Mathematical Model of Tumour Cell Transport in Cancer Metastasis

BMEG 371 - Research Paper

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***Abstract*—In this paper, we present a system of coupled partial differential equations (PDE) that model one dimensional tumour metastasis based on the concentrations of: tumour cell density, extracellular matrix (ECM), and degradation enzymes. Our numerical implementation suggests that in the case of a resected tumour that regression occurs in a site away from the primary tumour. Overall, our model suggests that tumour invasion is dependant on the permeability of the ECM and secretion rate of degradation enzymes. This system of coupled PDEs is a good avenue to investigate tumour metastasis.**

I. Introduction

A. The Clinical Context of Cancer

Cancer is a rapidly progressing disease that affects many people, and one of they main ways that cancer is able to spread throughout the body is through metastasis. In fact, one of the ways that healthcare professionals characterize malignant tumours is by its ability to metastasize. Thus, it is clear that metastasis is an interesting biomedical phenomena since it describes how cancer spreads throughout our body. The transport of tumour cells throughout the body is very complex since we are taking into consideration the effect of several bodily systems, such as circulatory, immunological and even lymphatic. Not only is this particular phenomena interesting, but it is incredibly important to model since being able to predict the tumour invasion distance can let physicians decide early preemptive treatment plans or give insight to post-operative tumour resection cases. A model that describes the movement of tumours in a body can significantly aid physicians when treating cancer patients in a number of ways. Refer to Figure 1 for a rough timeline of the evolutionary process of normal tissue to an invasive carcinoma. Tumour models of growth have well have been well established in literature, moreover, many models attempting to describe tumour growth are closely based on cell population dynamics.

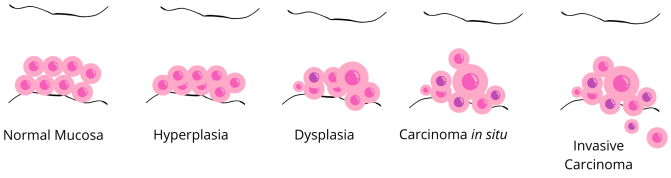


Figure 1: Progressive stages of the evolution of cancer in bloodstream over from early normal tissue (**Left**) to late stage aggressive cancer (**Right**)

Thus, there exists a need for a quantitative approach to modelling tumour cell transport in the body during cancer metastasis.

B. Considering Physiological Factors in Model

In order to understand what mathematical components we must include in our model, we must first look at the actual biological phenomena that occurs during tumour metastasis. As we have shown in the previous section, once a tumour becomes an invasive carcinoma it begins to metastasis. As shown in Figure 2, the multiple stages of metastatic dissemination follow a general pattern of transport through blood vessels; although this is mainly seen in solid tumours and not cancers like lymphoma or leukemia.

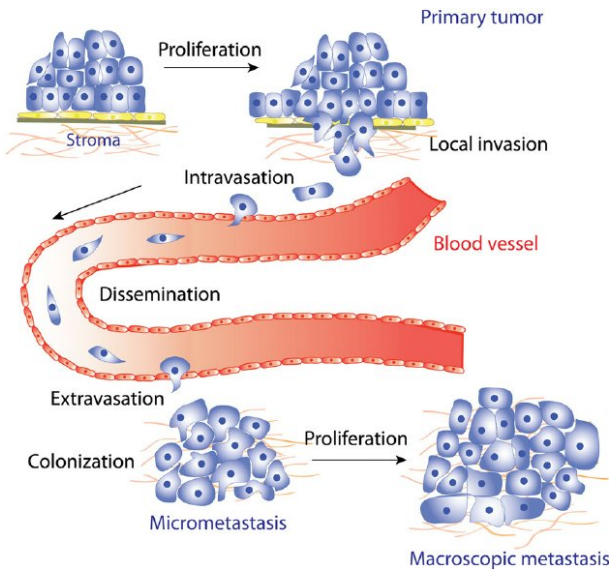


Figure 2: Cartoon describing multiple stages of metastatic dissemnination of cancer cells, figure adapted from Saxena et Al [1]

The key stages of the tumour metastasis are:

1) Deterioration of local tissue and extracellular matrix
2) Local invasion of tumour cells from primary tumour to blood vessel
3) Intravasation of cells into blood stream
4) Cell transport through blood vessel
5) Extravasation of cells out of bloodsteam to new tumour site

6) Tumour angiogensis and proliferation

In order for the tumour to penetrate the extracellular matrix (ECM) it secretes proteolytic degradation enzymes that deteriorate the surrounding tissue [2]. Once the tumour has broken through the ECM, it begins to randomly diffuse into the ECM as well move up a gradient of chemoattractant cytokines [3]. These chemokines are an important family of proteins that induce motility in tumour cells. Thus, we can note that tumour cell migration occurs through two main modalities: diffusion and hapatotaxis. Additionally, we can also note that the concentration of ECM and the degradation enzymes play an important role in tumour transport.

