Proposed Model of Collective Tumor Cell Autologous Chemotaxis to the Lymph

Team @SecondGradeScience
Maire Keene, Michael Sheets, and Meghan Tighe

***Abstract*—The metastasis of cancer cells through the lymphatic network is a poorly understood and often lethal process. Previous work has demonstrated the presence of mechanisms that aid in directing the cells toward functional lymphatics in the tumor periphery via autologous chemotaxis. The effects of these mechanisms on individual cells has been modelled, and cell population migration has been modelled separately. This paper proposes a model that incorporates previous work on the effect that the tumor cell microenvironment has on individual cell movement and applies it to cell population migration though the extracellular matrix (ECM) towards the lymph. We hope to use this model to better understand how cells shed by tumors metastasize to functional lymphatic vessels via directed chemotactic movement as well as by convective interstitial fluid flow.**

I. Introduction

Tumors that form as a result of metastasis are the primary cause of most cancer deaths [3]. Movement to the lymph network is the main metastatic pathway for many solid cancers, however, tumor cell metastasis is very complex and poorly understood [6]. Better comprehension of this process may allow for improved treatment and prevention of lymphatic metastasis, and an accurate model of the system could allow us to better understand the process and give us better insights to improve drug delivery.

Various researchers have created models of metastasis to the lymph. McDougall *et al.* have implemented a large-scale model of cell migration as a random walk, chemotactic, and haptotacic process [4]. Swartz *et al.* have characterized many aspects of the lymphatic system [9], and how interstitial flow to the lymph affects tumor cell migration [10]. Additionally, the effects of various signalling pathways such as CCR7 have been characterized, and models have been made to examine the impact of this pathway on the movement of individual cells [8][7], as shown in Figure 1.

Our work integrates various aspects of these models to create a mathematical framework that describes cells moving through the ECM to the lymph vessels and incorporates cell motion due to random walk, chemotaxis (movement up a chemical gradient) due to ligand signals, and haptotaxis (movement though the matrix as affected by interstitial flow). Chemotaxis and haptotaxis are critical factors to consider when modelling tumor cell migration as they both act to guide the cells to the lymph. We use the McDougall model as a base [4], however, modify their terms to examine large-scale cell migration caused by the effects characterized by the Swartz group *et al.* [10][8]. Integrating these models, we are able to track the movement of a collection of tumor cells through a tissue moving to a lymph vessel. This model may be used to better understand how collective autologous chemotaxis (cells moving up a gradient of a self-produced chemokine) in an interstitial fluid flow field influences cancer metastasis.

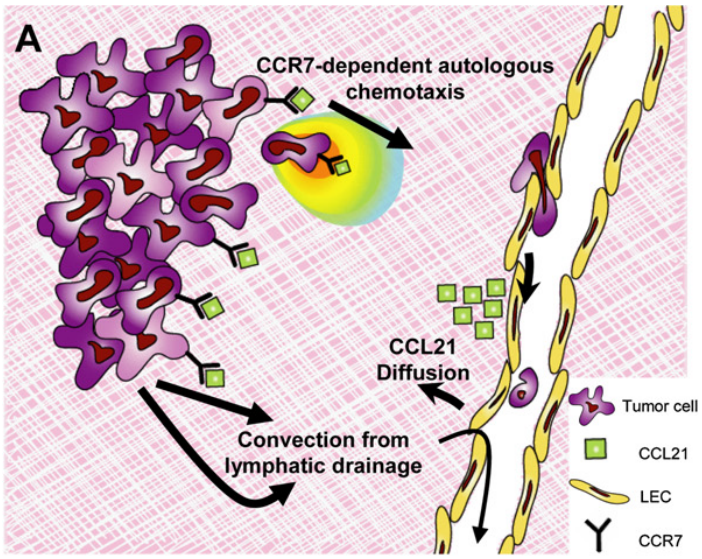

Fig. 1: Figure depicting the tumor microenvironment including draining of interstitial fluid, promoting flow from the tumor to lymphatic. Figure taken from Shields *et al.* [8].

II. Results & Discussion

A. Basic Tumor Model

This one-dimensional model looks at the space between a blood vessel and the functional lymphatics in the periphery of a solid tumor, as shown in Figure 2. This space in the ECM is estimated to be 500 μm [9]. The cancer cells and ligands are both modelled using chemical species diffusion. Interstitial flow was treated as a uniform velocity. Boundary conditions included a no flux boundary across the blood vessel wall for the diffusing species. It was assumed that on the other side, ligands were able to float freely across the barrier into the lymph. For the cells, boundary conditions assumed that there was 50% reflection of the cells migrating across the boundary into the lymph. At time=0, the entire system is considered to be ligand free and a clump of cancer cells is located at a central location between the blood vessel and lymph.

