Convection Enhanced Drug Delivery for the Treatment of Brain Gliomas

BEE 4530

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Executive Summary

Malignant brain gliomas are almost always fatal, with a five year survival rate of only 3%. This is due in part to the difficulty of treating tumors chemically or surgically. They are often deep within the brain, where drugs cannot easily diffusive due to the blood-brain barrier and where surgery could be deadly. Emerging techniques for improved treatment include direct infusion of treatment drugs, like Paclitaxel, into the tumor in a procedure known as convection-enhanced drug delivery. These procedures require days of carefully monitored infusion to ensure tumor destruction while preserving surrounding tissue. To better understand the drug distribution and dosing options for different tumor sizes without dangerous medical tests, we have modeled the drug distribution within the tumor and surrounding tissue computationally. The model shows drug distributions consistent with current clinical results after a five day procedure. This model could now be used to better define dosing levels and procedure parameters to maximize tumor removal while preserving healthy tissue in individually unique cases.

Introduction

Background Information

Approximately 200,000 people worldwide are diagnosed with a primary malignant brain tumor each year (1), with about 15,000 cases occurring in the United States (2). Despite the relative rarity of these tumors, they account for a disproportionate number of cancer-related deaths (2). Overall, the five year survival rate following a diagnosis with a primary malignant brain tumor is roughly 30% (3) and certain types are even more deadly, with a five year survival rates close to 3% (4).

Primary brain tumors are tumors that originate in the brain (2). This is in direct contrast with metastatic tumors, which are the result of the spread to the brain of cancerous cells originating elsewhere in the body. The most common type of primary brain tumors are malignant brain gliomas (2). Gliomas arise from glial cells and can either be malignant or benign (3). The malignancy of gliomas is characterized into grades that are based on the tendency for the tumor to spread, the tumor's growth rate and its similarities to normal cells (3). With each specific type

of tumor, the grade varies. Often, tumors contain various cells of different grades (3). The grading system is useful because treatment and prognosis depend on the type of tumor and the grade (3).

The current treatments rely on radiation therapy, chemotherapy, surgery, steroids, immunotherapy, and the use of cancer treatment drugs (3). Many neurologists will actually use a combination of these therapies to treat a tumor. However, there are problems with these therapies, including the high precision and sophisticated instruments required for surgery, the difficulty in delivering drugs across the blood-brain barrier and the troublesome side effects that can arise from damaging the brain (3). Because of these issues, these treatments tend to be less successful than similar treatments for solid tumor cases located in other parts of the body (2). Thus, a better treatment option is necessary.

One such option is the use of convection-enhanced drug delivery. By use of a positive pressure system, this method combats the rapid post-resection recurrence, which many relate to the low survival rate of patients with malignant gliomas (4). Convection-enhanced drug delivery lends itself to locally target the tumor by direct infusion of cancer treatment drugs such as Paclitaxel. This could result in improved clinical outcomes as the procedure limits the exposure of the surrounding healthy tissue to the toxic drugs while maximizing drug concentration within the tumor (4). The delivery system uses an implanted catheter to deliver drugs infused by a pump, as illustrated in Figure 1.

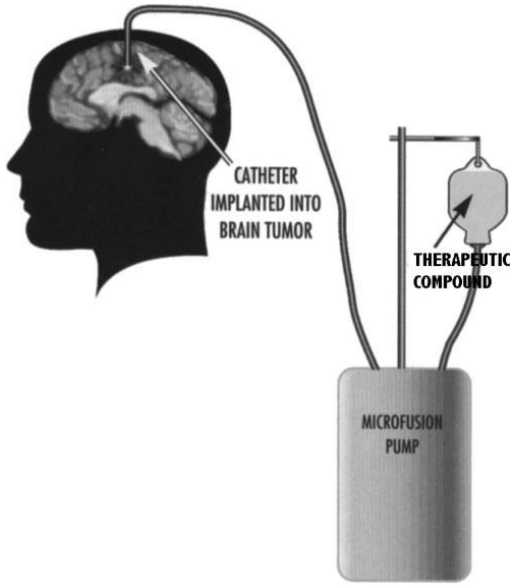

Figure 1. Diagram of convection-enhanced drug delivery system (4)

Clinical trials have showed improved results using this treatment. Brain gliomas, however, vary in size (5) and the procedural parameters do not take variability well enough into account. A mathematical model of the drug delivery could offer better tailoring of this procedure to individual cases by providing ideal dosing to eliminate the tumor while avoiding necrosis of surrounding healthy gray matter.

