b_{n-1} x_{n-1} \geq \frac{f_n}{2} x_n,$$

the amount of resistant cells will grow exponentially. This contradicts $x_n \rightarrow 0$, therefore $\limsup_{t \rightarrow \infty} x_i(t) > 0$ for every $1 \leq i \leq n$. $\square$

This shows that the origin will always be unstable in this model, with respect to the positive cone. This is mainly caused by the existence of a fully resistant phenotype. If we assume that there is no fully resistant phenotype, a sufficiently large value for c would allow for a stable origin, as the differential equation for the total tumor mass, obtained by addition of all the differential equations for the phenotypes, will certainly converge to 0 as soon as all $b_i < c_i(c)$.

4.3 Comparison of the results

We have seen that the origin will remain unstable for any concentration of the chemotherapeutic drug for both mechanisms, indicating that this model does not predict conditions under which the disease can be cured. This suggests that the models might need to be improved. All solutions of the respective systems are bounded, and the numerical estimates suggest that the total tumor mass is monotonously decreasing as the chemotherapy is increased. We observe that the distribution of the cancer cells is shifting towards the more resistant phenotypes as the chemotherapy is increased.

In the case of cell plasticity, there are initially $n + 1$ equilibrium points, which will decrease to 2 equilibrium points for sufficiently high concentrations of the chemotherapeutic drug. The vanishing equilibrium points leave the positive cone by passing through another equilibrium point. All but one of these equilibrium points are unstable. The remaining one appears to be stable in numerical simulations. If this particular equilibrium point leaves the positive cone, the stability is passed on to the equilibrium point through which it leaves the positive cone.

This causes a sequence of transcritical bifurcations. In each of these bifurcation points, another phenotype will lose the persistence property and will go extinct in the long-term behavior. The higher the level of resistance of the particular phenotype, the larger the necessary concentration of chemotherapeutic drug for this phenotype to lose persistence. As soon as all except for the entirely resistant phenotype have lost the persistence property, any further increase of the concentration does not have any effect on the long-term behavior of the system. Further research could address towards an analytical proof of the global stability of the equilibrium point whose first nontrivial component maximizes the fitness.

In the case of the mutation-selection mechanism, all phenotypes are persisting for any concentration of the chemotherapeutic drug. This ensures that an increase of the concentration always has an effect on the long-term behavior of the system, since the system cannot reach a steady state of purely fully resistant cells. Numerical observations show that there appears to be a globally stable equilibrium point in the open positive cone, whose total cancer mass is monotonously decreasing as the chemotherapy is increased. We provided a lower and an upper bound for the total cancer mass in the possibly existing equilibrium points, which are monotonously decreasing as the concentration is increased. Further research could target towards the question of existence and uniqueness of a stable equilibrium point in the open positive cone.

This shows that the main difference between both mechanisms is the fact that the more sensitive phenotypes will go extinct in the system with cell plasticity, while all phenotypes will persist in the mutation-selection case. This aligns with the observations in the two-dimensional case. We have also noticed that for either one of the models, the assumption of no fully resistant phenotype would allow the origin to be stable for a sufficiently large concentration of the chemotherapeutic drug. This alteration of the model could be addressed by further research, as well as the generalization to a continuous set of resistance levels, yielding a partial differential equation.

5 Summary and own results

In this project, I analyzed the dynamic behavior of four versions of a model of tumor growth under the influence of a chemotherapy treatment, incorporating different mechanisms of resistance development and different discretizations of the possible resistance levels.

- In the case of cell plasticity as a resistance mechanism and only fully sensitive or fully resistant cells, I have fully described the dynamic behavior of the resulting two-dimensional system of nonlinear differential equations by determining the equilibrium points and their stability. I have analytically determined the global attractor of the system, which is a triangle in case the concentration of the chemotherapeutic drug is low enough for the fully sensitive phenotype to persist.

- In the case of mutation-selection as a resistance mechanism and only fully sensitive or fully resistant cells, I have again fully characterized the dynamic behavior of the two-dimensional system of nonlinear differential equations by determining the equilibrium points, their stability and the global attractor of the system. Additionally, I described the limits of the stable equilibrium point as the concentration of the chemotherapeutic drug approaches zero and infinity.
- In the case of cell plasticity as a resistance mechanism and a discretization of the resistance levels into n compartments, I have determined all equilibrium points for the resulting n -dimensional system of nonlinear differential equations, and the conditions for their existence in the positive cone. I described the sequence of transcritical bifurcations in which they disappear one by one. I have shown that at most one of the equilibrium points is stable, and investigated its stability numerically. I have shown that the phenotypes with a low resistance level will go extinct, as well as the persistence of those phenotypes with sufficient resistance level, where the sufficiency of a resistance level for the persistence of a phenotype depends on the concentration of the chemotherapeutic drug. If there is no fully resistant phenotype, the origin can be stabilized.
- In the case of mutation-selection as a resistance mechanism and a discretization of the resistance levels into n compartments, I have shown that for the resulting n -dimensional system of nonlinear differential equations, all phenotypes will persist, regardless of the concentration of the chemotherapeutic drug. I have shown that the origin will be unstable for all parameter configurations, and that under the assumption of no fully resistant phenotype, the origin can be stabilized. I have provided bounds on the total tumor mass in other equilibrium points, and numerically approximated the long-term behavior of the system.

This work contributes to a deeper understanding of tumor dynamics under chemotherapy, offering insights into the role of resistance mechanisms and the effects of the drug concentration onto the cancer cell population.

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