ANALYSIS OF MODELS FOR EVOLVING DRUG RESISTANCE IN CANCER CHEMOTHERAPY

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Abstract. We consider mathematical models for drug resistance in cancer chemotherapy that are based on the concept of gene amplification. Starting with a simple two-compartment model that only distinguishes between sensitive and resistant cells, we augment the model to include phase specificity and partially resistant subclasses under the action of one killing agent. This takes into account that drugs are only active in specific phases of the cell cycle and also allows for gradually developing acquired drug resistance. We formulate these models as optimal control problems and analyze qualitative properties of their solutions.

Keywords. optimal control, singular controls, cancer chemotherapy, drug resistance, gene amplification

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1   Introduction

Conventional cancer treatments aim at directly killing the tumor cells, be it by means of killing agents in chemotherapy or by means of radiation in radiation treatments. However, there exist many limiting factors, and in chemotherapy "probably the most important - and certainly the most frustrating - of these limiting factors is drug resistance" [8, pg. 335]. Some cancer cells simply may not be receptive to the action of certain drugs to begin with, so-called *intrinsic drug resistance*. Even if chemotherapy starts out successfully, the treatment may just have killed off the sensitive subpopulation, but then cancer comes back in a drug resistant form from the small residuum of intrinsically resistant cells. In addition, since cancer cells are often genetically unstable, mutations and amplifications of genes, combined with fast duplications, are but two of several mechanisms which allow for quickly developing *acquired resistance* to anti-cancer drugs.

While modelling of cancer chemotherapy has a long history (e.g. [4,18,22]), in the early models drug resistance is not considered. More realistic mathematical models for cancer chemotherapy, specifically, models which would

consider treatments over successive therapy cycles need to take drug resistance into account. Several probabilistic models for developing drug resistance exist in the literature (e.g. [2,6,10,27]). In these models the tumor size is analyzed as a stochastic process and some associated probability, like the probability to have no resistant cells [2], is maximized. These models and their predictions can often be tested against clinical data and thus provide quantitative information. More recently, a probabilistic model for the evolution of the cancer population that takes into account acquired and intrinsic resistance has been modelled and analyzed numerically by Westman et al. in [26,27] in a cell-cycle specific context. Deterministic models for the evolution of the tumor under drug resistance based on the underlying probabilistic effects contribute to a qualitative understanding of the phenomenon. A model of this type that was not cell-cycle specific was given in [3]. All the early models have in common that they analyze developing drug resistance with respect to a single cytotoxic agent or a group of drugs which can be lumped together in their effect. In a different direction, in [17] we considered a mathematical model, formulated jointly with A. Swierniak in [16], for combination cancer chemotherapy under evolving drug resistance with two killing agents acting separately.

In this and earlier papers drug resistance is treated as a sudden event, only distinguishing resistant and sensitive cells. While drug resistance may be induced by a single mutational event (clinical resistance sometimes appears so rapidly in patients that this would be a plausible explanation,) the more common mechanism seems to be random mutations over time; "... a partially resistant clone may ... undergo further mutations and become progressively more resistant" [7, pg. 64]. A broad class of models which describe drug resistance in this sense as a branching process was developed by Harnevo and Agur [5,6] and Kimmel and Axelrod [9,10]. Based on these models Swierniak and Smieja in [21] considered infinitely many levels of partial drug resistance evolving during the treatment and corresponding deterministic models have been formulated and analyzed by Swierniak et al. [11,24,25]. However, due to high dimensionality these models often only allow for a limited analysis.

Thus, assuming some level of simplification and staying within a finite-dimensional structure, in this paper we go back to the two-compartment model with a single cytotoxic agent distinguishing only resistant and sensitive cells where drug resistance is treated as a "complete event" [27], and develop it further in two directions. Since drugs are only active in specific phases of the cell cycle, the first is to augment the basic model by taking cell cycle specificity into account. The class of sensitive cancer cells is divided further into two compartments, G_1/S and G_2/M, depending on the location of cells in the cell cycle and the action of the killing drug takes place in the second one. The second generalization leads to a model with one level of partial drug resistance taken into account, i.e. cancer cells are divided into compartments of sensitive, partially resistant and resistant cells. Both of these models have been formulated jointly with A. Swierniak in [16].

