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RESEARCH

Computer Modeling of Drug Delivery to the Brain

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ABSTRACT

Treatment of neurological disease has been impeded by limited drug diffusion across the blood-brain barrier. Convection-enhanced delivery is a drug administration method that can be used to treat diseases of the central nervous system by directly injecting a drug into a patient's brain and allowing the drug to circumvent the blood-brain barrier. However, the transport of a drug in a patient's brain following convection-enhanced delivery is often difficult to predict due to the brain's anisotropic properties, which differ according to direction of measurement. Here, we use the software *ANSYS* to model a patient's brain using MRI data, and apply rigorous mathematical models to predict the mechanism of drug transport in an individual patient's brain. This report provides a detailed discussion of how *ANSYS* was used to model convection-enhanced drug delivery to the brain, by describing two simulations. The results can be used to assist physicians in designing patient-specific drug administration using convection-enhanced delivery.

Keywords: Convection-enhanced delivery, *ANSYS*, Computational Fluid Dynamics

INTRODUCTION

Diseases of the central nervous system afflict thousands of people each year. It is estimated that 150,000 Americans are diagnosed with hydrocephalus; 30,000 Americans have Huntington's disease; and 50,000 Americans have Parkinson's disease each year (NIH 2006). The number of people diagnosed with neurodegenerative diseases has sharply risen in recent years. The blood-brain barrier is composed of endothelial cells bound via tight junctions around capillaries which only allow small, hydrophobic molecules to enter the brain (Loch-Neckel et al., 2010). Because therapeutic molecules are typically higher molecular weight hydrophobic molecules, they are unable to penetrate the blood-brain barrier, making drug delivery extremely difficult.

Convection-enhanced delivery is a promising method that can be used to administer drugs to a patient's brain. It involves using a catheter to directly inject a drug into the brain so that the drug can circumvent the blood-brain barrier. The positive pressure from convection allows the drug to penetrate deeply into the brain and travel over the large distances needed to reach the target areas of infection (Raghavan et al., 2006). Previous studies have shown the effectiveness of convection-enhanced delivery in animal models, such as canines (Dickinson et al., 2008).

One main challenge associated with convection-enhanced delivery is that the spatial drug distribution in a patient's brain is unpredictable. Targeting a specific area of the brain for drug delivery does not always result in the drug reaching that particular area (Debinski and Tatter, 2009). The human brain integrates a variety of input sensory information in a compartmental manner. Properties such as conductivity and diffusivity

have different magnitudes and directions within the white matter of the brain. This means that the numerical values of these properties vary and have vectors acting in different directions at every point in the region (Lebihan et al., 2001). Computer-assisted

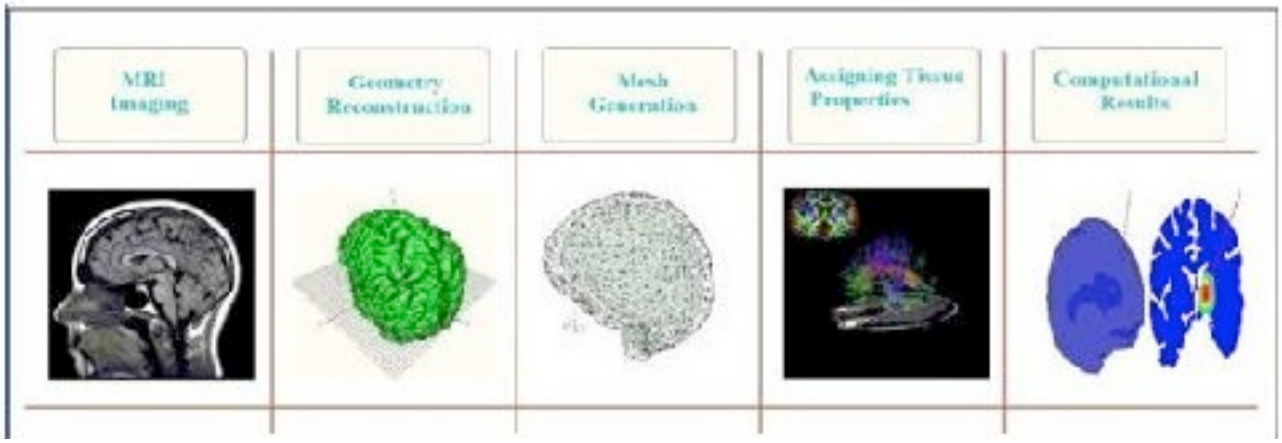


Figure 1. Overview of computer-assisted brain analysis for systematic design of drug delivery

