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Model for acid-mediated tumour invasion with chemotherapy intervention II: Spatially heterogeneous populations

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ABSTRACT

This paper extends the model for acid-mediated tumour invasion with chemotherapy intervention examined in part I. The model presented in part I considers the interaction between tumour cells, normal cells, acid and drug in a well mixed (i.e. spatially homogeneous) setting, which is governed by a system of nonlinear differential equations. The model examined here removes the assumption that the populations are spatially homogeneous resulting in a system of nonlinear partial differential equations. Numerical simulations of this model are presented for different treatment methods displaying several possible behaviours. Asymptotic approximations are also derived for a special case of the treatment method and set of parameter values. This analysis then allows us to draw conclusions about the effectiveness of treating acid-mediated tumours with chemotherapy.

1. Introduction

This article seeks to extend the model proposed in [21], that considers the acid-mediation hypothesis with the added interaction of a tumour treatment protocol, to a spatially heterogeneous setting. The acid-mediation hypothesis is the assumption that tumour invasion is facilitated by acidification of the region around the tumour-host interface caused by aerobic glycolysis, also known as the Warburg effect [45]. This acidification creates an inhospitable environment and results in the destruction of the normal tissue ahead of the acid resistant tumour, thus enabling the tumour to invade into the vacant region. This hypothesis was first examined mathematically by [15] with a system of reaction-diffusion equations that consider the interaction between the tumour, host and acid. Recent extensions to this model include the reduction of acid by use of a bicarbonate solution [36], the addition of tumour sensitivity to the presence of acid [35] and the use of an acid production term that is a nonlinear function of the tumour cell density [22]. The acid-mediation hypothesis was examined in [39], where a cellular automaton based model was used that considered the effect vascular densities and tumour metabolism had in determining optimal conditions for tumour invasion. Interaction of the extracellular matrix and matrix metalloproteinases was considered in [33] where it was suggested there exists an optimal level of tumour aggressiveness. An experimental investigation of the tumour microenvironment in [10] showed evidence that increased acidity of tumours increases invasion and furthermore, this invasion could be slowed by decreasing the acidity with a regular administration of an acid buffer such as bicarbonate solution. We note that the majority of articles that consider the acid-mediation hypothesis have examined the process as a relatively closed system, that is, without considering some form of external intervention such as treatment of the tumour with chemotherapy. Hence we propose and subsequently analyse a model for acid-mediated tumour invasion whilst treatment for the tumour is being administered. We determine the conditions in our model when the treatment is effective/ineffective, how treatment affects the strength of the acid-mediated invasion and if a treatment can slow, stop or reverse the invasion of a tumour.

There are many models that have considered chemotherapy and the corresponding effect on the growth of solid tumours. Continuum models have been considered in which the dynamics of total cell populations and average chemotherapy drug concentration were examined by employing the use of ordinary differential equations (ODEs), some examples include [4,7,8]. There have been recent models that considered the addition of an immune response in tumour cell and chemotherapy models [6,8] encouraged by experimental results suggesting an important impact of the host immune response on the effectiveness of a chemotherapy treatment. The effects of normal cell populations in models that consider chemotherapy have largely been neglected. Hence it is an aim of this article to determine whether the presence of normal cells can alter the perceived effectiveness of chemotherapy.

The model considered in [21] examines the acid-mediation hypothesis with chemotherapy by the use of a system of nonlinear

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ordinary differential equations that examines the interaction of tumour cells, normal cells, acid and a cytotoxic chemotherapy drug. This model considers Lotka–Volterra dynamics for the tumour and normal cells, the tumour is destroyed by the presence of chemotherapy drug which is infused as a function of time and normal cells are destroyed by interacting with acid. We wish to consider a spatially heterogeneous model that extends the simpler spatially homogeneous model presented in [21] due to two key reasons, the first of which being the unrealistic nature of the assumption underpinning a spatially homogeneous model. The use of a spatially homogeneous model assumes that the populations considered are well mixed and hence have no significant spatial variations. However we are proposing to consider tumour and normal tissue populations and, in a reductionist view, tumours form as insular masses surrounded by normal cells [19,20]. Hence the assumption that these populations are well mixed is not realistic. The second important consideration in using a spatially heterogeneous model is the extra insight that can be gained about the key processes governing the dynamic behaviour of the system, an example of this being the acid-mediation hypothesis. Should the model considered by [15] have been modelled in a spatially homogeneous setting with no influence of spatial variances, then due to the governing dynamics of the production of H^+ ions, one would determine very similar behaviour between a model that considers acid-mediation and one that considers purely population competition. One could conclude that the additional tumour aggressiveness associated with the acid-mediation hypothesis as being attributed to the tumour population having more dominant population competition dynamics. However in the spatio-temporal model as considered by [35] this confusion could not so easily be made with behaviours such as the development of an interstitial gap, which occurs in invading tumours where the H^+ ions have a strong destructive effect, only being possible with the inclusion of the acid-mediation hypothesis. Whilst we still acknowledge that much insight can be gained from the spatially homogeneous model, much of which can be used to predict behaviour in a spatially heterogeneous setting, we feel that to truly determine the behaviour of the system and the important components that govern it, the model must be considered in a spatio-temporal setting.

