Safe Relief: Modeling concentration profiles of Baclofen deposited in the intrathecal space by a pump-operated drug delivery system

BEE 4530: Computer Aided Applications to Biomedical Engineering

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May 3, 2012

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1 Executive Summary

Muscle spasticity is a common and debilitating complaint among patients with cerebral palsy, multiple sclerosis, or spinal cord injury (Albright et al. (1991)). A drug called Baclofen has been developed that functions by affecting certain GABA neurotransmitter receptors in the spine. This problem has been partially addressed by modern treatment methods. One of these methods is one through which drugs are pumped directly into the intrathecal space of the spine rather than being administered systemically. However, since slight changes in drug concentrations in the intrathecal space may have much more severe consequences to a patient, the delivery of Baclofen must be subject to stricter control over pump input and flow parameters. A safe range of input concentrations and flow rates must be proposed. This will result in a safer method of optimizing these parameters so that the reliance on potentially lethal clinical trials ceases.

To address these requirements, a computational domain was created, modeled as two concentric cylinders (purely containing cerebrospinal fluid and the other containing the grey and white matter), and restricted to the lumbar region of the spine. The results of these experiments address the need for a safe and effective range of concentrations and flow rates for pump-driven delivery of Baclofen. The input concentration of Baclofen was 500 g/m^3 and the input pump velocity was 2 m/s. The COMSOL simulation demonstrated a saturation the vertebral column with the drug spread confined to a 30 mm distance from the injection site. We determined an optimal concentration of 250 g/m^3 at a pump velocity of 10 m/s. The model was insensitive to changes in diffusion and changes in pressure boundary conditions. Note that ultimately, the choices for injection flow rate and injection concentration were produced only for a 1 minute duration of treatment. This portrayed a computational model of a single bolus injection of Baclofen rather than a continuous drug pump. With more resources to run the model for a longer time duration, a more accurate model can be achieved.

These results should be tested experimentally before being put to widespread use. However, it is likely that they can be used to direct the placement of a Baclofen pump and the concentration and flow rate of Baclofen through that pump. Using these results, doctors will be able to minimize adverse drug effects while simultaneously providing adequate concentrations of Baclofen to the target areas. This computational method of optimizing input concentration and flow rates in the intrathecal space can be expanded to attain these parameters for other drugs.

2 Introduction

2.1 *Background*

Muscle spasticity is a condition where a patient exhibits a progressively increasing pathologic muscle tonus until voluntary movement of the affected limb(s) is severely limited. This condition affects two-thirds of patients, primarily children, with cerebral palsy (Albright et al. (1991)). Similarly, patients with certain forms of spinal cord injury or multiple sclerosis and those who often exhibit symptoms with a similar pathophysiology to that of cerebral palsy, experience chronic spasticity that drastically degrades their standard of living. Baclofen, a synthetic derivative of the neurotransmitter gamma-Aminobutyric acid (GABA), was first synthesized by Heinreich Keberle in 1962 (Watve et al. (2011)). It has become the leading therapeutic drug in the management of chronic spasticity.

Baclofen affects GABA receptors at the spinal level and reduces propagation of action potentials along alpha motor neurons. In other words, it behaves as a potent, targeted muscle relaxant. Keberle designed the drug for oral administration. Due to the molecules similarity to GABA (Watve et al. (2011)), he increased its lipophilicity to improve the molecules ability to penetrate the blood-brain barrier into the cerebrospinal fluid (CSF) above the dorsal nerve roots supplying the affected muscles (Blackburn (2010)). As an orally dosed medication, Baclofen was a partial success. The drug could reach clinically effective concentrations in the CSF, but not without introducing a host of debilitating over-dose effects due to its systemic delivery route. Patients complained of hypotension, bradycardia/tachycardia, flaccid paralysis, among other symptoms (Haranhalli et al. (2011)).

In clinical trials by Richard D. Penn and his colleagues, the drug was administered directly to the target region, the CSF proximal to the affected dorsal roots. The patients in the studies were experiencing spasticity so severe that surgeons considered completely transecting the nerve roots. After the treatment, they were able to walk again after 19 years of pain. A delivery pump was devised to administer low doses of baclofen directly into the CSF-filled subarachnoid space, or intrathecal space, of the spine (Haranhalli et al. (2011)) (Penn (1988)). Earlier, the treatment involved 100 mg bolus oral dose of baclofen to achieve a concentration of $<$3 ng/g in the targetted locale in the CSF, a 600 ug dose could achieve local concentrations of 5-20 ng/g (Haranhalli et al. (2011)). Penn proposed a course of treatment where fluid from a reservoir could be pumped 5 muL/hr to deliever 25-50 ug doses within a course of 8-12 hours (Penn (1988)).