C. Development of Mathematical Model

Consider Figure 3 for high level overview of the mathematical model

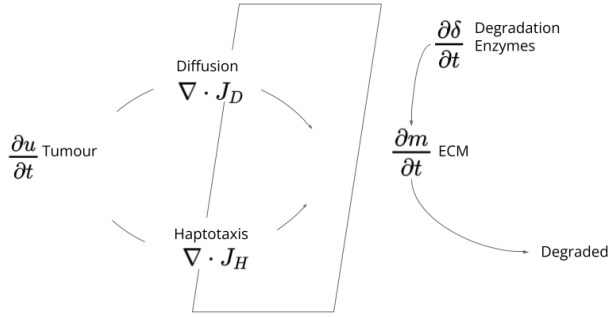


Figure 3: Simple line diagram showing flow of tumour transport with associated transport equation and notation

Let $u(x,t)$ be the concentration of tumour cell density, $m(x,t)$ be the concentration of the ECM, and $\delta(x,t)$ be the concentration of degradation enzymes. We will not consider the effects of cell proliferation and apoptosis in our model. We can describe the movement of tumour cells into the ECM using the diffusive flux and hapatotaxic flux. We will assume that the cytokinetic chemoattractants are embedded within the ECM. Lastly, we assume that the degradation rate follows simple diffusion and first order chemical kinetics.

II. Methods

We can begin developing our model by considering the continuity equation for the total tumour cell density. We expect that to see that total tumour cell density is conserved and thus can assume a 0 control volume term.

$$\frac{\partial u}{\partial t} + \nabla \cdot (J_D + J_H) = 0$$

We can use Fick's first law to expand the diffusive flux term and we can use the Keller-Segel Model to describe the hapataxic flux [4], [5].

$$\frac{\partial u}{\partial t} = D\nabla^2 u - \zeta \nabla \cdot (u \nabla m)$$

Where D is the diffusion constant for tumour cells and ζ is the hapatotaxis constant describing rate of diffusion and chemoattraction respectively.

We can also formulate equations for the ECM and degradation enzymes concentration by using the aforementioned assumptions.

$$\frac{\partial m}{\partial t} = -\delta m$$
$$\frac{\partial \delta}{\partial t} = D_\delta \nabla^2 \delta + k_+ u - k_- \delta$$

Where D_δ is the diffusion constant for the degradation enzymes, k_+ is the rate of production, and k_- is the rate of decay. Combining all these equation we can write a coupled system of partial differential equations (PDEs).

$$\frac{\partial u}{\partial t} = D\nabla^2 u - \zeta \nabla \cdot (u \nabla m) \tag{1}$$
$$\frac{\partial m}{\partial t} = -\delta m \tag{2}$$
$$\frac{\partial \delta}{\partial t} = D_\delta \nabla^2 \delta + k_+ u - k_- \delta \tag{3}$$

We will state zero flux boundary conditions as we want to observe the model in a closed system. We will further state that there is initially no degradation enzymes in the system. Lastly, we will state that the tumour is initially isolated and follows an exponential decay for its spread [5]. Moreover we will also normalize all of our units into dimensionless groups, thereby constraining distance and concentration on the interval $[0,1]$.

$$-D\nabla u + \zeta(u\nabla m) = 0$$
$$-D_\delta \nabla \delta = 0$$
$$\delta(x,0) = 0$$
$$u(x,0) = \begin{cases} e^{-\alpha x^2} & 0 \le x \le 0.25 \\ 0 & 0 \ge 0.25 \end{cases}$$

Refer to Table I for the list of biologically relevant parameter values that were used to normalize and solve the model.

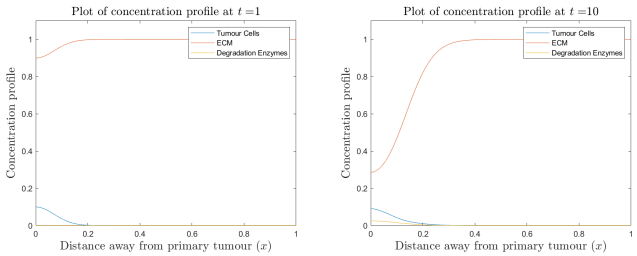
Table I: Table of parameter values available from existing literature

Term	Description	Value	Unit	Sources
D	Diffusion coefficient of tumour cells	10E-9	$cm^2 s^{-1}$-	[6]
D_δ	Diffusion coefficient of degradation enzyme	10E-9	$cm^2 s^{-1}$	[5]
ζ	Haptotaxis coefficient towards ECM	2600	$\frac{cm^2}{M \cdot s}$	[6]
α	Rate constant for initial spread of tumour	1000	s^{-1}	[6]
L	Characteristic length scale	1	cm	[6]
τ	Characteristic time scale	20	$hour$	[6]
D_{ref}	Reference diffusion coefficient	10E-6	$cm^2 s^{-1}$	[6]
k_+	Rate constant for production of ECM	0.15	s^{-1}	[7]
k_-	Rate constant for decay of degradation enzyme	0.001	s^{-1}	[5]

Solving systems of coupled PDEs is not in the scope of BMEG 371 and, as such, we can not confidently describe the analytical solution. However, we will use MATLAB to solve the system numerically and show plots of the predicted solutions instead.