This paper is organised as follows. In Section 2 we discuss the formulation of our model and provide details of a corresponding non-dimensionalisation. In Section 3 we examine the model numerically and present some analytical and heuristic analysis of the results. Section 4 presents the arguments for the determination of asymptotic approximations to the solutions of a special case of the model. A discussion of results and some concluding remarks are presented in Section 5.

2. Model formulation

Here, the basic assumptions used to develop the model in [21] are recalled along with additional assumptions required due to the spatially heterogeneous populations.

(i) Both normal and tumour cells are governed by logistic growth in the absence of any kind of intervention [8,9,15];
(ii) Normal cells and tumour cells undergo cell diffusion. Furthermore, the diffusion coefficients may be dependent on the other respective cell density [15];
(iii) We consider a population competition relationship between the normal and tumour tissues [35];
(iv) The tumour tissue produces H^+ ions as a result of aerobic glycolysis [15,35] at a rate proportional to the tumour cell density;
(v) The normal tissue interacts with the excess H^+ ions, leading to a death rate proportional to the H^+ ion concentration [15,35];
(vi) Excess H^+ ions diffuse chemically with a constant diffusion rate and are produced at a rate proportional to the tumour cell density. Moreover, an uptake term is included to take account of mechanisms for increasing pH (e.g. buffering and large-scale vascular evacuation) [15];
(vii) Since chemotherapy is a systemic treatment, the simplifying assumption is made that the chemotherapy drug is infused homogeneously across the system at a rate given by a function of time. A term is included for removal of drug from the system by metabolic processes [4,8] and the drug is assumed to diffuse chemically at a constant rate;
(viii) The tumour tissue interacts with the chemotherapy drug leading to destruction of tumour tissue at a rate proportional to the concentration of drug [4,8];
(ix) The chemotherapy drug concentration is decreased by interaction with the tumour tissue [4].

Let the populations at time s (in seconds) and position $\mathbf{y}$ (in cm) be denoted by:

- $N_1(\mathbf{y}, s)$, normal cell density (in cells cm^{-3});
- $N_2(\mathbf{y}, s)$, tumour cell density (in cells cm^{-3});
- $H(\mathbf{y}, s)$, excess H^+ ion concentration (in M);
- $C(\mathbf{y}, s)$, chemotherapy drug concentration (in M).

Consider the following model

$$\frac{\partial N_1}{\partial s} = \underbrace{\nabla\cdot[D_1(N_2)\nabla N_1]}_{\text{cell movement}} + \underbrace{r_1N_1\left(1-\frac{N_1}{K_1}-\alpha_1\frac{N_2}{K_2}\right)}_{\text{logistic growth with cellular competition}} - \underbrace{d_1HN_1}_{\text{normal cell death by acid}}, \tag{2.1}$$

$$\frac{\partial N_2}{\partial s} = \underbrace{\nabla\cdot[D_2(N_1)\nabla N_2]}_{\text{cell movement}} + \underbrace{r_2N_2\left(1-\frac{N_2}{K_2}-\alpha_2\frac{N_1}{K_1}\right)}_{\text{logistic growth with cellular competition}} - \underbrace{d_2CN_2}_{\text{tumour death by drug}}, \tag{2.2}$$

$$\frac{\partial H}{\partial s} = \underbrace{D_3\nabla^2H}_{\text{acid diffusion}} + \underbrace{r_3N_2}_{\text{acid production}} - \underbrace{m_3H}_{\text{acid uptake}}, \tag{2.3}$$

$$\frac{\partial C}{\partial s} = \underbrace{D_4\nabla^2C}_{\text{drug diffusion}} + \underbrace{r_I(s)}_{\text{drug infusion}} - \underbrace{m_4C}_{\text{drug decomposition}} - \underbrace{d_4N_2C}_{\text{drug–tumour interaction removal}}. \tag{2.4}$$

We have used the convention of the subscripts for each parameter corresponding to the relevant equation: r represents growth rate; K represents carrying capacity; α represents population competition strength; d represents rate of decrease due to interaction; D is diffusion coefficient; m represents decrease through system mechanisms. Examples of possible values and range of values for these parameters can be found in Table C.1 in Appendix C. Note that we have assumed the use of a stage-specific drug that targets rapidly dividing cells, which will primarily target tumour cells. Since normal cell division is a well regulated process [20] we have assumed that the chemotherapeutic effect on the normal tissue can be approximated by reducing the normal tissue's competitive effect and resistance to the presence of acid.

In the models considered by [15,22] and [35] the following diffusion coefficients were used

$$D_1(N_2) = 0, \quad D_2(N_1) = D\left(1-\frac{N_1}{K_1}\right); \quad D > 0.$$

These were chosen since it was assumed that the normal cells were well regulated and hence the motility would be negligible. Furthermore, it was assumed that the presence of normal cells inhibited the