INVESTIGATION OF THE EFFECT OF DRUGS ON SOLID TUMOURS WITHIN A SYSTEMS-BASED MATHEMATICAL MODELLING FRAMEWORK

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ABSTRACT

The study develops a skeletal modeling framework to systematically evaluate the effect of anticancer drugs on solid tumors, especially from the perspective of cellular signaling. The modeling framework incorporates interstitial drug transport, intracellular apoptosis signaling and the dynamics of tumor cell density, which are regarded as the essentially minimal elements. The study deliberately starts with coarse grained descriptions of the cellular signaling, which nevertheless are capable of correctly capturing the qualitative dynamics involved. A series of simulations have been performed to provide mechanistic and predictive insights into cellular response towards different forms of drug stimuli. It is found qualitatively different intracellular signaling models can give rise to similar tissue behavior. Within the context, validating the models must be performed with care by considering a variety of drug stimuli.

Keywords: drug transport and effect, intracellular signaling, systems modeling framework, solid tumors

1. INTRODUCTION

It is a highly challenging multi-scale problem to elucidate the effects of anticancer drugs on solid tumors, concerning tremendous complexities associated with transport and cellular response (Minchinton and Tannock 2006; Kreeger and Lauffenburger 2010). Several attempts have been made to mathematically model the anticancer effects (Liu, Krishnan, Stebbing and Xu 2011); however, they failed to offer a transparent systems level description of the sources of these complexities, in particular a dynamical systems basis for the description of the cellular signaling. Considerable amounts of research activity in unraveling cell signaling processes under the umbrella of systems biology are especially relevant in the current context.

This study takes the first steps towards developing a systems-based modeling framework, which is capable of capturing the information flow correctly and in particular, should be modular and transparent to allow for further systematic refinement and augmentation. This study integrates basic descriptions of essentially minimal elements, namely interstitial drug transport, apoptosis signal transduction and tumor cell density dynamics, in tumor cord geometry (Figure 1). A particular focus is paid on how to appropriately incorporate the complexities of cellular response which is characterized by highly non-linear chemical signal transduction. The efficacy of drugs is examined under simple (persistent and square pulse) drug signal (Liu, Krishnan and Xu 2011) and physiologically realistic signals with exponential decays. The modeling framework intends to yield mechanistic predictions of drug effect and provide clear-cut insight into the interconnections among the constituent elements.

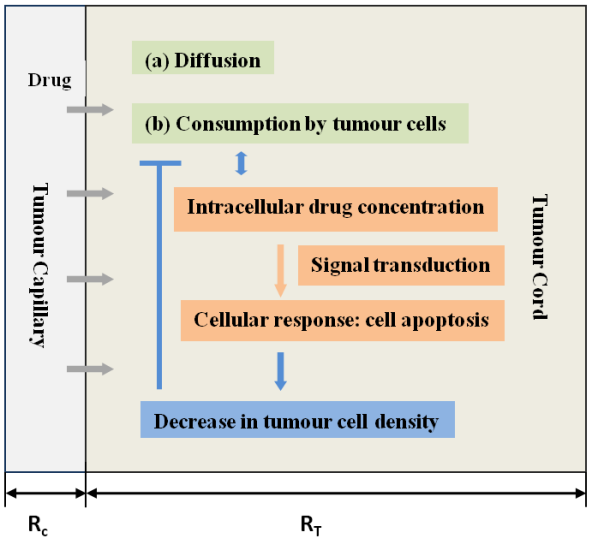

Figure 1: Diagrammatical representation of information flow incorporated in the modeling framework in the tumor cord geometry.

2. METHODS

Key descriptions of the modeling framework are presented as follows. The main assumptions of the model are:

1. Cells are initially alive and uniformly distributed in the tumor cord.
2. Cells are assumed to be stationary in the tumor cord.
3. Homogeneous conditions are assumed inside the tumor cord prior to injection of the drug.
4. Cellular variability and stochasticity are ignored.