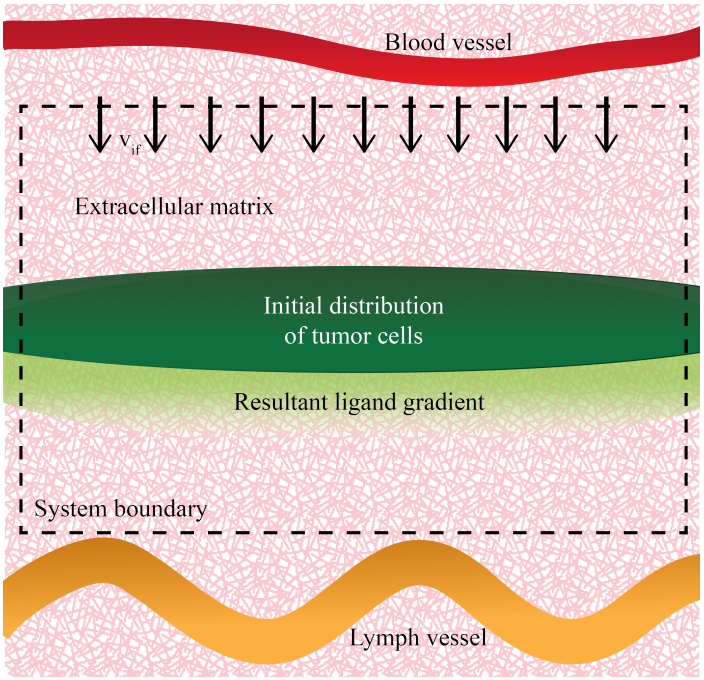

Fig. 2: Figure depicting the macroenvironment of our model, constituted of the tumor cells and ligand gradient in the ECM between a blood and lymph vessel.

B. Cell Movement as Random Motility & Convection

Cell movement through the ECM via haptotaxis has in the past been modelled as a random walk process, described with the standard random walk migration [4]. It has also been shown that flow influences the direction of a cell's migration, promoting movement along the streamlines [7]. Therefore, we described the cell migration with two methods of movement: random motility and convection. The ligands released by the cells in an autologous chemotactic process described by Swartz *et al.* move by diffusion and convection through the ECM, a porous media.

C. Following the Ligand Gradient

Shields *et al.* furthered this literature by including the movement of cells up an autologous CCR7 ligand gradient [8]. Including this effect allows a more accurate picture of how cells are guided to the lymph by this gradient, as they not only attempt to move down their own gradient by random walk, but also up the ligand gradient. This was mathematically introduced in our model through a chemotactic term, where the cancer cells migrate via a random walk process up the gradient of the released ligands. We found that this framing of the chemotactic process is very similar to that used by McDougall *et al.* in their model of tumor-induced angiogenesis. A key difference here is removal of the chemotactic scaling term's sensitivity to the saturation of chemokine–an important consideration in more nuanced explorations, and a possible subject of future work in this model.

D. Governing Equations

Combining the effects of the sections above,

$$\frac{\partial C_i}{\partial t} = -\underbrace{\psi \vec{v}_{IF} \cdot \nabla C_i}_{\textit{Flow-Induced Migration}} + \underbrace{D_{CC}\nabla^2 C_i}_{\textit{Random Migration}} - \underbrace{\nabla \cdot (D_{CG} C_i \nabla G_i)}_{\textit{Chemotactic Migration}}, \quad (1)$$

where C_i, and G_i are the concentrations of cancer cells and CCR7 ligands respectively at a given location and time, both in mol/m^3. D_{CC}, a parameter characterizing the random walk migration of cancer cells down their own concentration gradient in the ECM, would take the form of a regular diffusion constant with units of m^2/s, but the chemotactic scaling coefficient D_{CG}, which describes the movement of the cancer cells up the ligand gradient, is in units of $m^5/(mol \cdot s)$. In this equation ψ is the dimensionless haptotactic scaling coefficient and $\vec{v_{IF}}$ is the interstitial flow.

For the ligands,

$$\frac{\partial G_i}{\partial t} = -\underbrace{\vec{v}_{IF} \cdot \nabla G_i}_{\textit{Convective Flow}} + \underbrace{D_{GG}\nabla^2 G_i}_{\textit{Random Diffusion}} + \underbrace{k_p C_i}_{\textit{Cellular Production}} + \underbrace{k_d G_i}_{\textit{Ligand Degradation}}, \quad (2)$$

where k_p is the first order reaction constant for the production of the ligand by the cancer cells and k_d is a first order reaction constant for the degradation of ligand. Similar to D_{CC}, D_{GG} describes the movement of the ligands down their own concentration gradient, would be in m^2/s. The reaction rates k_p and k_d would both be in $1/s$. This model does not currently account for the binding and unbinding of other signaling molecules from the ECM.