They involve a three dimensional dynamics which falls into a well researched class of bilinear optimal control problems [13,14,15,23]. The analysis of these problems is pursued with a linear objective that encompasses the numbers of cancer cells both at the terminal and at intermediate times and includes a penalty term on the total amount of drug given to measure side effects. The initial candidates for optimality resulting from the Maximum principle are bang-bang controls corresponding to a therapy of full dose treatments with rest periods in between and singular controls representing time-varying partial doses. This second class of candidates is eliminated in both models with the use of high order conditions of optimality. While acquired drug resistance in the models analyzed here is based on the mechanism of *gene amplification*, the equations can easily be adjusted to fit other mechanisms as well.

2 A 2-compartment Model for Drug Resistance under Gene Amplification

Amplification of a gene is an increase in the number of copies of that gene present in the cell after cell division, *deamplification* corresponds to a decrease in its number of copies. Cancer cells are genetically highly unstable and due to mutational events and gene amplification during cell division, cells can acquire additional copies of genes which as a result make the cells more resistant to certain drugs, for example by addition of genes which aid removal or metabolization of the drug. The more copies of such a gene will be present, the more resistant the cells become to even higher concentrations of the drug. Gene amplification is thus well-documented as one of the reasons for evolving drug resistance of cancer cells (see, for example, [1,7,20]). Mathematical models for drug resistance based on gene amplification have been proposed and analyzed probabilistically by Harnevo and Agur [5,6] in connection with a *one-copy forward gene amplification hypothesis* which states that in cell division at least one of the two daughter cells will be an exact copy of the mother cell while the second one with some positive probability undergoes gene amplifications.

In this section we formulate a basic underlying 2-dimensional model in which we only distinguish two compartments consisting of drug sensitive and resistant cells under a one drug treatment. We then use this model as starting point for extensions that take into account cell-cycle specificity and various levels of drug resistance. We denote the numbers of cells in the sensitive and resistant compartments by S and R, respectively. Within the one-copy forward gene amplification model, once a sensitive cell undergoes cell division, the mother cell dies and one of the daughters will remain sensitive. The other daughter, with probability s, $0 < s < 1$, changes into a resistant cell. Similarly, if a resistant cell undergoes cell division, then the mother cell dies, and one of the daughters remains resistant. However, for cancer cells (and

different from viral infections like HIV) it is possible that a resistant cell may mutate back into a sensitive cell. This phenomenon is well-documented in the medical literature where experiments have shown that the resistant cell population decreases in a drug free medium [20]. We therefore include a probability $r \geq 0$ that one of the daughters of a resistant cell may become sensitive. Generally r will be small. The case $r = 0$ where this is excluded is called *stable gene amplification* while *unstable gene amplification* refers to the phenomenon $r > 0$.
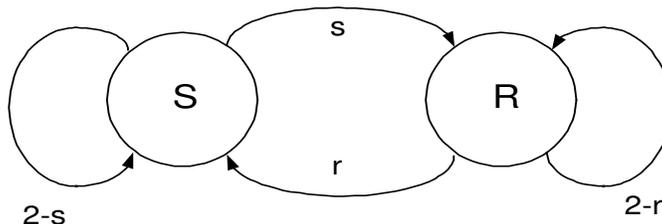