Bearing in mind that the study focuses on developing a skeletal systems platform for gradual expansion and incorporation with further cellular/transport complexities, data fitting is not attempted at the current stage.

2.1. Interstitial drug transport

Interstitial drug transport is described by diffusion-reaction equation in 1D tumor cord geometry with both axial and radial symmetry (Eikenberry 2009). The model examines the spatio-temporal distribution of extracellular free, extracellular bound and intracellular drug concentration. Extracellular drugs can bind to, or unbind from proteins, such as albumin; in addition, the free form of extracellular drugs are taken up or released (pumped out) by tumor cells. Their dynamics are governed by:

Extracellular free drug:

$$\frac{\partial c_E}{\partial t} = D_{\mathrm{E}}\nabla^2 c_E + c_t\left(\frac{V_2 c_I}{k_2+c_I} - \frac{V_1 c_E}{k_1+c_E}\right) - k_a c_E + k_d c_B \quad (1)$$

Extracellular bound drug:

$$\frac{\partial c_B}{\partial t} = D_B\nabla^2 c_B + k_a c_E - k_d c_B \quad (2)$$

Intracellular drug:

$$\frac{\partial c_I}{\partial t} = \frac{V_2 c_I}{k_2+c_I} - \frac{V_1 c_E}{k_1+c_E} \quad (3)$$

2.2. Intracellular apoptosis signaling

In the current study, the main intracellular process of interest is drug induced apoptosis. Concerning the facts that many mechanistic details in the intracellular response are yet to be fully understood, but it is urgently needed to incorporate the key features of cellular effects identified already at an appropriate level, the modeling strategy adopted is to deliberately start with simpler descriptions. Meanwhile the validity of the simplified models is checked by comparing to sample detailed models, especially for the types of drug stimuli encountered by cells.

Two key features must be reflected in any apoptosis model that there must be threshold effect present and apoptosis must be 'switched' on in an irreversible manner. Bistable switches which have self-contained threshold behavior and irreversibility have been adopted in modeling cellular signal transduction leading to apoptosis (Eissing, Conzelmann, Gilles, Allgower, Bullinger and Scheurich 2004; Legewie, Bluthgen and Herzel 2006). However, there is still a debate in the literature of systems biology as to the qualitative nature of signal processing leading to cell killing. The irreversibility exhibited in cell apoptosis might arise from a simple irreversible reaction triggered in very special contexts (Albeck, Burke, Spencer, Lauffenburger and Sorger 2008; Gu, Zhang, Chen and Lei 2011), rather than is necessarily or even reasonably reflected as a steady state. Therefore, two types of apoptosis models are employed here: a bistable apoptosis model and a monostable switch sequentially connected to a downstream irreversible reaction effect.

Both models are essentially minimal but include a downstream intermediate element connecting input to response and a response element responsible for triggering apoptosis.

The study adopts a sample bistable model arising from a positive feedback, which is catalyzed by the upstream signal (the intracellular drug concentration c_I) (Ferrell Jr, Pomerening, Kim, Trunnell, Xiong, Huang and Machleder 2009).

$$\frac{dR}{dt} = \frac{V_f(1-R)}{K_{m1}+(1-R)} + (p+qc_I)k_{fb}R(1-R) - \frac{V_r R}{K_{m2}+R} \quad (4)$$

When the signal c_I crosses a threshold value for sufficient time, a sharp increase in the steady state of R is attained, even in the case of transient signal. The response in turn drives the activation of downstream species R_1 from its inactivation form, which results in a different higher steady state of R_1. Cell death is triggered when R_1 is across its threshold. When cellular apoptosis is reflected to the cell population density, it is modeled in a reversible manner.

$$\frac{dR_1}{dt} = k_f R(1-R_1) - k_r R_1 \quad (5)$$

The monostable switch in the second model is described by a Hill-type non-linearity, where the intracellular drug concentration acts as the upstream signal.

$$\frac{dR}{dt} = k\left(\frac{c_I^n}{k_h+c_I^n} - R\right) \quad (6)$$

The output drives the same activation of R_1 as before. Only when the upstream monostable switch is kept 'on' for a substantial period of time, can R_1 reach its threshold, which signifies cell death. In this case, such effect is reflected at the population level in an irreversible fashion.