Computer-assisted modeling and simulations can serve as powerful tools to predict the drug distribution in a patient's brain before the drug is delivered. Accurately reconstructing a patient's brain geometry using medical imaging data and software, followed by the application of rigorous mathematical equations to these models can provide physicians with information about the brain's mechanism and pathology. Medical imaging techniques like MRI and computer tomography (CT) can provide qualitative images of a patient's brain, but they provide no quantitative measure of transport in the brain due to diffusion and convection. Computer-aided simulations can serve as virtual therapy for surgeons before they conduct clinical trials using convection-enhanced delivery. They can predict the pressure and velocity of a drug in an individual patient's brain and model state changes of drug delivery that cannot be obtained experimentally. The results of the simulation can be compared to experimental data and imaging to evaluate the accuracy of the simulation. If the simulations match the experimental data, then it can be concluded that the remainder of the simulation results will resemble drug transport in the patient's brain once convection-enhanced delivery is administered. Physicians can use these results to design patient-specific treatments and make decisions regarding catheters and stents for drug delivery or in initial drug velocities to use to achieve a particular local concentration or steady-state concentration.

Previous studies in computational modeling have used the combinations of *Gambit* and *Fluent*, two powerful softwares, to reconstruct brain geometry and apply mathematical equations, respectively. However, in 2009, *ANSYS* merged with *Fluent* and integrated the solver into its software package (ANSYS, 2009). *ANSYS* is capable of modeling geometry, solving equations, and post-processing the results. This research aims to study how *ANSYS* version 11.0 can be used to model convection-enhanced drug delivery to the brain. The functions of *ANSYS* were extensively studied and compared to those of *Fluent* (refer to Appendix A).

METHODS

A four step method, outlined in Figure 1, was developed to integrate computational methods and clinical imaging, and model drug delivery to the brain (Linninger et al., 2008, Computational). The following sections give detailed descriptions of each step.

Patient-specific brain geometry reconstruction

MRI scans are taken from patients to obtain specific, anatomically accurate images representing the size and shape of the patient brain's target region (Linninger et al., 2008, Computational) .These data points are extracted using *ImageJ* software. The points obtained from *ImageJ* are exported to *Gambit*, which is used to modify the two-dimensional planar slices using smoothing and edge resolution functions. The brain slices are converted to geometric surfaces and merged into a volume (Linninger et al., 2008, Rigorous). Alternatively, after the brain slices have been smoothed and simplified, the images can be exported to *ANSYS*. *ANSYS* was used in this study to create geometric entities

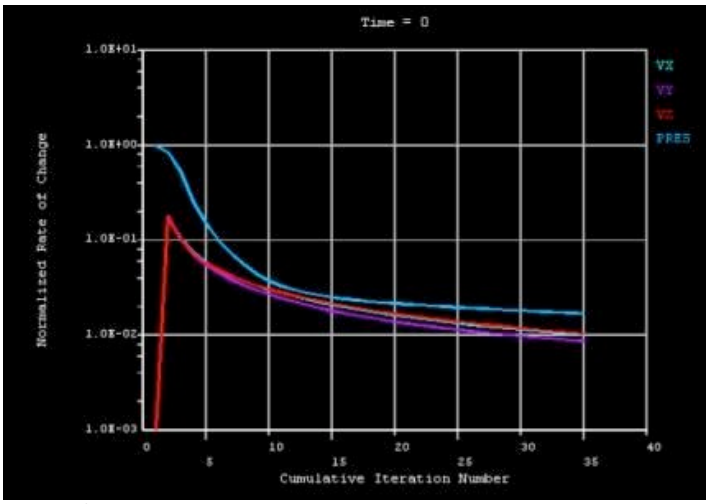


Figure 2. This graph shows the rate of change of pressure and velocity in the X, Y and Z directions when mathematical equations are applied to a Flotran CFD model. There are 35 iterations of the equation sets.

from the two-dimensional slices, connect the edges of each slice, and create a three-dimensional volume of the patient's brain.