Figure 1: A 2-compartment model with sensitive and resistant cells

If we denote the inverses of the transit times of cells through the sensitive and resistant compartments by a and c, respectively, then the uncontrolled dynamics takes the form

$$\dot{S} = -aS + (2 - s)aS + rcR, \tag{1}$$

$$\dot{R} = -cR + (2 - r)cR + saS. \tag{2}$$

Here the first terms on the right hand sides account for the deaths of the mother cells, the second terms describe the return flows into the compartments, and the third terms give the cross-over flows. We now add a cytotoxic agent that kills sensitive cells, but has no effect on the resistant population. Let u denote the drug dose, $0 \leq u \leq u_{\max} \leq 1$, with $u = 0$ corresponding to no drug being used and $u = u_{\max}$ corresponding to a full dose. For simplicity it is assumed that the dosage, the concentration and the effect of the drug are equal, i.e. pharmacokinetics (PK) or pharmacodynamics (PD) are not modelled. It is assumed that the drug kills a fixed proportion u of the outflow of the sensitive cells at time t, $aS(t)$, and therefore only the remaining fraction $(1 - u)aS(t)$ of cells undergoes cell division. Of these new cells then $(2 - s)(1 - u)aS(t)$ remain sensitive, while a fraction $s(1 - u)aS(t)$ mutates to resistant cells. It is assumed that the drug has no effect on resistant cells. Thus overall the controlled dynamics can be represented as

$$\dot{S} = -aS + (1 - u)(2 - s)aS + rcR, \tag{3}$$

$$\dot{R} = -cR + (2 - r)cR + (1 - u)saS, \tag{4}$$

and the initial condition is given by positive numbers S_0 and R_0 at time $t = 0$. We could also allow for $R_0 = 0$, but it is clear that we then will simply have $R(t) \equiv 0$ on some interval $[0, t_0]$ provided that $u(t) \equiv 1$ on this interval, and that $R(t)$ will become positive as soon as $u(t) < 1$. Hence we only consider positive initial conditions. Setting $N = (S, R)^T$, the dynamics is described by a bilinear system

$$\dot{N} = (A + uB)N \tag{5}$$

where

$$A = \begin{pmatrix} (1-s)a & rc \\ sa & (1-r)c \end{pmatrix} \quad \text{and} \quad B = a \begin{pmatrix} s-2 & 0 \\ -s & 0 \end{pmatrix}. \tag{6}$$

3   A General Mathematical Model

A bilinear dynamics (5) is also characteristic to the higher-dimensional more general models considered below and therefore in this section we develop the mathematical aspects common to all of them for a general system with a state $N \in \mathbb{R}^n$. In all our applications the components of the state vector $N = (N_1, \ldots, N_n)^T$ denote the average numbers of cancer cells in the some compartments. *Admissible controls* are Lebesgue measurable functions u with values in a given interval $U = [\alpha, \beta] \subset [0, \infty)$. In the dynamics A and B are constant $n \times n$ matrices which describe the transitions (in- and out-flows, respectively) of cells between the compartments and are such that all the matrices $A + uB$ have non-negative off-diagonal entries. We make this as a **general assumption**:

(+) All the matrices $A + uB$, $u \in U$, have non-negative off-diagonal entries.

Condition (+) implies that solutions N to (5) will remain positive and thus the required positivity on the states need not be imposed as axtra constraint.

Proposition 3.1 *For any Lebesgue measurable control $u : [0, \infty) \to U$ the solution $N(\cdot)$ exists on $[0, \infty)$ and if N_0 has positive components, then all components of N remain positive.*

Proof. For any control u defined on $[0, \infty)$ this is a linear system with bounded coefficients and thus solutions exist over $[0, \infty)$. Define τ as the supremum over all times η such that all N_i, $i = 1, \ldots, n$, are positive on $[0, \eta]$,

$$\tau = \sup\{\eta \geq 0 : N_i(t) > 0 \text{ for } i = 1, \ldots, n \text{ and } 0 \leq t \leq \eta\}.$$