Design Objectives

The primary objective for this design is to provide an experimentally validated COMSOL model of convection enhanced drug delivery that can be optimized to kill the tumor but preserve healthy tissue. More specifically, this design is to provide a reasonably accurate mathematical model to better understand the drug distribution of this 5-day long process and guide the individualization of the medical procedure parameters, such as procedure time, Paclitaxel infusion concentration and pressure for variations between patients.

Problem Schematic

To implement convection-enhanced drug delivery into a tumor as a COMSOL model, we first had to consider an appropriate geometry. We assumed the tumor was essentially spherical in shape, extracting values for its size from the literature. Since the tumor size values from the literature were rather small relative to the amount of surrounding healthy tissue, it was reasonable to assume a semi-infinite geometry. That is, the surrounding healthy tissue is taken in COMSOL to be just large enough that it provides the same drug concentration profile as a model with a larger healthy tissue radius. These concentric spheres of tumor and healthy tissue have a catheter going down their vertical axis to their center. The symmetry in this geometry along this vertical axis allows us to simplify the geometry into a half circle, as shown in Figure 2.

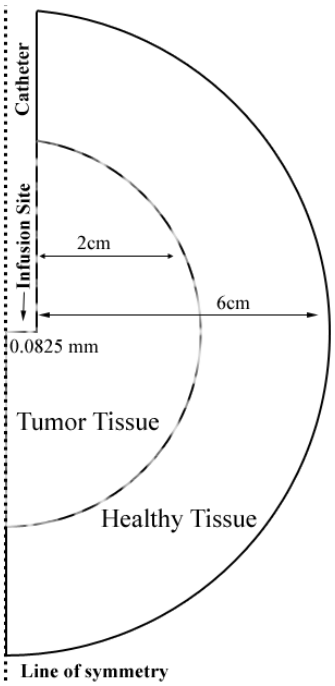

Figure 2. Model Schematic. 2-D Axisymetric
schematic used for mathematical modeling. (not to scale)

Results and Discussion

We modeled the distribution of Paclitaxel using the schematic provided above and the properties listed in Appendix A obtained from literary accounts of real medical procedures. These parameters, including tissue properties and boundary conditions, were used to solve the mass transfer and fluid flow equations also listed in Appendix A using COMSOL over an appropriate mesh described in Appendix B. A solution for the drug concentration profile after the 5-day procedure was obtained.

Initially, to better understand the individual contributions of convection and diffusion in the final solution, we obtained uncoupled solutions for mass transfer and fluid flow. A close up of the velocity profile obtained from the fluid flow model and the concentration profile obtained from the diffusion only model are shown in Figure 3 and Figure 4, respectively. Neither seems to have a significant impact far from the catheter tip. This shows that the coupling of the two factors is required for an accurate model, and that both contribute to the distribution of the drug throughout the brain.

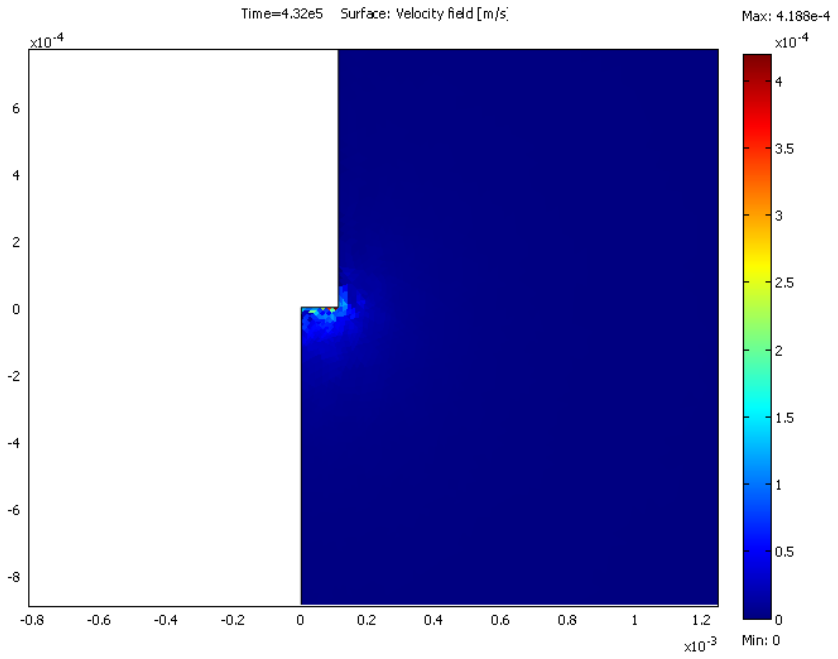

Figure 3: Fluid Flow Model. The velocity profile of the solution obtained from only the fluid flow portion of the model.