The current generation of intrathecal delivery pumps, such as the Medtronic Intrathecal Baclofen Treatment pumps shown in Figure 1, treat not only muscle spasticity but also chronic conditions such as nonmalignant pain (Hettiarachchi et al. (2011)). They administer low doses of opioids to limit the effects of tolerance. These devices use a silicone catheter, inserted posteriorly to target the arachnoid membrane, and a battery-driven pump that draws fluid from a sub-dermal reservoir (Coffey et al. (2002)). The devices come with several different tunable settings for pump flow.

Figure 1: A representation of the intrathecal delivery pump in the spinal canal. An illustration from Medtronic detailing the use of the Baclofen pump on an individual with severe muscle tonus or pain. The needle is inserted directly into the spinal cord to directly provide pain relief at the source.

Devices, such as the one in Figure 1, have existed to treat chonic conditions such as muscle spasticity or nonmalignant pain (Hettiarachchi et al. (2011)). These devices use a catheter, inserted posterior to target the space under the arachnoid membrane of the spinal cord. Spasticity management, an uneasy balance between alleviating unmanageable

pathological tonus and moderating collateral damage to organs serving as intermediate checkpoints in the delivery route, often involves the injection drugs such as Baclofen; however, localization of the drug in the desired target locus along the spinal canal requires pre-modeling of the pump insertion site and flow rates (Hettiarachchi et al. (2011)).Taking into account the natural periodic flow of cerebrospinal fluid in the spinal canal (Sweetman and Linninger (2011)), surgical considerations for the catheter insertion approach, and the device's flow settings, we expect to suggest device flow rates and insertion sites to restrict drug delivery so that the minimal effective concentration is attained only in the affected region of the spine, restricted in both vertical and cross-sectional directions.

Despite these devices providing fine control over delivery of Baclofen, spasticity management remains an uneasy balance between alleviating unmanageable patholgical tonus and moderating collateral damage and over dose. The trade-off inherent in directly accessing the intrathecal space is that any minor miscalculation in dosing has several orders of magnitude higher affect than a similar miscalculation in oral dosing. In our study, we expect to anticipate these problems by varying pump flow and concentration parameters and examining simulated concentration profiles that take into account the natural periodic flow of the CSF in the spinal canal (Sweetman and Linninger (2011)), surgical considerations for the insertion of the catheters.

2.2 *Design Objectives*

The first objective is to demonstrate the efficacy of the model to predict accurate outcomes given the standard treatment procedure. The second objective is to determine optimal injection concentrations and flow settings to minimize overdose and maximize drug functions.

This project aims to select and specify a safe pump concentration of Baclofen and an injection velocity by comparing maximum concentrations in the L1 - L3 region, which is located in the mid to lower torso of the spinal chord to ensure they lie within the minimal effective concentration range. Further investigation will be done to ensure that this method of delivery is practical and safe for patients patients with spastic pain.

Numerical and analytic methods were used to model the spinal cord while also considering drug concentration gradients that occur vertically and laterally along the canal. In doing so, the curvature of the spine, the widths of vertebra, the direction and speed of cerebrospinal fluid flow, and the natural diffusive properties of Baclofen must be considered. After injection, the drug will not just follow a simple diffusion problem. It will also have a convective component as prescribed by a sinusoidal approximation of the periodic flow of CSF in the intrathecal space (Sweetman and Linninger (2011)), which characterizes our top and bottom boundary conditions.

3 Problem Formulation

3.1 *Schematic*

From the current intrathecal delivery pumps (Hettiarachchi et al. (2011)), an anatomically correct schematic of the spinal cord is shown in Figure 2.

