PhD Dissertation Summary: In search of concise mathematical description of drug-resistant tumour growth

Piotr Bajger

Supervisors:

- prof. dr hab. Urszula Foryś
- prof. dr hab. inż. Krzysztof Fujarewicz

In this dissertation we developed a mathematical model of a drug-resistant tumour growth and its response to chemotherapy, with an aim to study the phenomenon of acquired drug resistance. Acquired drug resistance is a process which poses a major obstacle to effective chemotherapy planning. Even though a tumour may respond to the treatment very well initially, drug resistance often renders the treatment less (if at all) effective as the therapy progresses. A new trend in chemotherapeutic planning (the metronomic therapy) has emerged relatively recently which aims to tackle this issue by adapting a low-dose, high-frequency dosing schedule, as opposed to a standard maximum tolerated dose (MTD) schedule in which high doses are administered with prolonged drug-free intervals [21]. In the dissertation we use a mathematical model to investigate how such a change in schedule would affect tumour and surrounding vasculature, particularly in the context of drug resistance.

The main motivation behind this thesis is the fact even though our understanding of the biological processes associated with tumour growth has improved, there is effectively no comprehensive mathematical framework to study the underlying data [11]. The nature of acquired drug resistance, in particular the interactions between sensitive and resistant cells in cancer, appears to be non-linear and may escape our typical intuition. We

therefore view this process as an example of an area to which mathematics can contribute in order to gain better understanding of the qualitative and quantitative properties of the interplay between different components of this complex biological system.

Rather than constructing a highly complicated model with several of dependent variables and tens of parameters, we intentionally aim to develop simple models which nevertheless capture the key dependencies and interactions in the system (hence the word "concise" in the title). We believe that such minimal models are very much capable of capturing the essential features of the process, although additional care is needed to ensure that no key elements of the process were omitted.

As a consequence, in this dissertation we focus only on a subset of "hallmarks of cancer" [14, 15]: (i) enabling replicative immortality, (ii) genome instability and mutation, and (iii) angiogenesis (sprouting of new blood vessels from existing ones).

We adapted a bottom-up approach to model construction when we start with the simplest possible mathematical model and then add new features to it and investigate which model properties carry over to the more complicated and biologically relevant models. This is motivated by the fact that even for relatively small models of three equations the theoretical analysis becomes so difficult that one has to resort to numerical simulations. Having obtained analytic results for a simpler model we may get some some additional confidence in the validity and robustness of the numerical simulations.

As a starting point for our model building we chose the models used in mathematical ecology. We model the process of acquired drug resistance as a competition between two subpopulations of malignant cells – sensitive and resistant – so that the mathematical ecology framework seemed like a natural choice and is widely used by other authors, e.g [13, 17]. Hence the first "baseline" mathematical model (which we consider in Chapter 3) reads as follows:

$$\begin{aligned} \dot{N}_1 &= \lambda_1 N_1 \left(1 - \frac{N_1 + N_2}{K}\right) - \beta_1 N_1 u(t), \qquad & N_1(0) &= N_1^0, \\ \dot{N}_2 &= \lambda_2 N_2 \left(1 - \frac{N_1 + N_2}{K}\right), & N_2(0) &= N_2^0, \end{aligned} \tag{1}$$

where N_1 and N_2 denote the sizes (volumes) of the populations of sensitive and resistant cells respectively and $u(t)$ is the chemotherapy dose at time t

(expressed as a fraction of maximum dose). This model serves as a starting point for our analysis and – from the biological perspective – has certain limitations: most importantly, it does not take into account mutations to the resistant phenotype (or in the opposite direction). We have nevertheless found that some of the properties of this model carried over to more complicated ones.