E. Predicted Results and Future Work

Possible results of this model would show concentrations of the cancer cells and the ligands spatially at different points of time. The most relevant concentrations, those of the cancer cells in the blood vessels and the lymph, could be explored as a result of changing key parameters such as haptotactic and chemotactic coefficients, ligand production and degradation rates, and the ratio between the random and chemotactic cellular migration coefficients. These results could possibly predict the speed and likelihood of a tumor metastasizing via the lymph and suggest possible methods of preventing metastasis.

In future iterations, it would be useful to include a mechanism in the cellular movement, suggested in the work of Polacheck *et al.*, which competes with the autologous chemotaxis described by Shields *et al.* by promoting migration towards the blood vessel. It was suggested that this mechanism would depend on shear force experienced by the cells from the interstitial flow, as its effects seem to be independent of cell density and amplified by increasing the fluid flow [7]. This

mechanism would be useful to understand more thoroughly due to its role in determining the likeliest path for metastasis under various clinical conditions, and therefore needs to be investigated more thoroughly. Furthermore, in future work the validity of the boundary and initial conditions could be further investigated, for example, the assumption that initial ligand concentration is 0 throughout the ECM. It was documented by Shields *et al.* that there is a gradient of other ligands that are useful to cellular migration that diffuse from the lymphatic capillaries into the ECM independently of cellular production, and the effect of these ligands currently remain unaccounted for in this model.

Some parameters needed to implement our model (ψ, k, various diffusion coefficients) are not fully reported in literature and radiolabelling or other cell and ligand tracking methods may help elucidate the values for these constants. Estimates for some of these parameters are reported in previous work [5] [10].

One interesting case to explore with this model would be the impact of densely clustered cells on the effectiveness of autologous chemotaxis. When many cells are all releasing ligands, the signal strength of the gradient may be diminished for cells in the interior and lower edges, potentially influencing which of the mechanisms investigated by Polacheck *et al.* comes to dominate a particular system, and the likelihood of whether the cancer will metastasize by the circulatory or lymphatic systems.

III. Conclusion

We believe that tissue scale models would benefit from the incorporation of the effects that a tumor cell's microenvironment has on its movement. Further implementation of this model and determination of the necessary constants could improve our understanding of lymphatic metastasis, which could contribute to the treatment and prevention of cancers.

References

[1] Baxter, L. T., Jain, R. K. (1989). Transport of fluid and macromolecules in tumors. I. Role of interstitial pressure and convection. Microvascular research, 37(1), 77-104.

[2] Baxter, L. T., Jain, R. K. (1991). Transport of fluid and macromolecules in tumors. III. Role of binding and metabolism. Microvascular research, 41(1), 5-23.

[3] Chambers, A. F., Groom, A. C., MacDonald, I. C. (2002). Metastasis: dissemination and growth of cancer cells in metastatic sites. Nature Reviews Cancer, 2(8), 563-572.

[4] McDougall, S. R., Anderson, A. R., Chaplain, M. A. (2006). Mathematical modelling of dynamic adaptive tumour-induced angiogenesis: clinical implications and therapeutic targeting strategies. Journal of theoretical biology, 241(3), 564-589.

[5] Munson, J., Shieh, A. (2014). Interstitial fluid flow in cancer: Implications for disease progression and treatment. Cancer Management and Research CMAR, 317-328.

[6] Nathanson, S. D. (2003). Insights into the mechanisms of lymph node metastasis. Cancer, 98(2), 413-423.

[7] Polacheck, W. J., Charest, J. L., Kamm, R. D. (2011). Interstitial flow influences direction of tumor cell migration through competing mechanisms. Proceedings of the National Academy of Sciences, 108(27), 11115-11120.

[8] Shields, J. D., Fleury, M. E., Yong, C., Tomei, A. A., Randolph, G. J., Swartz, M. A. (2007). Autologous chemotaxis as a mechanism of tumor cell homing to lymphatics via interstitial flow and autocrine CCR7 signaling. Cancer cell, 11(6), 526-538.

[9] Swartz, M. A. (2001). The physiology of the lymphatic system. Advanced drug delivery reviews, 50(1), 3-20.

[10] Wiig, H., Swartz, M. A. (2012). Interstitial fluid and lymph formation and transport: physiological regulation and roles in inflammation and cancer. Physiological reviews, 92(3), 1005-1060.