Mesh generation

After creating a geometric volume, a mesh is generated on *ANSYS* for finite element analysis. A mesh is a regularization method that divides the entire volume into small tetrahedral or quadrangular volumes. The mesh allows for use of the finite element method which solves partial differential equations (Linninger et al., 2008, Rigorous). *ANSYS* contains tools that allow users to define the size and shape of each mesh element.

Application of transport and conservation equations

ANSYS needs users to specify the type of element being used in the simulation. These elements range from different types of solids to Flotran CFD fluids. The software also allows users to define material properties, such as density, viscosity, specific heat, and conductivity. Loads can be applied to the material, such as forces, velocities, and pressures. Properties of the objects exerting the loads can be defined. Figure 2 shows a sample residual output graph after the *ANSYS* solution is completed. It graphs Cumulative Iteration Number vs. Normalized Rate of Change and shows how the X, Y and Z components of velocity, as well as pressure, reach a constant value after approximately 30 iterations. The figure shows the differences in the rates of change of velocity and pressure at each iterative step.

Analysis of generated results

Once the simulation on *ANSYS* is completed, we can obtain several quantitative values pertaining to the model. There are complete listings of the coordinates of every single node in the mesh. A node is a single point in the mesh, and an element is a shape within the mesh composed of nodes. All the elements and their geometries can also be listed, including the nodes that compose the elements. Three-dimensional plots of pressure and velocity can be generated based on the nodal or elemental results of the simulation. The plots can be enlarged, and rotated with respect to the X, Y or Z axes. Additionally, slices within the interior of the object can be viewed. There is an animation feature that allows users to view drug distribution through a selected plane within the brain. Vector plots are available for velocity profiles, while contour plots are available for pressure profiles, and numerical results for the equations can be listed for every node. A more detailed listing of *ANSYS* post-processing functions can be found in Appendix A.

RESULTS

The goal of this research was to use *ANSYS* to model convection-enhanced drug delivery to the brain and obtain quantitative data about drug transport. Two different simulations conducted on *ANSYS* are examined. The first simulation, discussed in section 3.1, models drug infusion to the brain, and the second simulation, discussed in section 3.2, models pressure differences in the brain after a pressure is applied to the ventricle interior.