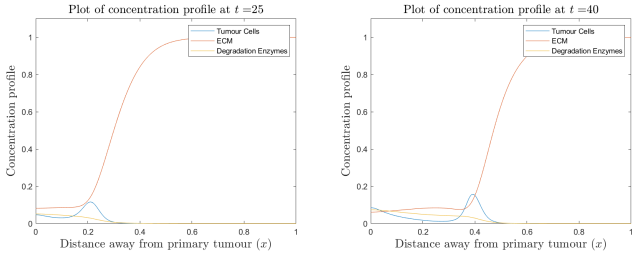
III. Results

We will simulate the tumour transport of cells in a situation where a surgeon has removed 90% of the original tumour mass. In this scenario, we state that roughly 10% tumour mass is still left and continues to be aggressive. This is a common situation in many post-operative tumour removal surgical cases.



(a) t=1

(b) t=10

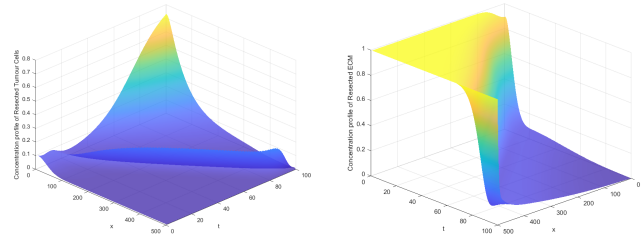


(c) t=25

(d) t=40

Figure 4: Plots of concentration profile of tumour cells, ECM, and degradation enzymes over t=40 time steps for resected tumour situation.

Moreover, we can observe the macroscopic trends of tumour transport by looking at the surface plots specifically of the tumour cell density and the ECM.



(a) (b)

Figure 5: Surface plot of resected tumour cells (**a**) and of ECM in resected environment (**b**)

IV. Discussion

As shown in Figure 5, we can see the general trends that occur in the system over the total time. Namely, we can notice in Figure 5a that initially the small primary tumour spends time to proliferate locally and degrade the surrounding ECM prior to migrating. This can also be seen in Figure 4b, where there is a rapid decrease in concentration of the ECM which allows an increase in tumour cell density. Our model suggests that the tumour will secrete degradation enzymes to permeabilize the ECM prior to cell migration. This suggestion is further corroborated by Figure 5b by its steep and rapid decay. This rapid decay of the ECM, as shown in Figure 5b and Figure 4, follows the expect behaviour of biological tumours. Additionally, our model highlights degradation enzymes as a potential target for drug development as inhibiting degradation enzyme expression could diminish tumour migration.

Furthermore, Figure 4d seems to suggest that the primary and secondary tumour sites might not necessarily form within close distance of one another. This has some clinical insight as it could possibly provide further explanation as to why clinicians see tumour formation in other areas than the primary tumour site. Being able to predict how far away the secondary site is from the primary site can allow an opportunity for preemptive therapy.

In order to assess the biological fidelty of the mathematical model with the actual reality of tumour metastasis, we will consider a study conducted by Yong et Al [8]. This study measures the invasion distance of two pancreatic cancer cell lines (PC3 and DU145) [8] by culturing tumour spheroids; after normalizing the data from Yong et Al, we found that our tumour model was progressing at a rate slower than what was actually observed. This suggests that our tumour model is lacking in regards to its biological accuracy.

There are several limitations of this tumour transport model that contribute to reason why the model is not accurate with biological findings. The tumour was considered in a close system and did not consider cell proliferation and apoptosis which means that external factors, such as the immunological response of the body, are not considered. Moreover, in this model we generalize all degradation enzymes as matrix metalloproteinases which does not incorporate tumour specificity. Lastly, we do not consider the heterogeneity of the tumour micro environment, which is a recent discovery that has changed our outlook on cancer [9].

In regards to future investigation, we think it could be interesting to introduce advection as a term in the model. The blood flow rate could be an important factor during extravasation. Moreover, introducing equations that govern immunological responses are crucial to increasing the fidelity of the model. Lastly, exploring possible one dimensional *in vitro* tumour cultures could provide further validation of our model.

V. Conclusion

We have determined that tumour invasion is dependant on the permeability of ECM and secretion rate of degradation enzymes. The model gives an approximate lower bound for aggressive metastatic tumour invasion showing characteristic features of metastasis. This has demonstrated that this system of coupled PDEs is a good avenue to investigate the math model of tumour metastasis

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