2.3. Tumor cell density

The tumour cell density is governed by logistic equations. As it is described in a continuous form, the triggering of cellular apoptosis is represented as sharp decrease in growth rate at the population level. In this context (when $a < 0$), the only biologically relevant

steady state is the zero steady state, which indicates all the cells will perish eventually.

$$\frac{\partial c_t}{\partial t} = ac_t - bc_t^2 \qquad (7)$$

It should be noted that computational implementation of this threshold effect is achieved in a reversible way in the bistable model, while in a unidirectional (irreversible) way in the monostable model.

3. RESULTS

Analysis of numerical results is presented by considering both variants of the intercellular signal transduction models and multiple types of drug stimuli. Here, doxorubicin is chosen as the anticancer drug for parameterization purpose.

3.1. Persistent drug input

Drugs are assumed to be injected directly at the entry to the tumor cord. Upon persistent drug infusion, a homogenous distribution of drug concentration is established throughout the tumor cord; and depending on the input intensity, drug concentration is either above or below the threshold. As a result, homogeneous cell response is observed that tumor cells are either killed or alive as shown in Figure 2. This trend is seen for both variants of intracellular apoptosis models.

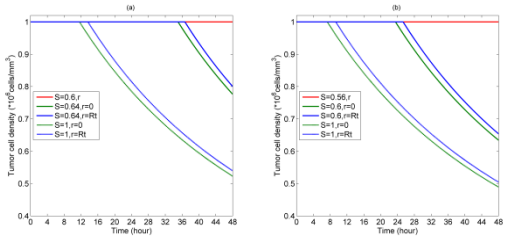

Figure 2: Temporal profiles of cell density at specific spatial locations for persistent infusion for different drug intensities. (a) Bistable switch case, (b) Monostable switch case. Note drug input S in the dimensionless form normalized by 0.001μg/mm^3 for convenience.

3.2. Square pulse drug input

A square pulse drug input is assumed to be imposed at the inner capillary wall as well. Temporal profiles of intracellular drug concentration and tumor cell density are presented in Figure 3. A pulse injection generates a transient period of elevated intracellular drug concentration (Figure 3(a)), which is able to activate intracellular apoptosis pathway. This aspect is clearly revealed in Figure 3 (b), where the tumor cell density in the proximal starts to decline and would eventually becomes zero while it is kept as its initial state in the distal of the tumor cord. It suggests that a single pulse can kill tumor cells in a certain region only. Additional simulations show that an increase in the pulse strength/infusion time results in a broader cell death region, even the entire domain and the trend is in a strongly non-linear fashion for both bistable and monostable apoptosis models (Liu, Krishnan et al. 2011).

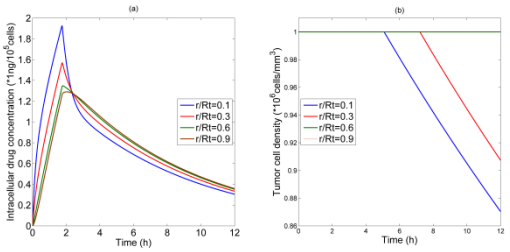

Figure 3: Time course of (a) intracellular drug concentration and (b) tumor cell density at various radial locations under pulse injection S=4, T=1.75h, for bistable apoptosis switch.