To represent the shift in therapeutic paradigm from maximising cell kill through maximum tolerated dose [22] to minimising drug resistance, we formulated a bespoke objective functional which explicitly penalises not only tumour volume, but also drug resistance. The objective function (which we will attempt to minimise through appropriate chemotherapy dosing) is defined is in its most general form given by:

$$J(u(\cdot)) = \omega_1 N_1(T) + \omega_2 N_2(T) + \int_0^T \eta_1 N_1(t) + \eta_2 N_2(t) + \xi G\left(\frac{N_2(t) - N_1(t)}{\varepsilon}\right) dt, \tag{2}$$

with $\omega_{1,2}$, $\eta_{1,2}$ and ξ being weights responsible for penalising different components of our objective. To additionally penalise resistant cells we always choose $\omega_1 \leq \omega_2$ and $\eta_1 \leq \eta_2$. The non-linear function G is responsible for penalising drug resistance. For all practical purposes (e.g. numerical simulations) we chose G to be

$$G(z) = \frac{1}{2}\left(1 + \tanh(z)\right),$$

but the theoretical results are obtained for more general function G of which the above is a good representative. The function G and the scaling factor ε in general are chosen so that $G \approx 1$ when $N_2 > N_1$ and $G \approx 0$ when $N_1 < N_2$, i.e. the penalty is applied when the tumour is resistant ($N_2 > N_1$).

The problem which we consider throughout the dissertation then becomes: for a fixed terminal time T find a measurable function $u : [0, T] \to [0, 1]$ such that the objective functional (2) is minimised subject to the dynamics (1).

The main result from Chapter 3 of the dissertation is that there exist locally optimal singular controls of order one. What is more, we were able to compute the singular control explicitly as a feedback function of the state variables. We were also able to prove some additional constraints on the control structure (e.g. that an optimal treatment needs to end with a full-dose interval and that a switch from a singular dose to no dose is not optimal).

We then used a gradient method (an extension of the method originally proposed by Śmieja et al. [23] which we developed in [4]) to solve the optimal control problem. We found that the optimal control is of the form 1-singular-1 and that the singular control becomes a part the final solution.

The main oversimplification we have made so far is that we ignored the process of mutations which is generally thought to be the driving mechanism behind acquired drug resistance [10, 12]. In Chapter 4 of the dissertation we therefore extended model 1 to account for mutations:

$$\begin{aligned} \dot{N}_1 &= \lambda_1 N_1 \left(1 - \frac{N_1 + N_2}{K}\right) - \tau_1 N_1 + \tau_2 N_2 - \beta_1 N_1 u(t), & N_1(0) &= N_1^0, \\ \dot{N}_2 &= \lambda_2 N_2 \left(1 - \frac{N_1 + N_2}{K}\right) + \tau_1 N_1 - \tau_2 N_2, & N_2(0) &= N_2^0, \end{aligned} \tag{3}$$

where τ_1 and τ_2 are the (non-negative) mutation rates respectively from the sensitive to resistant phenotype and vice-versa. Note that the flows in and out of each compartment are balanced: as expected, no cells appear or disappear as a result of mutations. The mutation rates τ_1 and τ_2 can be interpreted as follows: τ_i/λ_i for $i = 1, 2$ is the fraction of proliferating cells which undergo a mutation per day. As a result, we must have $\tau_i < \lambda_i$ for $i = 1, 2$. Note that the way in which the mutations were to be included was not obvious with different approaches being used in the literature [16, 17, 24]. We have justified our choice in the following way: tumour cell subpopulations in our model follow logistic growth for which we assume that the tumour cells proliferate at a rate proportional to the volume of cells, while the death rate scales with the square of the volume of cells. The mutation rates are assumed to be proportional to the proliferation rates as the cells may undergo mutation upon division with some positive probability.

We performed an analysis similar to that present in Chapter 3 and found that the mutation rates do not alter the structure of the optimal control (although the switching times were marginally different). We have also found that the System (3) has a single positive attracting steady state and analytically found a maximum chemotherapy dose which can be administered before the tumour turns resistant (i.e. there are more resistant than sensitive cells at the steady state). This dose was found to be:

$$\bar{u} = \frac{1}{\beta_1} \max\left(0, \min\left(\frac{(\lambda_1 + \lambda_2)(\tau_2 - \tau_1)}{\lambda_2}, \frac{2\lambda_2\tau_2 + \lambda_1\tau_2 - \lambda_2\tau_1}{\lambda_2}\right)\right).$$

The results from this chapter were published in [4].

In Chapter 5 of the dissertation we proposed two more extensions of the model. Firstly, we introduced competition coefficients to measure the competitive effect one type of cells may have on the other. In experimental practice it turns out that in the absence of the drug the sensitive cells win the competition and overcome the resistant ones, leaving only a small subpopulation of the latter. It is only when a strong selective force is imposed due to the presence of a cytotoxic agent that balance tips over in favour of the resistant cells which are then capable of overcoming the sensitive population [12].