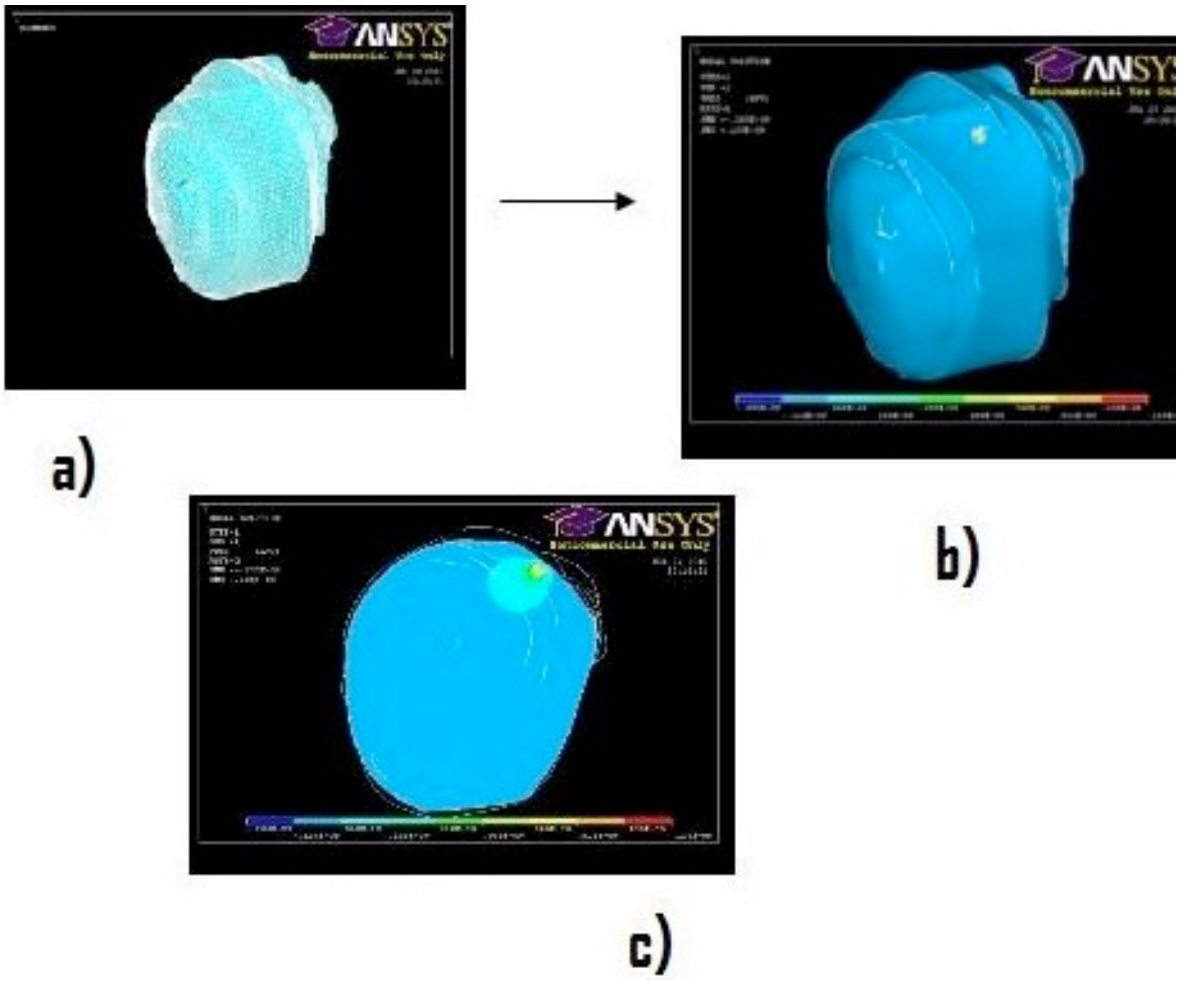


Figure 3. Pressure profiles of the drug in the brain generated on ANSYS following convection-enhanced delivery. Each letter (a,b,c) is listed below its prespective figure. a) Three-dimensional reconstructed brain mesh, showing location of catheter insertion for drug delivery with a sphere in upper right corner. b) Pressure distribution on surface of three-dimensional brain. Yellow areas correspond to areas of high pressure,and pressure gradient decreases as one moves away from injection point c) Pressure profile in a two-dimensional slice of brain, created when three-dimensional model was cut with a plane parallel to the Z-axis. As in b), yellow areas correspond to areas of high pressure, and surrounding areas of light green are decreasing pressure

Drug Infusion

ANSYS was used to model catheter insertion and drug release into the brain tissue. MRI scans from a patient's brain were used to

construct a three-dimensional volume on *Mimics* software. This volume was imported to *Gambit* software to smooth out the brain slices, and then imported to *ANSYS*. The final brain volume was constructed on *ANSYS*, and a small sphere was used to model the location of drug injection. The brain was modeled as a fluid, using the Flotran CFD feature on *ANSYS*, because the actual transport of the drug is taking place in the extracellular space of the brain. Density and viscosity were set to be uniform throughout the brain, at 1500 kg/m^3 and 0.001 Pa*s, respectively. However, the conductivity was modeled as orthotropic and was set as a 3 x 3 matrix (Akhtari et al., 2010). The brain was segmented into three zones and a different matrix for conductivity was applied to each zone. This simulated conductivity having varying magnitudes with different directions of movement. Fluid properties of the drug were set to the density and viscosity of water. Once the element and material properties were set, the volume was meshed using tetrahedrons. The mesh contained 43614 nodes and 243293 elements. Boundary conditions were applied, and the velocity at the point of drug infusion was set to -1e-6 m/s, which was taken from experimental data. The negative sign is present because the drug is flowing outward from the catheter. Pressure on the outer surface of the brain was