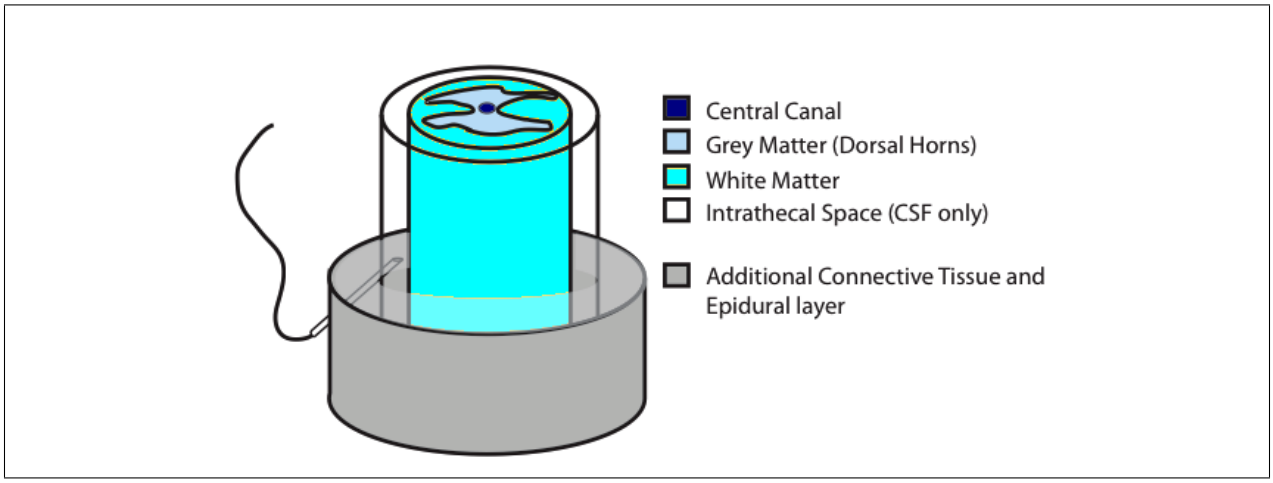


Figure 2: A 3-D Representation of the anatomy of the spine and how the Medtronic Baclofen pump would be surgically placed in a patient. This diagram portrays the spatial layout of the spinal chord, intrathecal space, and the catheter needle with respect to each other.

3.2 *Assumptions*

The model focuses on investigating a portion of the lumbar region of the spine, specifically the L1-L3 vertebrae. The model is restricted to regions of relatively constant diameters without the tapered ends of the sacrum. The solid core diameter is also approximated to be the size of intrathecal space subtracted from diameter of spinal canal (this is overly emphasized in the schematic in Figures 2 and 3).

An idealized cylindrical model (Figure 3) of the intrathecal space provides a more practical computational domain for actual drug transport than a model that expands the computational domain to include the bony structure of the vertebral column in which the space is sequestered (Figure 2). As drug distribution is most rapid through fluids, the distribution of the drug will most likely be influenced by the regions containing cerebrospinal fluid (CSF).

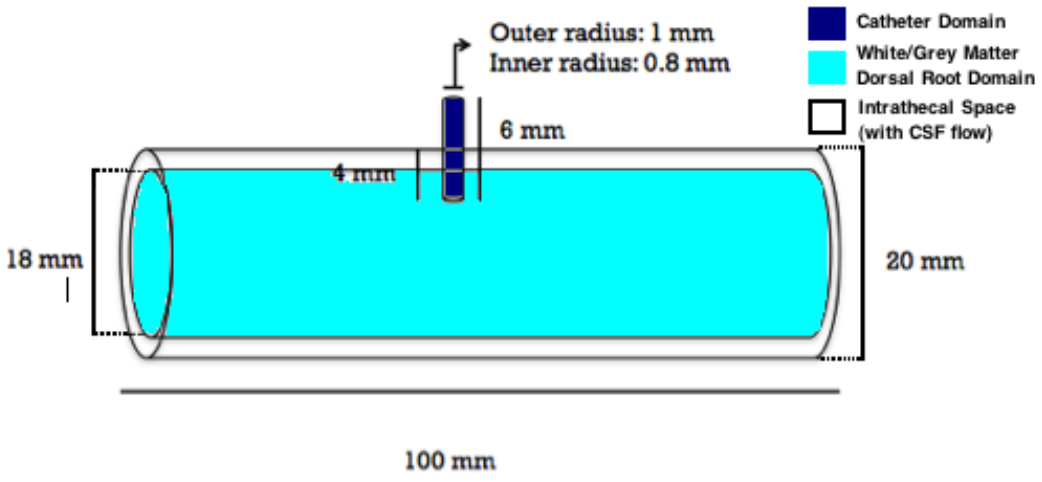
The flow of the CSF, a function of the cardiac cycle due to its close connection to the systemic flow of blood, contributes an additional complexity to the model of the distribution of Baclofen. Studies have argued that this flow has a nontrivial impact on the distribution of a drug from the injection site along the spinal canal (Sweetman and Linninger (2011)). The flow of CSF has been experimentally designed between the L1 and L3 vertebrae of the spine, between which catheters pump spine-targeting drugs in clinical trials of intrathecal delivery systems.