If τ were finite, at least one of the components of N, say N_i, must vanish at τ while all components are positive on $[0, \tau)$. Define $\mu(t) = N_i(t)$ and set $\alpha(t) = a_{ii} + u(t)b_{ii}$ and $\beta(t) = \sum_{j \neq i} (a_{ij} + u(t)b_{ij}) N_j(t)$. It then follows

from assumption (+) that $\beta \geq 0$ on $[0, \tau]$. The stated invariance property is a consequence of the following well-known comparison lemma for 1-dimensional linear ODE's: Suppose α and β are bounded Lebesgue-measurable functions on $\mathbb{R}$ and consider the ODE $\dot{\mu} = \alpha\mu + \beta$. If $\mu(t_0) > 0$ and $\beta(t) \geq 0$ on $[t_0, T]$, then $\mu(t) > 0$ on $[t_0, T]$. This is obvious from the representation

$$\mu(t) = \exp\left(\int_{t_0}^{t} \alpha(s)ds\right)\left[\mu(t_0) + \int_{t_0}^{t} \exp\left(\int_{s}^{t_0} \alpha(r)dr\right)\beta(s)ds\right].$$

Hence no component N_i can vanish at τ. Contradiction. $\square$

Mathematically the problem of cancer chemotherapy can be considered as an optimal control problem over a fixed therapy interval with the aim to minimize the number of cancer cells at the end of therapy while keeping the side effects tolerable. There exist many, and non-equivalent, ways of how to model this mathematically with no current consensus of what a good functional form of the objective should be. Both linear and quadratic functions on the control are in use. In this paper we consider an objective given in Bolza form as

$$J(u) = rN(T) + \int_{0}^{T} \ell N(t) + u(t)dt \tag{7}$$

where $r = (r_1, \ldots, r_n)$ is a row-vector of positive weights and the penalty term $rN(T)$ gives a weighted average of the total number of cancer cells at the end of the fixed therapy interval $[0, T]$. In order to prevent that cancer cells grow to unacceptable limits during therapy also a penalty term ℓN with $\ell = (\ell_1, \ldots, \ell_n)$ a row-vector of non-negative weights is added. (Depending on the role of some of the compartments here it may be desirable to choose $\ell_i = 0$ for some compartments.) Although the main aim is to have a small number of cancer cells at the end of the therapy session, including cumulative effects has the advantage of implicitly monitoring the growth of the cancer and preventing that it exceeds unacceptable levels. The Lagrangian is chosen linear in the control, the killing agent, since $u(t)$ is proportional to the fraction of ineffective cell divisions which is identified with the number of cancer cells killed. Since the drug kills healthy cells at a proportional rate, the control $u(t)$ is also used to model the negative effect of the drug on the normal tissue or its toxicity. Thus the integral in the objective models the cumulative negative effects of the killing agent in the treatment.

First order necessary conditions for optimality are given by the Pontryagin Maximum principle [19]. It is easily seen that all extremals must be normal and therefore, if u_* is an optimal control, then it follows that there exists an absolutely continuous function λ, which we write as row-vector, $\lambda : [0, T] \rightarrow (\mathbb{R}^n)^*$, satisfying the adjoint equation

$$\dot{\lambda} = -\lambda(A + u_*B) - \ell, \qquad \lambda(T) = r, \tag{8}$$

such that the optimal control u_* minimizes the Hamiltonian H,

$$H = qN + u + \lambda(A + u_*B)N, \tag{9}$$

over the control set along $(\lambda(t), N_*(t))$.

We show that assumption $(+)$ also implies that the first octant in the dual space $(\mathbb{R}^n)^*$ is negatively invariant under the flow of the adjoint equation.