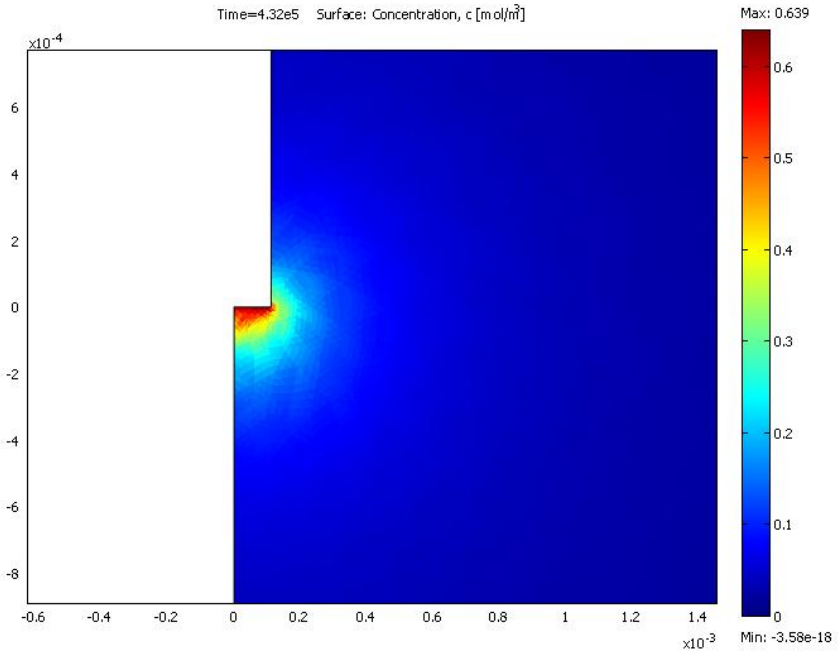

Figure 4: The concentration profile from the diffusion only model.

Figure 5 below shows the drug concentration in the tumor and surrounding tissue after 5 days with mass transfer and fluid flow coupled through the convection term. The drug

concentration is highest near the catheter tip, reaching a value of 639 M (infusion concentration) and effectively zero in the surrounding tissue. This drug distribution is much more extensive than was suggested by each of the uncoupled solutions. Literature values place the toxicity of Paclitaxel around 280 nM (6). Using this value, Figure 6 was obtained, showing the projected tissue necrosis in red where the concentration had reached or exceeded the toxicity value. The boundary between the tumor and healthy tissue is shown as a solid black line.

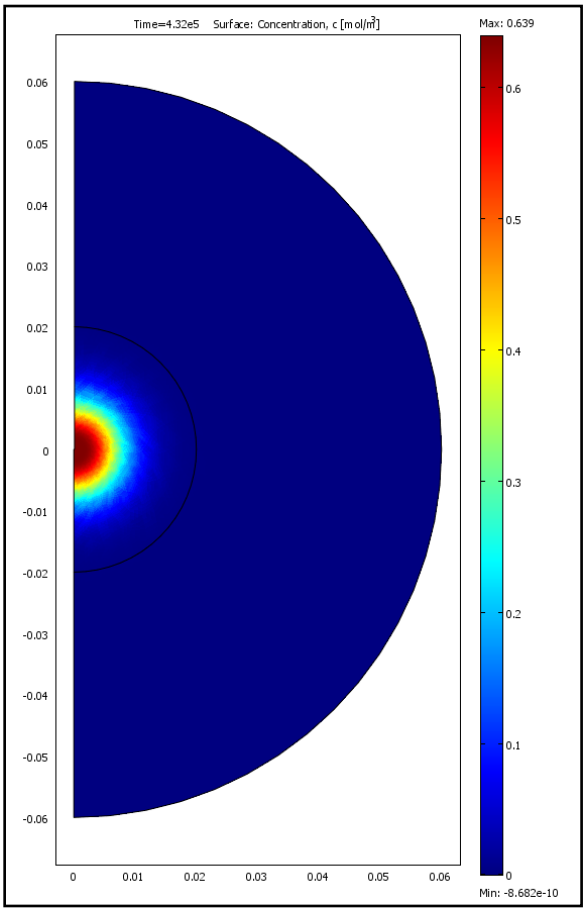

Figure 5: Concentration Profile. Drug distribution after 5 days of infusion.