3.3 *Model Development*

In COMSOL, a computational domain, modeled as two concentric cylinders (one purely containing CSF and the other containing the dorsal nerve roots) was created (Figure 3). This model was restricted to the lumbar region of the spine. The concentration of Baclofen was calculated using the mass species general equation. The injection needle is modeled with the Navier Stokes equations to determine the velocity of the drug flowing into the CSF. The flow of CSF is calculated using Darcy's Law. This design takes into account the natural periodic flow of the cerebral spinal fluid (CSF). This flow characterizes our top and bottom boundary conditions, and was approximated as a periodic function (with a single period being that of the cardiac cycle)(Sweetman and Linninger (2011)).

3.3.1 *Governing Equations*

The geometry that was implemented in COMSOL consists of a simplification of the scenario seen in vivo, as shown in Figure 2. Figure 3 shows all of the subdomains and the governing equations important in the implementation of the model.



$$\textbf{(1)} \quad \frac{\partial C}{\partial t} + \vec{\nabla} \cdot (\vec{u}(t)\, C) = \vec{\nabla} \cdot \left(D \vec{\nabla} C \right)$$

$$\textbf{(2)} \quad \vec{q} = \frac{-k}{\mu} \vec{\nabla} P$$

$$\textbf{(3)} \quad \frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u} \cdot \nabla)\mathbf{u} = -\frac{1}{\rho}\nabla p + \gamma \nabla^2 \mathbf{u} + \frac{1}{\rho}\mathbf{F}$$

Figure 3: The schematic of the 3D model, as used in COMSOL and in relation to Figure 2, with the governing equations: (1) Mass Species General Equation is implemented in all three subdomains, (2) Darcy's Law is implemented in the subdomains of the spinal chord, and (3) The Navier-Stokes Equations are implemented in the injection needle

Figure 3 is modeled after Figure 2, and it shows the parameters of the COMSOL geometry. The governing equations that were used in COMSOL are also included. The dimensions chosen for the geometry in COMSOL were taken from typical values determined by previous studies in the literature (Gilad and Nissan (1985), Gra (1919)).

3.3.2 *Boundary and Initial Conditions*

Each governing equation requires separate boundary conditions. The mass species general equation is implemented so that there is no flux of Baclofen at the epidural boundary layer. At the solid core there is a continuity condition so that the amount of Baclofen being transported is preserved within the model. At the top and bottom portions of the spinal cord, there is convective flux due to the pressure flow of the CSF (Table 1). Figure 4 shows the schematic with the mass species boundary conditions.

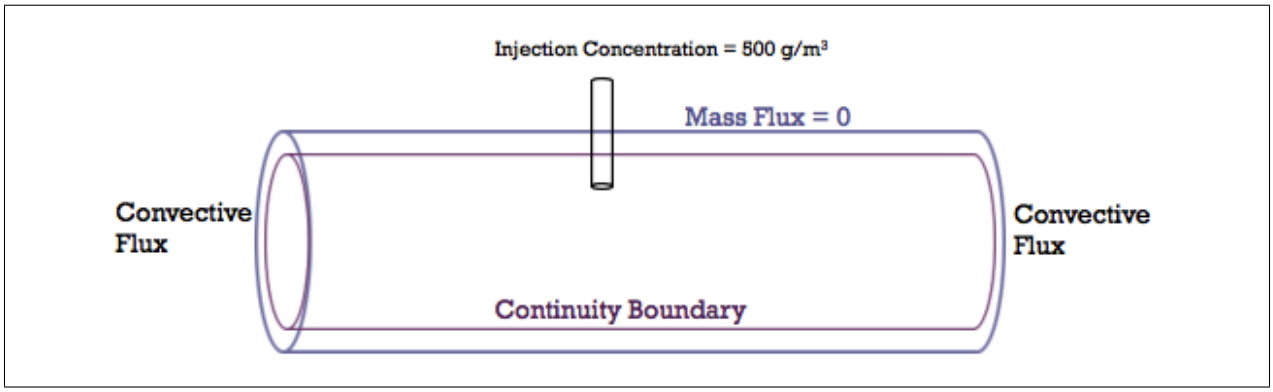


Figure 4: The 3D COMSOL model with the Mass Species General Equation's Boundary Conditions. The specific boundary conditions can be referenced in Table 1.