3.3. Exponentially decaying pulse drug input

The study also examines the case where drug is injected intravenously and the drug concentration input is determined by adopting a pharmacokinetic model (Robert 1982). Herein, the drug input is expressed in the exponentially decaying terms Presented in Figure 4 are temporal profiles of intracellular drug concentration and tumor cell density, which display dramatic similarities to those in Figure 3. All these demonstrate that our model can be used as a platform to systematically investigate the cellular response to various forms of drug injections, and even various forms of drugs (free drug versus drug delivery systems) in the future study.

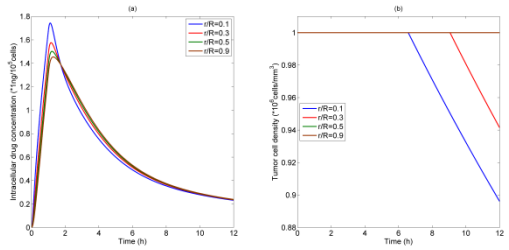

Figure 4 Time course of (a) intracellular drug concentration and (b) tumor cell density at various radial locations following a 1hour infusion of a dosage 300mg/m^2, for bistable apoptosis switch.

3.4. Double square pulse drug inputs

The study also examines the effects of double pulse injections and finds that a second pulse injection does indeed expand the cell death zone as shown in Figure 5. It is also shown that the time interval between pulses is a key parameter in determining the efficacy of the following pulse injection. Doubling the time interval substantially reduces the width of cell death region, which is because the second pulse cannot take advantage of the residual effect from the first pulse. It should be noted that a second bolus has little effect on the time course of cell death in regions which stand already. Similar trends are observed in the case of monostable apoptosis switch.

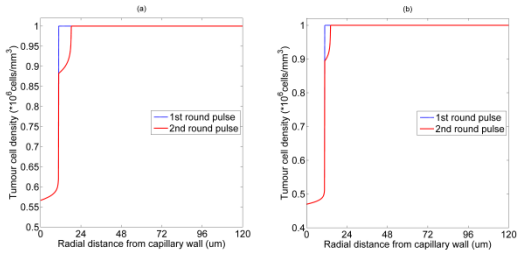

Figure 5: Spatial profiles of cell density for two rounds of pulse injection with the same pulse characteristics, S=4, T=1.5h for bistable apoptosis switch, (a) tumor cell density at 36h with 24h interval between pulses, (b) tumor cell density at 60h with 48h interval between pulses.

4. DISCUSSION

The modeling framework incorporates the essential descriptions of interstitial drug transport, intracellular signal processing and tumor cell density dynamics, which are regarded as minimal elements connecting drug input to cell killing.

It should be mentioned that coarse grained descriptions of signaling pathways are adopted to qualitatively capture the input-output characteristics of the signal transduction dynamics while to retain the predictive advantages of mechanics models. The immediate focus of the present study is not on obtaining quantitative values to fit data rather than predictions regarding qualitative trends

Two variants of intracellular apoptosis models (one involving a bistable switch and the other a monostable irreversible switch) are examined. Interestingly, qualitatively different characteristics of the signal transduction notwithstanding, both models predict the essentially similar trends, suggesting that such difference plays a minor role in determining the responses to simple (and typical) stimuli encountered in realistic drug treatment. Difference might arise when more complex temporal signals are applied.

Alongside the simplified apoptosis signaling models, a sample detailed caspase activation model of type II apoptosis (intrinsic pathway) (Legewie, Blüthgen and Herzel 2006) has been examined here at the ODE level. From the perspective of input-output characteristics, the detailed bistable apoptosis model and the simplified one adopted in this study display qualitatively similar trends under simple (and typical) stimuli (discussed in Appendix A). Taken together, it can be speculated that additional biochemical details involved in the signaling network may play a more important role in the quantitative effect on the tumor dynamics, but not in the qualitative trends.

5. CONCLUSION

The study takes the first steps towards creating a skeletal systems-based modeling platform with integration of essential descriptions of drug transport, cellular signaling and tumor tissue evolution. The modeling framework is modular and transparent to allow for systematic refinement and augmentation that could be incorporated in each module and between modules, and in tumor type- and anticancer agent-specific application. It is expected that the modeling strategy is capable of pinning down the roles that additional layers of complexities play in the system and yielding more comprehensive and predictive insight into the effects of anticancer drugs on solid tumors.