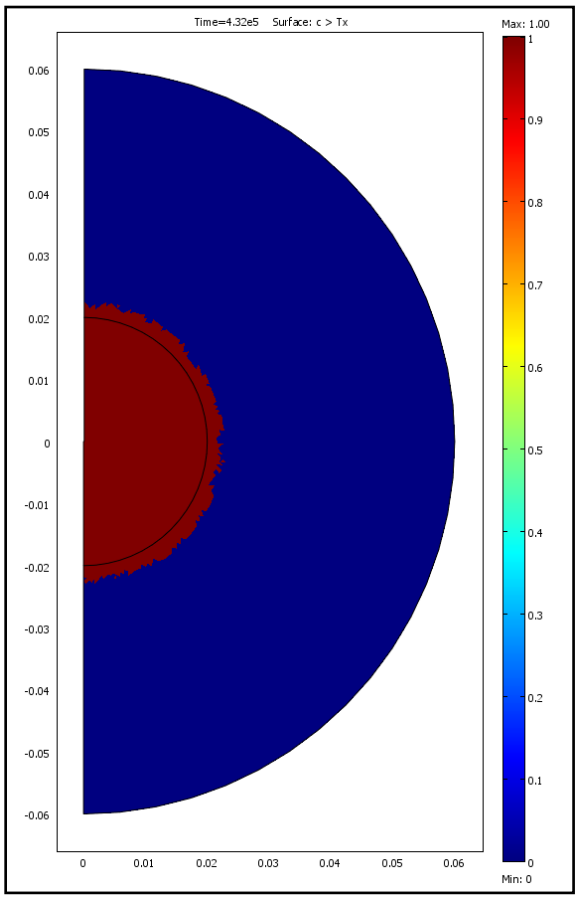

Figure 6: Expected Necrosis. Red portion has reached toxic concentrations.

It is clear from the uncoupled and coupled results of diffusion and convection that convection plays an important role in the dispersion of drug throughout the tissue. To better measure this significance, the drug concentration along a radial line from the catheter tip to outer tissue boundary was measured in the uncoupled (diffusion only) and coupled (diffusion and convection) models. This collected data, presented in Figure 7 below, shows the increase in

distance of travel of the drug when convection is included, verifying the important role of the infusion pressure in the procedure.

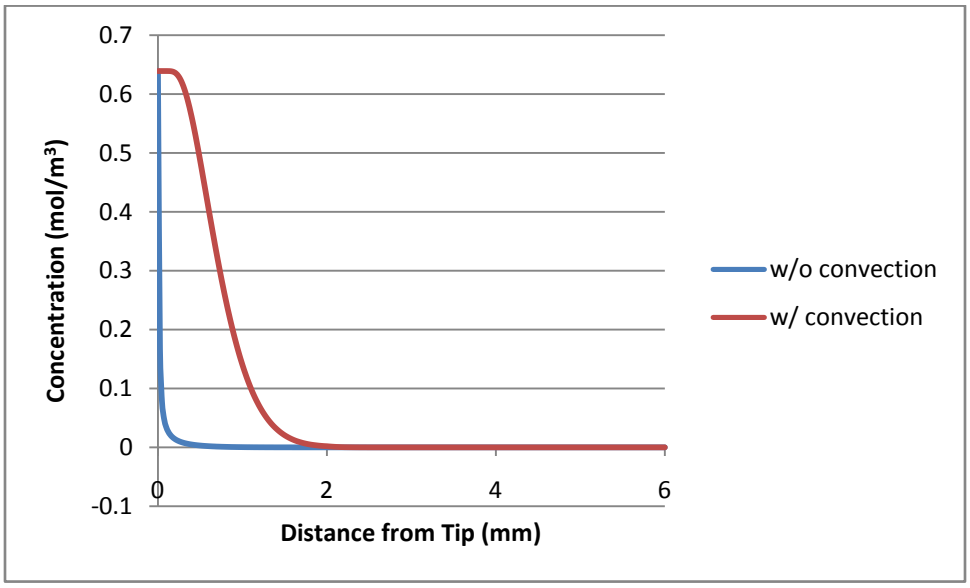

Figure 7: Comparison of Uncoupled and Coupled Results. Concentration profile along radial line with diffusion only (blue line) and with convection (red line).

To validate these results, the plot of expected necrosis above in Figure 6 was compared with medical procedure results of similar conditions (6). This had to suffice as validation because there was no literature available reporting the extent of healthy tissue damage or the drug distribution profile after the procedure. The fact that the tumor was completely removed in both cases, however, does provide some important validation. In addition to validation of the results, mesh convergence was also performed, the results of which are available in Appendix B.

This computational solution can be used to optimize the medical procedure to further achieve the design objectives. The concentration along a radial line extending from the catheter tip to the outer geometry boundary was used again, and the distance along this line at which necrosis had extended was measured. This measurement was made at several stored solution times to produce the plot in Figure 8 below. This plot shows the extent of necrosis from the catheter tip as a function of procedure time and could be used by a physician to tailor a procedure time given a discovered tumor size.