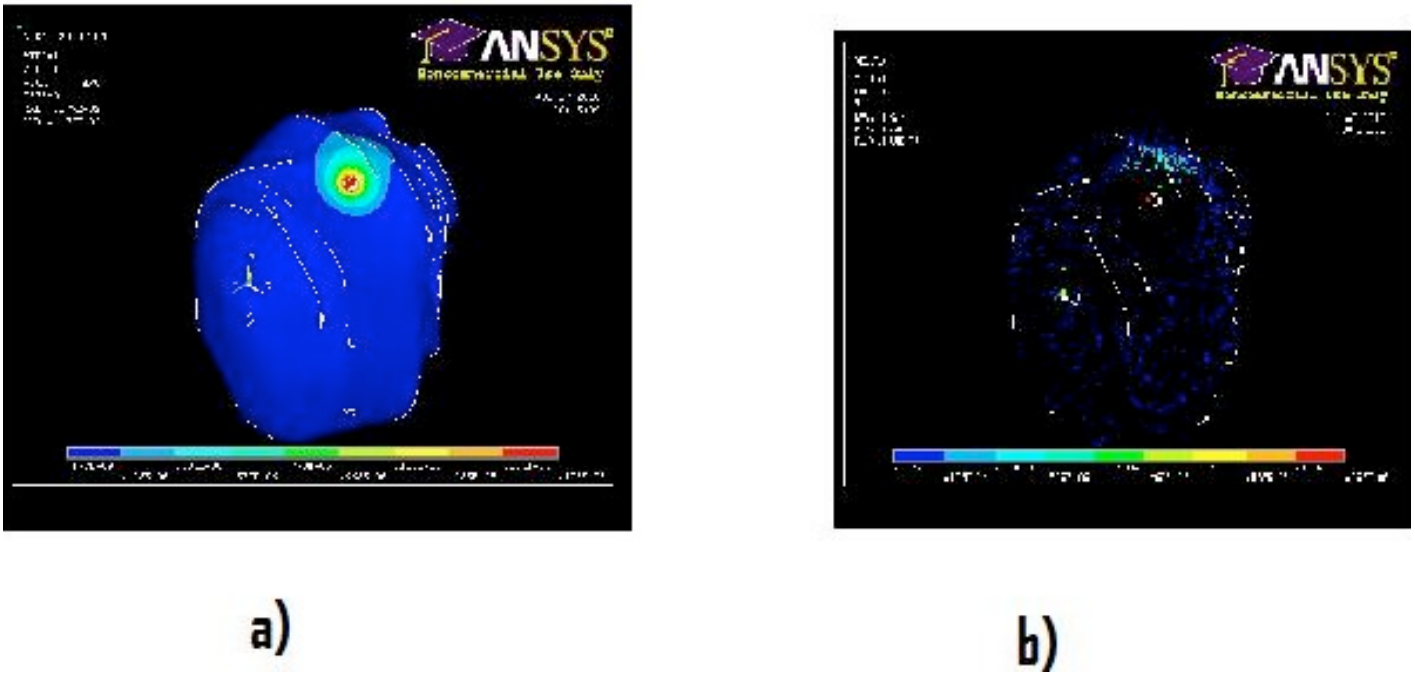


Figure 4. Velocity profiles of the drug in the brain following convection-enhanced delivery. a) Drug velocity on surface of three-dimensional brain. Areas of red are highest velocity at point of drug insertion, and the velocity decreases as one moves away from this point b) Vector plot of drug transport in three-dimensional brain. Vectors decrease in magnitude as one moves away from point of injection, and vectors point radially away from point of injection

zero to represent gage pressure. The solver utilizes the finite element method to solve equations within a control volume to ensure exact conservation of flow qualities. Results for for pressure in the brain following drug infusion are shown in Figure 3.

Figure 3a) shows the reconstructed brain mesh and includes a sphere representing the location of catheter insertion for drug delivery. After modeling, the pressure on the entire surface of the three-dimensional brain can be viewed, as shown in Figure 3 b). The Q-slice Z-buffer function in *ANSYS* can cut the

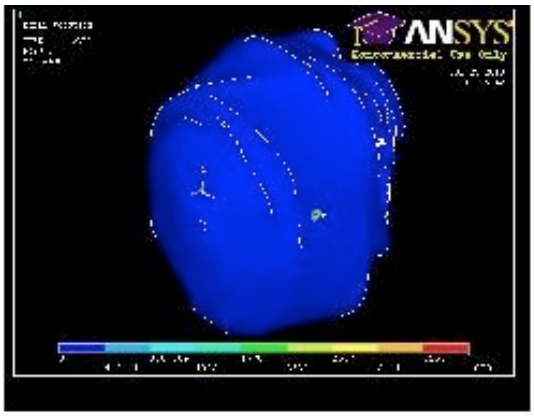
three-dimensional brain model parallel to the Z axis and display a slice of the brain with contour lines, as shown in Figure 3 c). Figure 3 c) shows that the pressure is highest inside the brain at the point of drug injection. This is a good finding because it is congruent with the actual procedure of convection-enhanced delivery, and thus validates the model. The pressure surrounding the area of drug delivery will begin to decrease over time, until it reaches a value of zero on the brain surface. This model shows how the drug flow causes a pressure drop from where the drug was inserted to the surface of the brain.

