

## Introduction and Motivation of Research

For the effectiveness of drug delivery for the treatment of cancerous tumors, modeling efforts play an important role in promoting understanding of fundamental aspects of both the transport and reaction of drug delivery to the tumor. Both the motion of drugs through the capillary of the microcirculatory system and the reaction, which take place within the tumor domain, must cooperate to eliminate cancer cells for an effective treatment of the tumor over the entire tumor domain. By assuming that this domain is closely described by a medium with a porous-like structure, the biophysical situation is very similar to that encountered in a catalytic pellet found in heterogeneous catalytic reactions. In this contribution, we will apply the fundamental principles of diffusion and reaction to a solid tumor (Arce et al, 2007), typically found in the pancreas or other human organs. By following suitable assumptions, we will present a diffusion and reaction microscopic model at the pore level. This model will then be upscaled to a macroscopic domain (i.e. the pore domain) and further to the tumor domain. As part of this process, the effective diffusion coefficient and the effective rate constant of reaction will be identified. Potential solutions for the model and predictive outcomes will be outlined.

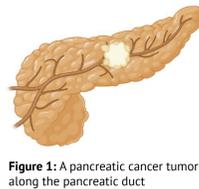


Figure 1: A pancreatic cancer tumor along the pancreatic duct

## Methodology

### Porous Level Equation in Gamma Phase (Blood Phase)

$$\frac{\partial C_{AY}}{\partial t} = D_Y \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial C_{AY}}{\partial z} \right) + \frac{\partial^2 C_{AY}}{\partial z^2} \right] \quad (1)$$

### Boundary Conditions in Gamma Phase:

$$C_{AY} = C_{AY}^0 \quad @ \quad z = 0 \quad (2)$$

$$\frac{\partial C_{AY}}{\partial z} = 0 \quad @ \quad z = L \quad (3)$$

$$-D_Y \frac{\partial C_{AY}}{\partial r} = k C_{AT} \quad @ \quad r = r_o \quad (4)$$

$$\frac{\partial C_{AY}}{\partial r} = 0 \quad @ \quad r = 0 \quad (5)$$

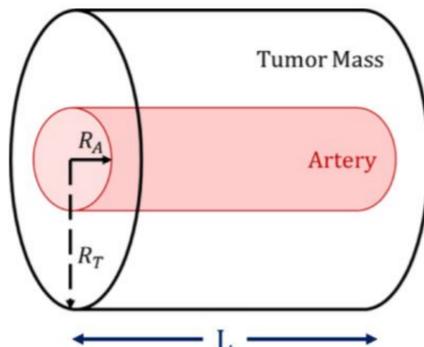


Figure 2: A depiction of the two domains we are considering. (Blanton, 2020)

In this transient model, we must make several assumptions along with the above boundary conditions. The first is that convection is negligible because the pores in the catalytic pellet model (in our case, the interstitial matrix are sealed at one end so there is no bulk motion). The second assumption is that the reaction is occurring with a zero order rate constant and only occurs at the walls of the pores.

## A Visual Representation of the Scaling Process

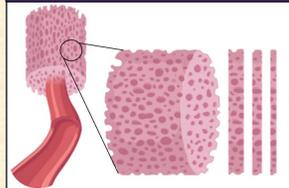


Figure 3: A scaling from the entire tumor domain surrounding an artery (left) to a portion of the porous tumor domain (right).

Before we can apply any of our equations, we must first designate our domains and consider the idea of multiple scales. For our model we will have three scales. The first is the entire tumor domain (Figure 3), which is the artery surrounded by the tumor, a porous media consisting of the cells and the interstitial matrix.

In our second scale we are looking at a portion of the tumor (Figure 3), which has its own microcirculatory system. Our third and smallest scale is a section of the capillary domain within the tumor (Figure 4). We will begin by applying our boundary conditions and equations to this domain and scale up to the first domain.

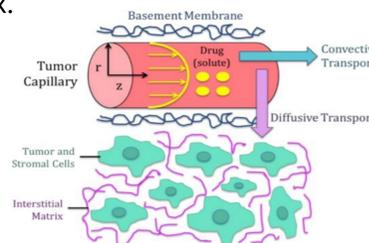


Figure 4: A model of the convective and diffusive transport within the capillary domain. (Blanton, 2020)

## Results and Discussion

### 1) Area Average of Concentration in the Gamma Phase

Equation (6) serves as a useful tool to conduct an integration of the species continuity equation.

$$\langle C_{AY} \rangle^Y = \frac{1}{\pi r^2} \int_{r=0}^{r=r_o} 2\pi r C_{AY} dr \quad (6)$$

### 2) Area-Averaged Porous Level Equation in Gamma Phase

By applying a variety of algebraic operations you can reach equation (7), and serves as a macro-scaled transport equation.