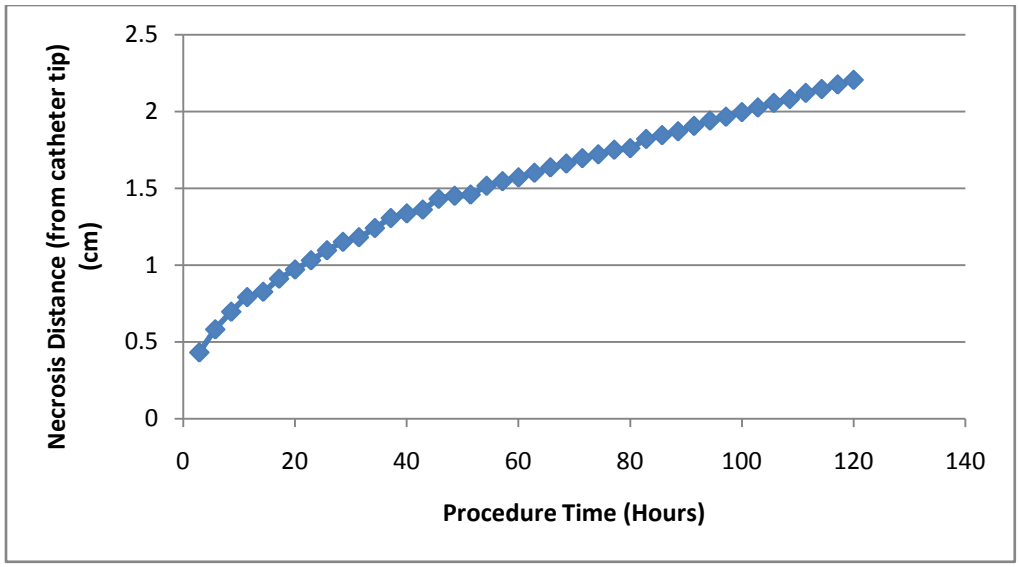

Figure 8: Optimization of Procedure for Specific Tumor Size. This figure shows the necrosis distance from catheter tip during the procedure.

Sensitivity Analysis

We encountered some difficulty in locating literature values for some of the properties. The properties with the most variation between sources and in which we had the least confidence were the tissue permeability, tumor permeability and porosity (considered equal in both the tumor and tissue). To better understand the effect of these parameters on the solution obtained, we performed sensitivity analysis. We varied these three parameters independently and then calculated the average drug concentration within the tumor and compared this average value to the average of the original. The individual sensitivity analysis results for each of tumor permeability, tissue permeability and porosity are displayed below in Figures 9, 10, and 11, respectively.

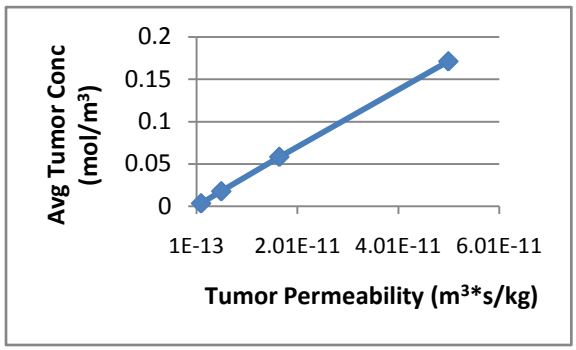

Figure 9: Tumor Perm. Sensitivity. Results of sensitivity analysis on tumor permeability.

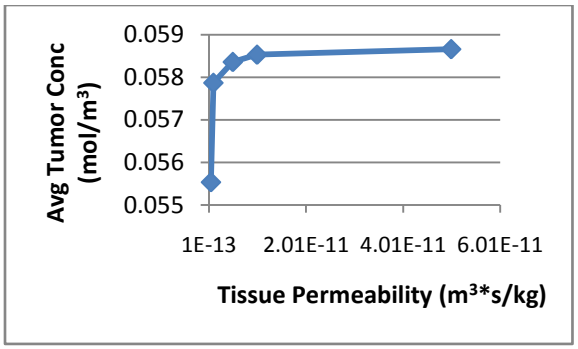

Figure 10: Tissue Perm. Sensitivity Results of sensitivity analysis on tissue permeability.