APPENDIX A

Examined first is the threshold effect that arises from the bistability exhibited in both the sample detailed and simplified bistable cases. The steady-state stimulus-response curves shown in Figure A1 depict that the systems remains the 'off' (lower) steady state even with increasing stimuli and are switched to the 'on' (higher) steady state until the stimuli reaches the threshold. It should be noted that the bistable system in the concrete models displays irreversibility; in other words, the system remains in the 'on' state permanently even after the removal of the signal. To capture the irreversibility in the abstract bistable apoptosis model, the upstream signal (c_I) is linearly factored in the form $p + qc_I$, where the basal level p lies in the bistable regime.

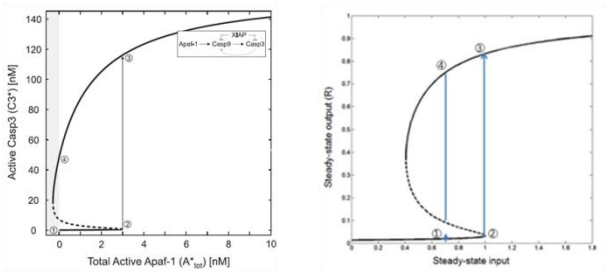

Figure A1: Steady-state stimulus-response curve of (a) caspase cascade in detailed apoptosis model adopted from (Legewie, Blüthgen et al. 2006), (b) the simplified bistable model in this study.

REFERENCES

Albeck, J. G., J. M. Burke, et al. 2008. Modeling a snap-action, variable-delay switch controlling extrinsic cell death. *PLoS Biol* 6: 2831-2852.

Eikenberry, S. 2009. A tumor cord model for doxorubicin delivery and dose optimization in solid tumors. *Theor Biol Med Model* 6: 16.

Eissing, T., H. Conzelmann, et al. 2004. Bistability analyses of a caspase activation model for receptor-induced apoptosis. *Journal of Biological Chemistry* 279: 36892-36897.

Ferrell Jr, J. E., J. R. Pomerening, et al. 2009. Simple, realistic models of complex biological processes: Positive feedback and bistability in a cell fate switch and a cell cycle oscillator. *FEBS Letters* 583: 3999-4005.

Gu, C., J. Zhang, et al. 2011. A trigger model of apoptosis induced by tumor necrosis factor signaling. *BMC Syst Biol* 5 Suppl 1: S13.

Kreeger, P. K. and D. A. Lauffenburger. 2010. Cancer systems biology: a network modeling perspective. *Carcinogenesis* 31: 2-8.

Legewie, S., N. Bluthgen, et al. 2006. Mathematical modeling identifies inhibitors of apoptosis as mediators of positive feedback and bistability. *Plos Computational Biology* 2: 1061-1073.

Legewie, S., N. Blüthgen, et al. 2006. Mathematical modeling identifies inhibitors of apoptosis as mediators of positive feedback and bistability. *PLoS Comput Biol* 2: e120.

Liu, C., J. Krishnan, et al. 2011. Use of mathematical models to understand anticancer drug delivery and its effect on solid tumors. *Pharmacogenomics* 12: 1337-1348.

Liu, C., J. Krishnan, et al. 2011. A systems-based mathematical modelling framework for investigating the effect of drugs on solid tumours. *Theor Biol Med Model* 8: 45.

Minchinton, A. I. and I. F. Tannock. 2006. Drug penetration in solid tumours. *Nat Rev Cancer* 6: 583-592.

Robert, J. 1982. Pharmacokinetics of adriamycin in patients with breast cancer: Correlation between pharmacokinetic parameters and clinical short-term response. *European journal of cancer & clinical oncology* 18: 739-745.