Another important aspect of tumour growth which has been ignored is the process of angiogenesis, i.e. the recruitment of new blood vessels by hypoxic (oxygen-deprived) cancer cells [9]. This process is necessary for a tumour to grow behind an oxygen diffusion limit which corresponds to a tumour size of 1-2mm^3 [20]. When introducing this process into our model we follow closely a well-established model proposed by Hahnfeldt et al. [13] and analysed further by various other authors (us included) [1, 3, 8, 7, 18, 19]. The process of angiogenesis is particularly important in the context of metronomic therapy, as anti-angiogenic effects (which are included in our model) are hypothesised to be one of its additional benefits:

$$\begin{aligned}
\dot{N}_1 &= \lambda_1 N_1 \left(1 - \frac{N_1 + \alpha_{12} N_2}{K}\right) - \tau_1 N_1 + \tau_2 N_2 - \beta_1 N_1 u(t), \\
\dot{N}_2 &= \lambda_2 N_2 \left(1 - \frac{N_2 + \alpha_{21} N_1}{K}\right) + \tau_1 N_1 - \tau_2 N_2, \\
\dot{K} &= -\mu K + b\big(N_1 + N_2\big) - d\big(N_1 + N_2\big)^{2/3} K - \beta K u(t).
\end{aligned} \tag{4}$$

Equation for K is related to the size of the vasculature at the tumour site. Parameter μ denotes the natural death rate of endothelial cells, while parameters b and d control the rate at which the tumour cells secrete pro- and anti-angiogenic signals. It is assumed that both the resistant and sensitive cells secrete those signals at the same rates. The exponent 2/3 is the area/volume ratio which appears ultimately as a consequence of the half-life of angiogenic inhibitors greatly exceeding that of angiogenic stimulators. Not without significance is the fact that the chemotherapy is not selective – it affects vasculature as well as tumour cells.

We perform an analysis of the steady states of System (4) to find using Descartes' rule of signs, that, under certain assumptions regarding the compe-

tition coefficients α_{12} and α_{21}, the system exhibits bistability and a hysteresis loop may appear, as we first identified in [3] for a similar, slightly simpler model. This phenomenon is of major importance from the point of view ot chemotherapy planning. Once the critical dose is exceeded, the tumour locks in in the resistant phenotype which may be of disastrous consequences to the patient. Note that the upper bound for the chemotherapy dose $\bar{u}$ is effectively determined analytically:

$$\bar{u} = \frac{1}{\beta}\left(\lambda_1 - \tau_1 - \frac{\lambda_1(\lambda_2 - \tau_2)}{\lambda_2\alpha_{21}} - \frac{\lambda_1\alpha_{12}\tau_1}{\lambda_2\alpha_{21}}\right),$$

which holds under a few additional assumptions regarding the simultaneous existence of three steady states.

We then proceeded to solving the optimal control problem under the new dynamics (4). Given high uncertainty regarding the numerical values of the mutation rates and competition coefficients we performed a sensitivity analysis with respect to those parameters by choosing their values at random. What we found is that the results are quite robust, with the majority of controls having the expected 1-singular-1 profile. Note that we had to use a general direct optimisation method as the gradient method was not suitable for use in three dimensions. Again, the singular part of the control proved to be crucial in maintaining the tumour in a sensitive state.

The benefits of metronomic therapy were further confirmed by our analysis of the dependence of the survival time (i.e. time needed for a tumour to reach a critical, fatal volume) on the chemotherapy dose. We showed using numerical simulations that maximum survival times are achieved for intermediate doses.

The work performed in Chapter 5 has been submitted for publication [2].

Finally, let us note that the models investigated have a "block" structure in the sense that it is relatively easy to add new processes and/or therapies. As an example, we performed an investigation of combined radiochemotherapy in [5, 6].

We close these remarks by concluding that mathematical modelling supports the hypothesis that the risk of drug resistance can be mitigated by appropriate chemotherapy dosing, as is evident both from qualitative analysis of the differential equations, as well as the results from optimal control theory. The next steps would be to verify these theoretical results in an experimental setting and to fine-tune the model using experimental data.

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