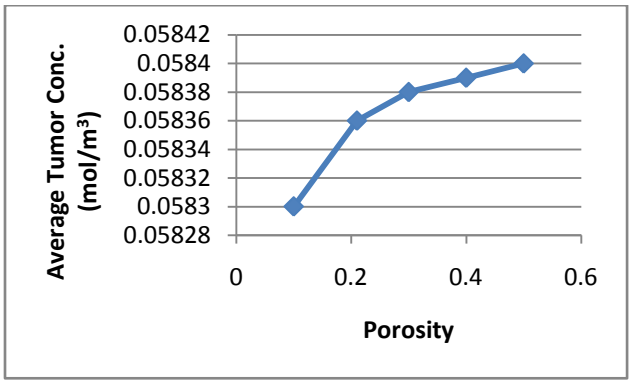

Figure 11: Porosity Sensitivty. Results of sensitivity Analysis on permeability of tumor and tissue.

The results of this sensitivity analysis suggest a linear relationship between tumor permeability and average tumor concentration, but a higher order relationship between the other two parameters. To compare the significance of a 20% variation of each parameter from the true value, the plot in Figure 12 was derived. This plot shows the change in average tumor drug concentration over a +20% to -20% variation of each parameter. This graph demonstrates that variation in the value used for the tumor permeability would have the greatest impact on the resulting solution compared to the other uncertain values. Thus additional research was performed to support the value used.

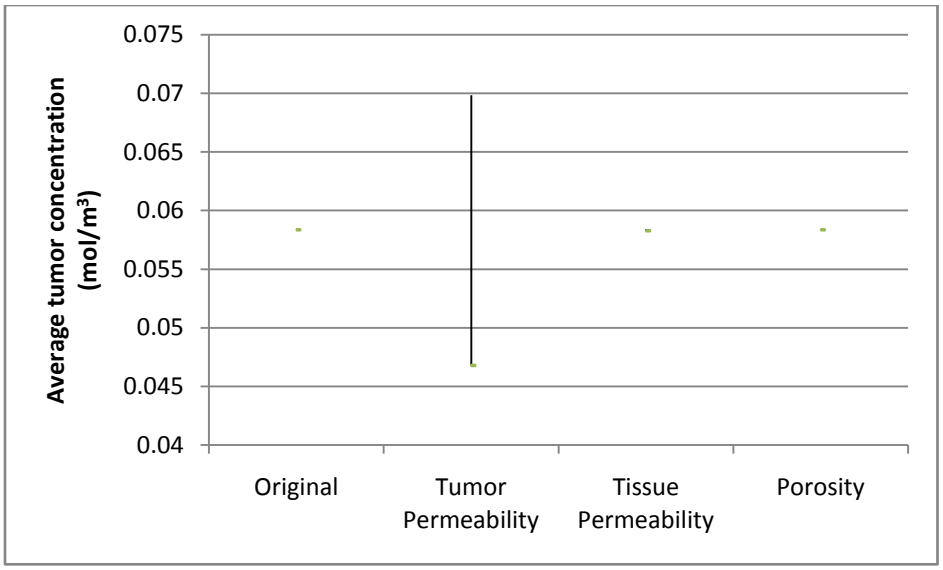

Figure 12: Sensitivity Comparison. Comparison of Sensitivity of solution on each of the three parameters.

Conclusion and Design Recommendations

Using COMSOL, we were able to model the distribution of Paclitaxel in a malignant glioma surrounded by healthy tissue delivered via convection-enhanced drug delivery. Using this model, we were able to optimize the combination of infusion pressure, infused drug concentration, and injection time to kill a maximal amount of malignant glioma cells and a minimal amount of healthy brain tissue. Using an infusion pressure of 666Pa, initial drug concentration of 639 M, and an injection time of 5 days, we were able to achieve a Paclitaxel concentration exceeding 280nM, the lethal concentration for tumor cells, in the entire tumor, while limiting the lethal concentration in the surrounding healthy tissue to a small radius. This result is supported by medical procedures which removed similar sized tumors using the same parameters.

Our model also illustrates the efficacy of the convection-enhanced drug delivery method, displaying the minimal drug distribution achieved by diffusion alone compared to the full tumor distribution achieved when coupled with fluid flow. The parameter that has the greatest effect on average Paclitaxel concentration in the tumor is tumor permeability, as a sensitivity analysis revealed a linear relationship between tumor permeability and average Paclitaxel concentration in the tumor. This could have serious implications for clinical use of this model to predict

procedural results, as tumor permeability is a parameter that can significantly vary both from tumor to tumor as well as within a single tumor.

Using this model, physicians could better tailor specific dosing of infusion Paclitaxel concentration, infusion pressure and procedure time to individual tumor sizes and even geometries. These benefits come without the dangers of medical trials with such an extreme procedure as the one required.