The velocity of bulk fluid in the brain was also graphically analyzed on *ANSYS*. The results are shown in Figure 4

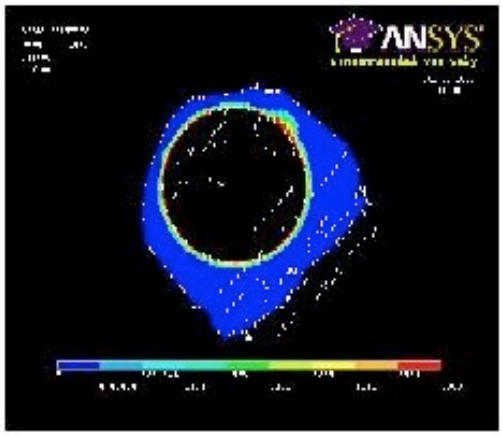
Figure 4a shows the drug velocity from the point of injection to the surface of the brain in a three-dimensional representation. The drug is at its highest concentration at the point where it leaves the catheter, and displays the highest velocity there at $0.173*10^{-5}$ m/s. The magnitude of the velocity gradually decreases as the drug diffuses outward. The vector plot in Figure 4b shows how the drug travels outward from the point of injection. The arrows represent the direction of bulk flow within the brain interior. The conductivity properties were set as orthotropic, meaning the vectors point outward from the sphere in varying directions, as shown in the figure.

Pressure Application to Ventricle Interior

ANSYS was used to model pressure differences in the brain. The same patient MRI data used in Case Study 1 was used to reconstruct three-dimensional brain geometry on *ANSYS*. *Mimics* and *Gambit* were used to simplify the data points and two-dimensional geometry before the final volume was constructed on *ANSYS*. A combination of two simple sphere cutouts was used to model the ventricle within the brain. Once again, the brain was modeled as a fluid using Flotran CFD. The material properties of the brain were set to be homogeneous. Density and viscosity were the same as described in Case Study 1 and conductivity was set to 0.077 S/m (Akhtari et al., 2010). The mesh was composed of 162953 tetrahedral elements and contained 31116 nodes. This case study applies a pressure of 4000 Pa inside the ventricle of the brain (NIH 2010). Pressure on the surface was set to zero, representing gage pressure. Figure 5 displays two different views of the resulting pressure inside the brain. Figure 5 a) depicts how a small portion of the three-dimensional brain surface has a pressure difference. The pressure is highest at an innermost location, and starts to decrease uniformly outward until it reaches zero. The Q-line Z-buffer feature on *ANSYS* lets us observe pressure differences in the interior of the brain, as shown in Figure 5 b). The pressure is highest along the interior of the ventricle, at about 3580 Pa, and starts decreasing to about 890 Pa around the ventricle until it reaches zero on the surface of



a)



b)

Figure 5. Pressure distribution in the brain after a pressure load was applied on the inner ventricle wall. a) Location of pressure differences when the brain is viewed as a three-dimensional surface. b) Two-dimensional slice of the brain interior portraying pressure differences around the ventricle. Pressure is highest at innermost location of ventricle as shown by red segments. Pressure starts to decrease as one moves radially away from the ventricle

the brain.

DISCUSSION

Simulation 1: Drug Infusion

The pressure and velocity profiles obtained from this simulation can be used by physicians to determine the optimal initial velocity to insert the drug into a patient's brain when using convection-enhanced delivery. Surgeons can also manipulate where the catheter is inserted, and the catheter design based on the target area of drug delivery. The simulation provides theoretical values of drug velocity and pressure in the brain that cannot be experimentally measured. The theoretical output can be compared to experimental data obtained from imaging techniques to determine the accuracy of brain geometry reconstruction and equation application.