Proposition 3.2 *For any admissible control u, if $\lambda_i(T) > 0$ for $i = 1, \ldots, m$, then $\lambda_i(t) > 0$ for all $t \leq T$ and all $i = 1, \ldots, m$.* $\square$

Proof. As solution to a linear ODE the adjoint variable exists over the full interval. Let σ denote the infimum over all times η such that all components λ_i are positive on $[\eta, T]$,

$$\sigma = \inf\{\eta \leq T : \lambda_i(t) > 0 \text{ for } i = 1, \ldots, n \text{ and } \eta \leq t \leq T\}.$$

The proof is exactly as for Proposition 3.1, but now using the reverse comparison: Suppose α and β are bounded Lebesgue-measurable functions on $\mathbb{R}$ and consider the ODE $\dot{\mu} = \alpha\mu + \beta$. If $\mu(T) > 0$ and $\beta(t) \leq 0$ on $[\sigma, T]$, then $\mu(t) > 0$ for $\sigma \leq t \leq T$. In this case, and also assuming that $\lambda_i(\sigma) = 0$, again set $\alpha(t) = a_{ii} + u_*(t)b_{ii}$, but now $\beta(t) = -\sum_{j \neq i} \lambda_j(t)(a_{ji} + u(t)b_{ji}) - \ell_i \leq 0$.
$\square$

Corollary 3.1 *If condition $(+)$ holds, then all states N_i and costates λ_i are positive over $[0, T]$.* $\square$

Optimal controls u_* minimize (9) over the interval $[\alpha, \beta]$. If we define the *switching function* as

$$\Phi(t) = 1 + \lambda(t)BN(t), \tag{10}$$

then optimal controls satisfy

$$u_*(t) = \begin{cases} \alpha & \text{if } \Phi(t) > 0 \\ \beta & \text{if } \Phi(t) < 0 \end{cases}. \tag{11}$$

A priori the controls are not determined by the minimum condition at times where $\Phi_i(t) = 0$. However, if $\Phi_i(t)$ vanishes on an open interval, also all its derivatives must vanish and this may determine the control. Controls of this kind are called *singular* while we refer to piecewise constant controls as *bang-bang* controls. Optimal controls then need to be synthesized from these and other possibly more complicated candidates. For this the derivatives of the switching function need to be analyzed. These derivatives are computed using the system and adjoint equations and the relevant relation can be summarized in the basic formula below which follows by a direct computation.

Lemma 3.1 *Suppose G is a constant matrix and let $\Psi(t) = \lambda(t)GN(t)$, where N is a solution to the system equation (5) corresponding to the control u and λ is a solution to the corresponding adjoint equation. Then*

$$\dot{\Psi}(t) = \lambda(t)[A + uB, G]N(t) - \ell GN(t), \tag{12}$$

where $[A, G]$ denotes the commutator of the matrices A and G defined as $[A, G] = GA - AG$.

Differentiating the switching function $\Phi(t) = 1 + \lambda(t)BN(t)$ twice gives

$$\dot{\Phi}(t) = \lambda(t)[A, B]N(t) - \ell BN(t), \tag{13}$$

$$\begin{aligned}\ddot{\Phi}(t) &= \lambda(t)[A + u(t)B, [A, B]]N(t) - \ell[A, B]N(t) - \ell B(A + uB)N(t) \\ &= \{\lambda(t)[A, [A, B]]N(t) - \ell[A, B]N(t) - \ell BAN\} \\ &\quad + u\{\lambda(t)[B, [A, B]]N(t) - \ell B^2 N(t)\}.\end{aligned} \tag{14}$$

If the control u is singular on an open interval I, then we have

$$0 \equiv \Phi(t) \equiv \dot{\Phi}(t) \equiv \ddot{\Phi}(t) \tag{15}$$

and formally the control can be computed as

$$u_{\sin}(t) = -\frac{\lambda(t)[A, [A, B]]N(t) - \ell[A, B]N(t) - \ell BAN(t)}{\lambda(t)[B, [A, B]]N(t) - \ell B^2 N(t)} \tag{16}$$

provided the denominator doesn't vanish. In this case the singular control is called of order 1 and it is then a necessary condition for optimality of $u_{\sin}$, the so-called **generalized Legendre-Clebsch condition** [12], that this denominator actually is negative, i.e. that we have

$$\frac{\partial}{\partial u} \frac{d^2}{dt^2} \frac{\partial H}{\partial u} = \lambda(t)[B, [A, B]]N(t) - \ell B^2 N(t) < 0. \tag{17}$$

Whether the singular control will be admissible, i.e. whether it will obey the control bounds $\alpha \leq u \leq \beta$, will depend on the parameter values, but also on the region in the state space where the state N lies and cannot be answered in general.