Design Recommendations

These results show that our computational model accurately describes the results of the convection-enhanced medical procedure. Doctors and drug companies could use this or a similar model to better describe dosing, infusion pressure and procedure time to limit the destruction of viable tissue. It could also be used to reduce the amount of time required for such an invasive infusion by optimizing other parameters, notably infusion concentration. In some procedures with larger or more complex tumors, multiple catheters are required. In these cases a 3D model obtained from CAT scans could be used to allow calculation of clinical parameters from the computational model to maximize tumor necrosis. To reduce invasiveness, smaller catheters could also be used with the model, again, to optimize other parameters to allow for this change. The procedure is so extreme, that the results of this computational model could be used to redesign these parameters to make it less invasive while still providing life saving results.

Realistic Constraints

The characteristics of convection-enhanced drug delivery that detract from its practicality are the invasiveness and significant injection times required for acceptable drug distribution. The procedure requires that the catheter is inserted directly into the center of the tumor. This requires a section of the skull to be removed to gain access to the brain, as well as insertion of the catheter through healthy brain tissue to reach the tumor. This drastically reduces the practicality of the process for tumors located deep in the brain tissue, as it increases the probability of injury to brain tissue during the insertion.

Perhaps the greatest limiting factor of this treatment becoming a primary option for brain tumors is the amount of time the process takes. Our model requires an injection time of 5 days to achieve the desired lethal concentration of Paclitaxel throughout the entire tumor. Under our conditions, the patient would have to remain stationary with a catheter in his/her brain for 5 days straight which is highly impractical. Patients receiving this treatment in clinical trials occasionally are treated using multiple injection sessions of up to 6 hours spaced out over a number of days, but the time in between injections likely decreases the distributive effects of the convection. Increasing the injected drug concentration is certainly a possibility, but with an increased drug concentration there is an increased risk of exceeding toxic drug concentration outside of the tumor in the brain tissue, killing healthy cells. The results of our model reveal a promising future for convection-enhanced drug delivery as both a primary and adjuvant treatment for malignant brain gliomas, but until the aforementioned limitations are addressed in clinical trials there is still much research to be done on the process.

Appendix A: Mathematical Formulation

For this model, we used COMSOL to solve coupled governing equations: that for mass transfer, and the equations for fluid flow. These governing equations solved are given in the following set of equations.

Mass transfer in either tissue in cylindrical coordinates (2D axi-symmetric):

$$\frac{\partial c}{\partial t} + u_r\frac{\partial c}{\partial r} + u_z\frac{\partial c}{\partial r} = D\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c}{\partial r}\right) + \frac{\partial^2 c}{\partial z^2}\right] - k_e c$$

Fluid Flow Equation:

For r:

$$\rho\left(\frac{\partial u_r}{\partial t} + u_r\frac{\partial u_r}{\partial r} + u_z\frac{\partial u_r}{\partial z}\right) = -\frac{\partial p}{\partial r} + \rho g_r + \mu\left[\frac{\partial}{\partial r}\left(\frac{1}{r}\frac{\partial}{\partial r}(ru_r)\right) + \frac{\partial^2 u_r}{\partial z^2}\right]$$

For z

$$\rho\left(\frac{\partial u_z}{\partial t} + u_r\frac{\partial u_z}{\partial r} + u_z\frac{\partial u_z}{\partial z}\right) = -\frac{\partial p}{\partial z} + \rho g_z + \mu\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial u_z}{\partial r}\right) + \frac{\partial^2 u_z}{\partial z^2}\right]$$

The boundary conditions and initial conditions used in this model are provided in Table 1 below.

	Variable	**Value**
Diffusion		
Initial tumor concentration	$c_{tumor}(t=0)$	0
Initial tissue concentration	$c_{tissue}(t=0)$	0
Concentration at catheter tip	$C_{cathter\ tip}$	Constant 639 M (infusion conc.)
Concentration at infinity (outer tissue boundary)	c_∞	0
Flux at catheter wall	N	0
Flux at line of symmetry	N	0
Fluid Flow		
Initial x-velocity throughout	$u_x(t=0)$	0
Initial y-velocity throughout	$u_y(t=0)$	0
Initial z-velocity throghout	$u_z(t=0)$	0
Cathode Infusion Pressure	$P_{cathode\ tip}$	Constant 666 Pa
Pressure at infinity (outer tissue boundary)	P_∞	0
Velocity at catheter wall	$u_{catheter}$	0 (no slip)

Table 1: Initial and Boundary Conditions

The subdomain and other properties used in the model were obtained from a number of different sources and are available in Table 2 below.