This case also measured heterogeneous conductivity properties, but in order to obtain a more accurate simulation, we can incorporate Diffusion Tensor Imaging (DTI) data for every cell of the mesh. This would allow the brain model to be anisotropic, meaning it would represent properties that differ according to direction of measurement, and would require utilizing the User Defined Function on *ANSYS*. There is a complex procedure involving writing additional programs that will integrate the DTI matrices into each mesh element, which is an area for future work. Additionally, a more accurate three-dimensional model of the brain can be generated if more MRI images of brain slices are used to construct the model. Further work could involve accurately crafting the interior ventricle of the brain using patient MRI scans. It was modeled using two spheres in the context of this study in the interest of time.

Simulation 2: Pressure Application to Ventricle Interior

This simulation can model pressure accumulation in the interior of the brain ventricle by applying a pressure load on the brain ventricle using the functions of *ANSYS*. In hydrocephalus, the pressure buildup leads to deformation of the brain tissue. If the brain was modeled as a porous solid, tissue displacement could be calculated to study deformation. Models similar to this case study can be used to predict pressures within the brain in patients with hydrocephalus. Experimental data can be compared to the pressure values generated by *ANSYS* to determine the accuracy of the simulation predictions. These pressures can be studied to design treatments for hydrocephalus. In order to simplify the brain reconstruction procedure, the model in this study utilized sphere cutouts to model the ventricle, but future studies should use patient MRI data points to accurately reconstruct the ventricle geometry.

CONCLUSIONS

Here, we have used *ANSYS* to reconstruct a patient's brain geometry and obtain drug velocity and pressure in the brain following convection-enhanced delivery. These models provide data that is not easily obtainable from experimental tests. The software uses the same equations for computational fluid dynamics analysis as *Fluent*, and contains a plethora of processing features that allow results to be easily viewed and interpreted. Although modeling a three-dimensional brain on *ANSYS* alone is challenging, other software like *Gambit* can be used to simplify the geometry. Future work involves generating more accurate brain models using imaging data, and incorporating DTI data into the mesh using additional programs. This work can also assist surgeons in creating patient-specific treatments to use convection-enhanced drug delivery to the brain, as well as help in predicting treatment delivery and effectiveness.

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Appendix A. Comparison of ANSYS and Fluent

The main difference between *ANSYS* and *Fluent* is in aspect of solver. Fluent uses the finite volume method to solve partial differential equations, which utilizes the divergence theorem to convert partial differential equations into surface integrals. *ANSYS* uses the finite element method, which converts partial differential equations into ordinary differential equations, which are then numerically integrated. Each method results in slightly different solutions. *ANSYS* contains several components that make it effective software to model drug delivery to the brain. One advantage of *ANSYS* is that it allows users to create a model, generate a mesh grid, apply boundary conditions, and post-process the results all within the same software. *Fluent* is only a solver, and requires other software, such as *Gambit* and *Mimics* to create the brain geometry and import it to the solver.

ANSYS contains functions that allow users to easily obtain mesh data, which is a great advantage. Under the utility menu, there are functions that list all the nodes in the mesh and their coordinates. The elements of the mesh and the nodes corresponding to each element can also be listed. These files can be saved and read as text documents. Every command that the user enters into the Graphic User Interface is documented in the *ANSYS* output window. Once a mesh is generated, the output window displays the type of shape used to make the mesh elements, the total number of nodes, and the total number of elements. In *Fluent*, a mesh can be imported as a *.msh file from *Gambit*. The *.msh file contains the same data as the *.cdb file generated by *ANSYS*, only in a different format. A *.cdb file from *ANSYS* can be read by *Fluent* and be used to generate a *.msh file.

Finally, *ANSYS* has several features that allow users to easily view post-processing results and interpret visual representations. For example, the user can display animations, manipulate background and color options, view detailed vector fields, and slice three-dimensional objects with contour lines on *ANSYS*. However, modeling three-dimensional brain geometry is a time-consuming process. *ANSYS* contains ready-made volumes that can be used for modeling, such as spheres and

cylinders, but creating an irregular volume from imported data points has proven to be challenging. The difficulty of creating a brain volume is not unique to *ANSYS*, as the process is also tedious in other modeling software like *Gambit* and *Mimics*. In order to ease brain volume reconstruction on *ANSYS*, the brain slice edges can first be smoothed out using *Gambit*, and then imported to *ANSYS*.

In conclusion, *ANSYS* can effectively be used to model convection-enhanced drug delivery to the brain, either alone or supplemented with *Gambit*. This software can provide quantitative data about drug transport in the brain which can be of great use in medical treatment.