For example, for the 2-compartment model described in section 2, it is shown in [17] that

$$\frac{\partial}{\partial u} \frac{d^2}{dt^2} \frac{\partial H}{\partial u} = 2a^2 rc \{(2 - s)\lambda_1 + s\lambda_2\} (qS - (2 - q)R). \tag{18}$$

Since the multipliers λ_1 and λ_2 are positive, singular controls are thus not optimal in regions of the state space where $qS > (2 - q)R$. As resistance builds up, however, this condition tends to become violated and thus singular controls in principle become a potential candidate for optimal strategies.

4   Introducing Cell-Cycle Specificity

We now expand the basic model above to include phase specificity in the sensitive compartment [16]. The purpose of introducing this additional compartmental structure is to better model the effects of the drugs used. The drug considered here is a killing agent, such as Taxol, or spindle poisons like Vincristine or Bleomycin which destroy a mitotic spindle. These drugs are

active during a second growth phase and in mitosis when the cell wall becomes very thin and porous. It is therefore natural to cluster these phases of the cell cycle, usually denoted by G_2/M as one compartment S_2 and combine the remaining phases (which include the dormant phase G_0, an initial growth phases G_1 and the synthesis phase) as the other compartment S_1. All cells in S_1 move into the second compartment S_2 where cell division occurs and it is here that cells are killed or gene amplifications take place. All cells leave, but only the surviving ones reenter the cell cycle. While one cells reenters its cell-cycle (i.e. sensitive ones go to S_1 and resistant ones reenter R), the second one may undergo gene amplification or deamplification. Fig. 2 gives a schematic representation of the flows of cells.
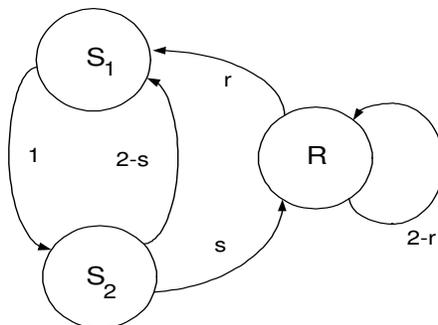

Figure 2: A cell-cycle specific extension

We denote the average numbers of cancer cells in these compartments by S_1, S_2, and R, respectively, and denote the corresponding inverse transit times of cells through these compartments by a_1, a_2, and c. The dynamics of the resistant compartment is not changed. A model which includes a G_2/M phase specific killing drug and resistance of cancer cells to this drug while allowing for *reverse* or *unstable gene amplification* can therefore be described by

$$\dot{S}_1 = -a_1 S_1 + (1-u)(2-s)a_2 S_2 + rcR, \tag{19}$$

$$\dot{S}_2 = -a_2 S_2 + a_1 S_1, \tag{20}$$

$$\dot{R} = (1-r)cR + (1-u)sa_2 S_2. \tag{21}$$

Defining $N = (S_1, S_2, R)^T$, the matrices A and B are given by

$$A = \begin{pmatrix} -a_1 & (2-s)a_2 & rc \\ a_1 & -a_2 & 0 \\ 0 & sa_2 & (1-r)c \end{pmatrix}, \quad B = \begin{pmatrix} 0 & -(2-s)a_2 & 0 \\ 0 & 0 & 0 \\ 0 & -sa_2 & 0 \end{pmatrix}, \tag{22}$$

and satisfy condition $(+)$ for any control u in $[0,1]$. The initial conditions for S_1 and S_2 at time 0 are positive while we also allow for $R(0) = 0$. In

this case, however, as soon as $u(t) < 1$, the variable R will become positive as well and thus the invariance properties stated above hold. We therefore have that:

Corollary 4.1 *The states S_1 and S_2 are positive, R is positive after possibly some initial interval on which it vanishes identically. All costates λ_i are positive over $[0, T]$.* □

Direct matrix computations verify that $B^2 = 0$ and that

$$[B, [A, B]] = -2a_1 a_2 (2 - s) B. \tag{23}$$

Hence for this model condition (17) reduces to

$$\begin{aligned}
\frac{\partial}{\partial u} \frac{d^2}{dt^2} \frac{\partial H}{\partial u} &= \lambda(t)[B, [A, B]]N(t) - \ell B^2 N(t) \\
&= -2a_1 a_2 (2 - s)\lambda(t)BN(t).
\end{aligned} \tag{24}$$

But if a control is singular on an interval I, then necessarily

$$\Phi(t) = 1 + \lambda(t)BN(t) \equiv 0 \tag{25}$$

and thus

$$\frac{\partial}{\partial u} \frac{d^2}{dt^2} \frac{\partial H}{\partial u} = 2a_1 a_2 (2 - s) > 0 \tag{26}$$

violating the strengthened Legendre-Clebsch for optimality of singular arcs. Thus we have:

Proposition 4.1 *Singular controls are not optimal if phase specificity is taken into account.* □

This then leaves bang-bang control as natural candidates and efficient computational schemes to find these exist.

5   Introducing Partial Resistance

As cancer cells obtain increasing numbers of copies of genes which aid removal or metabolization of the drug through gene amplification, the more resistant they become to increasingly higher concentrations of the drug. A second natural extension of the underlying model is therefore to consider various levels of drug resistance in the model and divide the resistant population into compartments according to the degree of drug resistance of the cells [16]. Here we formulate the simplest case when only two of these levels are distinguished, i.e. overall the model has three compartments consisting of *drug sensitive, partially resistant* and *resistant cells*. We denote the average numbers of cells in these compartments by S, P and R, respectively, and

denote the inverse of the average transit times through these compartments by a, b and c. In the model only transitions between sensitive and partially resistant cells and between partially resistant and fully resistant cells are allowed and we drop cell specificity. The corresponding transition rates are indicated in Fig. 3.
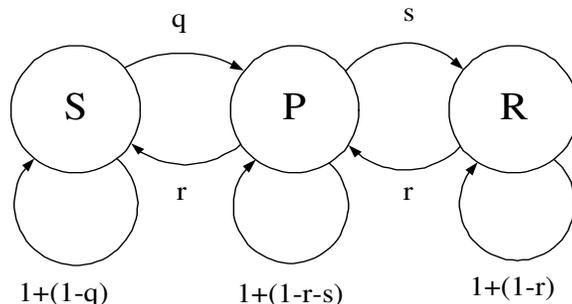

Figure 3: Gene amplification between sensitive, partially resistant and resistant cells

As above, let u denote the drug dose of a cytostatic killing agent, $0 \leq u \leq 1$, with $u = 0$ corresponding to no drug being used and $u = 1$ corresponding to a full dose. It is still assumed that the drug kills a fixed proportion u of the *outflow* of the sensitive cells at time t, $aS(t)$, and therefore only the remaining fraction $(1 - u)aS(t)$ of cells undergoes cell division. Of these new cells then $(2 - q)(1 - u)aS(t)$ remain sensitive, while a fraction $q(1 - u)aS(t)$ now mutates to partially resistant cells. The effectiveness of the drug on partially resistant cells is weaker, but not void yet, so we add a coefficient β, $0 < \beta < 1$ to represent it. Thus only a portion of the outflowing cells from the partially sensitive compartment proportional to βu is killed by the drug and the surviving portion $(1 - \beta u)bP$ undergoes cell division with one of the daughter cells possibly mutating. Thus, overall the controlled dynamics can be described by the following equations:

$$\dot{S} = -aS + (1 - u)(2 - q)aS + (1 - \beta u)rbP, \tag{27}$$

$$\dot{P} = -bP + (1 - \beta u)(2 - r - s)bP + (1 - u)qaS + rcR, \tag{28}$$

$$\dot{R} = -cR + (2 - r)cR + (1 - \beta u)sbP. \tag{29}$$

Here the first terms on the right hand sides account for the deaths of the mother cells, the second terms describe the return flows into the compartments and the remaining terms give the cross-over flows in the presence of a drug. Note that the effects of the drug show up at all return and cross-over flows except for the resistant compartment.

Defining $N = (S, P, R)^T$, the dynamics again is given by a bilinear system

(5) with the matrices

$$A = \begin{pmatrix} (1-q)a & rb & 0 \\ qa & (1-r-s)b & rc \\ 0 & sb & (1-r)c \end{pmatrix} \tag{30}$$

and

$$B = \begin{pmatrix} -(2-q)a & -\beta rb & 0 \\ -qa & -(2-r-s)\beta b & 0 \\ 0 & -\beta bs & 0 \end{pmatrix} \tag{31}$$

which also satisfy condition (+). Thus, similarly as above, we again have that

Corollary 5.1 *The state S is always positive; the states P and R are positive after possibly some initial interval on which they vanishes identically. All costates λ_i are positive over $[0, T]$.* $\square$

For the case of *stable gene amplification* $(r = 0)$, a direct calculation verifies that

$$[A, B] = \begin{pmatrix} 0 & 0 & 0 \\ qa(a + b\left((1-\beta)(1-s) - \beta\right)) & 0 & 0 \\ qa(1-\beta)sb & \beta sb(b+c) & 0 \end{pmatrix}.$$

The derivative of the switching function Φ is given by (13) as

$$\dot{\Phi}(t) = \lambda(t)[A, B]N(t) - \ell BN(t).$$

Here we have

$$-\ell BN(t) = -(\ell_1, \ell_2, \ell_3) \begin{pmatrix} -(2-q)a & 0 & 0 \\ -qa & -(2-s)\beta b & 0 \\ 0 & -\beta bs & 0 \end{pmatrix} \begin{pmatrix} S \\ P \\ R \end{pmatrix}$$

$$= aS\left((2-q)\ell_1 + q\ell_2\right) + \beta bP\left((2-s)\ell_2 + s\ell_3\right) > 0. \tag{32}$$

Since the components of λ and N are positive, also $\lambda(t)[A, B]N(t) \geq 0$ is guaranteed if all entries in $[A, B]$ are non-negative. Here only the $(1, 2)$-entry is not positive a priori, but it is positive, for example if $a \geq b\beta$. Realistically the parameters a and b will be similar, may even be set equal as a first approximation, and thus this is naturally satisfied. More precisely, the $(1, 2)$-entry is non-negative if and only if

$$\beta \leq \frac{\frac{a}{b} + 1 - s}{2 - s}. \tag{33}$$

Under this condition it is guaranteed that $\dot{\Phi}(t)$ is positive, regardless of the control used. This immediately gives the following result:

Proposition 5.1 *For the case of stable gene amplification, $r = 0$, and with β satisfying (33), optimal controls are bang-bang with at most one switch from $u = 1$ to $u = 0$.*

Thus, for small values of β, i.e. if resistance builds up too strongly, then optimal therapies would give initially a full dose treatment and then stop treatment as the side effects simply outweigh the benefits. For unstable gene amplification cells can lose resistance and then this direct monotonicity property on the derivative of the switching function does not hold any longer. In fact, preliminary calculations with $r > 0$ indicate that the derivative of the switching function can be decreasing if R gets large thus allowing for a reversal of resistance and continued treatments. However, this strongly depends on the values of the parameters and is left for further investigations.

6   Acknowledgements

7   References

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