Property	**Symbol**	**Value**	**Units**	**Source**
Tumor Density	p_u	1050	kg/m^3	(7)
Tissue Density	P_i	1050	kg/m^3	(8)
Tumor Diffusivity	D_u	4.16E-7	cm^2/s	(7)
Tissue Diffusivity	D_i	2.0E-7	cm^2/s	(7)
Drug Concentration (Paclitaxel)	C	6.39E-4	Moles/ L of saline	(9)
Infusion Pressure at Tip	P	666	Pa	(10)
Tumor Radius	r_u	2	cm	(5)
Tissue Radius (tested large enough)	r_i	6	cm	
Catheter Radius	r_c	0.0114	cm	(11)
Hydraulic Conductivity of Tumor	k_u	1.65E-11	m^3*s/kg	(11)
Hydraulic Conductivity of Tissue	k_i	5E-12	m^3*s/kg	(10)
Infusion density (approx. water)	p	1000	kg/m^3	
Infusion Flow Rate	Q	8.33E-5	cm^3/s	(10)
Dynamic Viscosity	μ	0.89E-3	Pa*s	(12)
Tissue Porosity	e_i	0.21		(12)
Paclitaxel Toxicity	Tx	280	nM	(6)

Table 2: Model Properties. Properties used in this model, their Symbol used, value and source

Appendix B: Solution Strategy

To obtain a solution to this model using COMSOL, the multiphysics functionality was used. It was used to couple the solution of the fluid flow equation into the mass transfer calculations via the convection term. Hence subdomain properties, boundary and initial conditions were used for each. The solution was computed using a direct (UMFPACK) solver. Time stepping occurred from 0 to 432000 seconds (5 days) with a relative tolerance of 0.01 and an absolute tolerance of 0.0010. Solutions were stored for every 500 seconds. These low tolerances were required for the fast-changing velocity profile at the tip of the catheter near the start of the simulation.

The mesh selected for obtaining the final solution is presented in Figure 13 below. This free mesh was defined to have a high density of mesh elements near the catheter tip, where change in velocity occurs most rapidly. The mesh has a total of 3392 mesh elements with a minimum quality of 0.7219. To test the convergence of this mesh, several other meshes were solved, with a varying number of mesh elements, and the average tumor drug concentration was compared. The results of this analysis are shown in Figure 14 below, where it is apparent that with this mesh size, the mesh has converged to a single solution.

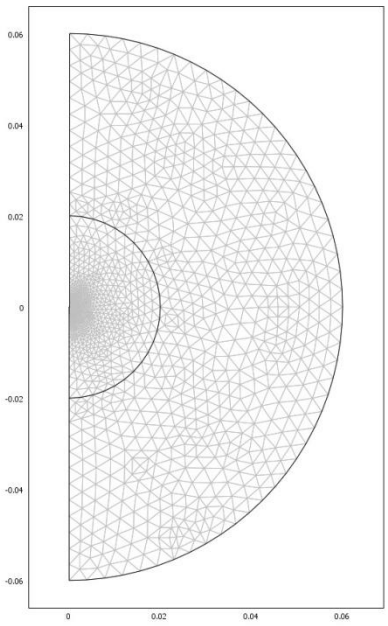

Figure 13: Mesh. Mesh used for model.

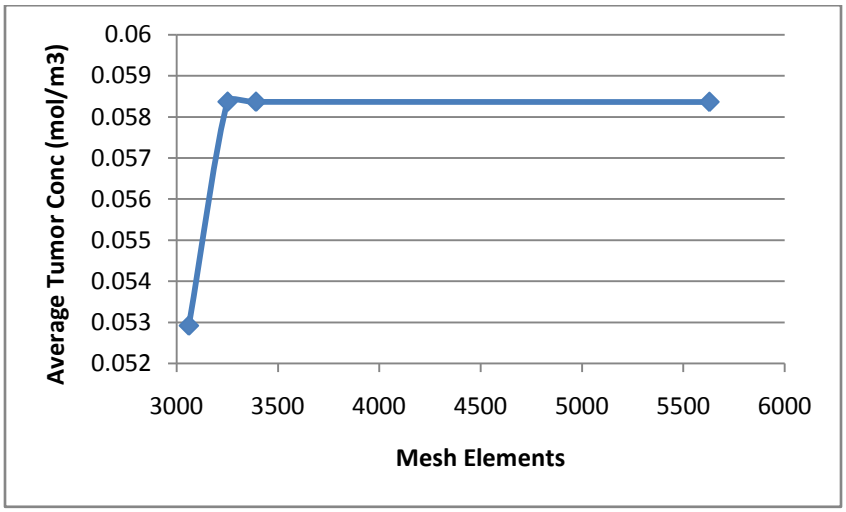

Figure 14: Mesh Convergence. Shows solution dependence on mesh.

Appendix C: Additional Figures

No additional figures are provided.

Appendix D

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