$$\frac{\partial \langle C_{AY} \rangle^Y}{\partial t} = D_Y \frac{\partial^2 \langle C_{AY} \rangle^Y}{\partial z^2} - \frac{2k}{r_o} C_{AT} \quad (7)$$

### 3) Closure Condition:

One of the issues we encounter with equation (7) is that it contains two unknown variables. Therefore, we need an equation that relates the two variables. This equation is called the "closure condition" at is shown in equation (8). Equation (9) is just a rearranged version of equation (8). If  $kr_o/D_Y \ll 1$ , then equation (10) becomes true and it will lead us to get our final Area-Averaged Equation (11).

$$D_Y \left( \frac{C_{AY}|_{r=0} - C_{AY}|_{r=r_o}}{r_o} \right) = O(k C_{AY}|_{r=r_o}) \quad (8)$$

$$\left( \frac{C_{AY}|_{r=0} - C_{AY}|_{r=r_o}}{C_{AY}|_{r=r_o}} \right) = O\left(\frac{kr_o}{D_Y}\right) \quad (9)$$

$$\langle C_{AY} \rangle^Y \approx C_{AT} \quad (10)$$

$$\frac{\partial \langle C_{AY} \rangle^Y}{\partial t} = D_Y \frac{\partial^2 \langle C_{AY} \rangle^Y}{\partial z^2} - \frac{2k}{r_o} \langle C_{AY} \rangle^Y \quad (11)$$

## Concluding Remarks

### Conclusions:

- We have shown the upscaling process for the Gamma Phase by mimicking the literature found in (Arce et al, 2007).
- Currently, progress has been made toward developing equations to model the transport of Gamma or Blood Phase between the capillary and the pores.

### Future Work:

Now that we have scaled our equations using the specified domains and boundary conditions, we plan to apply this mathematical model of an ideal tumor to a more realistic situation. This would include conditions such as a non-zero order reaction, bulk motion, non-uniform capillaries, and some reactions occurring within the bloodstream.

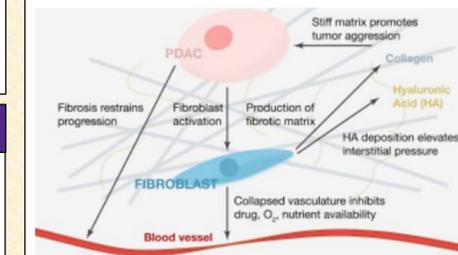


Figure 5: Some of the biophysical causes for the difficulty in treating pancreatic ductal adenocarcinomas. (Halbrook and Lyssiottis, 2017)

We also plan to adjust our equations to fit the specific conditions of pancreatic ductal adenocarcinomas (PDAC) in particular. This is the most common type of pancreatic cancer and, with a 5 year survival rate of just 8% in 2016, PDAC are on the way to being the second leading cause of death from cancer (Halbrook and Lyssiottis, 2017). This is largely due to the physiology being different from other types of cancers (Figure 5).

This unique physiology is the reason we cannot apply a simplistic equation to PDAC. Instead, we must take into account the differences in structure and microenvironment in order to correctly alter our equations. Our goal for this research is to gain a better understanding of the delivery of drugs to this cancer. This will allow us to have a deeper understanding of how to properly and effectively treat PDAC in order to increase the 5 year survival rate.

Another extension of this project could be calculating the effectiveness factor of the desired drug, to understand how beneficial the drug is in eliminating the tumor.

## References

1. Arce, P.E., Oyanader, M., and Whitaker, S. "The Catalytic Pellet: A Rich Prototype for Engineering Up-Scaling." *Chemical Engineering Education*. Vol. 41. 2007.
2. Arce, P.E., Pascal, J., and Torres, C. "The Soccer Ball Model: A Universal Visualization Protocol for Scaling Concepts in Continua." *Chemical Engineering Education*. Vol. 44. 2010.
3. Arce, P.E., Sanders, R., Arce-Trigatti, A., Loggins, L., Biernacki, J.J., Geist, M., Pascal, J.A., and Wiant, K. "The Renaissance Foundry: A Powerful Learning and Thinking System to Develop 21<sup>st</sup> Century Da Vinci Engineers." *Critical Conversations: An Interdisciplinary Journal*. Vol. 1. 2015.
4. Bird, R. B., Stewart, W. E., and Lightfoot, E. N. (2007). *Transport Phenomena*. New York: J. Wiley.
5. Blanton, S. 2019. "Understanding the role of mass transport in and assessing the effectiveness of drug delivery to cancerous tumors." MS thesis, Tennessee Technological University, Cookeville.
6. Halbrook, C. J. and Lyssiottis, C. A. "Employing Metabolism to Improve the Diagnosis and Treatment of Pancreatic Cancer." *Cancer Cell*. Vol. 31. 2017.

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