The initial condition is that there is there is a 500 g/m^3 injection of Baclofen at the injection needle. However, the concentration of Baclofen elsewhere in the system is zero (Table 1). The boundary at the injection site is modeled with a constant concentration boundary because it is most reasonable given that the Baclofen reservoir can be simplified as an infinite source for the drug.

Darcy's Law calculates the flow of CSF due to a pressure difference profile between the top and bottom of the schematic's geometry. This data was calculated from Sweetman and Linninger (2011).

In Figure 5, the pressure boundary conditions at the top and bottom of the schematic are shown. The injection velocity is specified at 2 m/s at the injection needle. Meanwhile, there is an insulated boundary condition at the epidural layer, and there is a continuity boundary condition at the solid core boundary (Table 1).

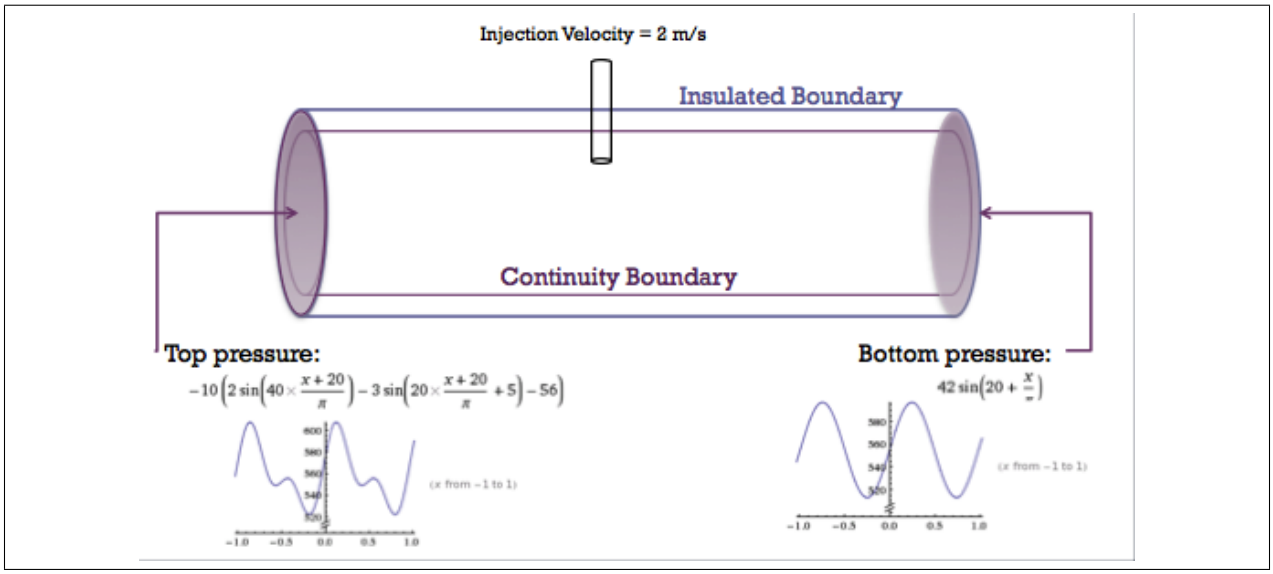


Figure 5: The 3D COMSOL model with the Darcy's Law Boundary Conditions. The specific boundary conditions can be referenced in Table 1.

These pressure profiles closely match the natural flow of CSF in the body (Table 1).These profiles were determined by data from Sweetman and Linninger (2011). The data was taken and transformed into the frequency domain by the Fourier transform. The largest components of this transform were taken as simplified functions for the top and bottom boundary conditions.

3.3.3 *Limitations*

The main limitations of this model are the simplifications made from deviating from the anatomy of this problem. The oversimplification of the CSF flow profile may affect the distribution of Baclofen in this study. The original spinal chord processes that affect the canal and the intrathecal space. Another limitation is that the injection needle, in the COMSOL geometry, is perpendicularly placed to the vertical axis of the spinal chord.

4 Results

Following simplifications of the computational model to accommodate difficulties encountered with computational time and memory allocation (namely a shortened run time and a coarser mesh than recommended through mesh convergence analysis), COMSOL returned a solution for the concentration distribution of Baclofen, shown in Figure 6, given an initial injection concentration of 500 g/m^3 and an initial pump velocity of 2 m/s.

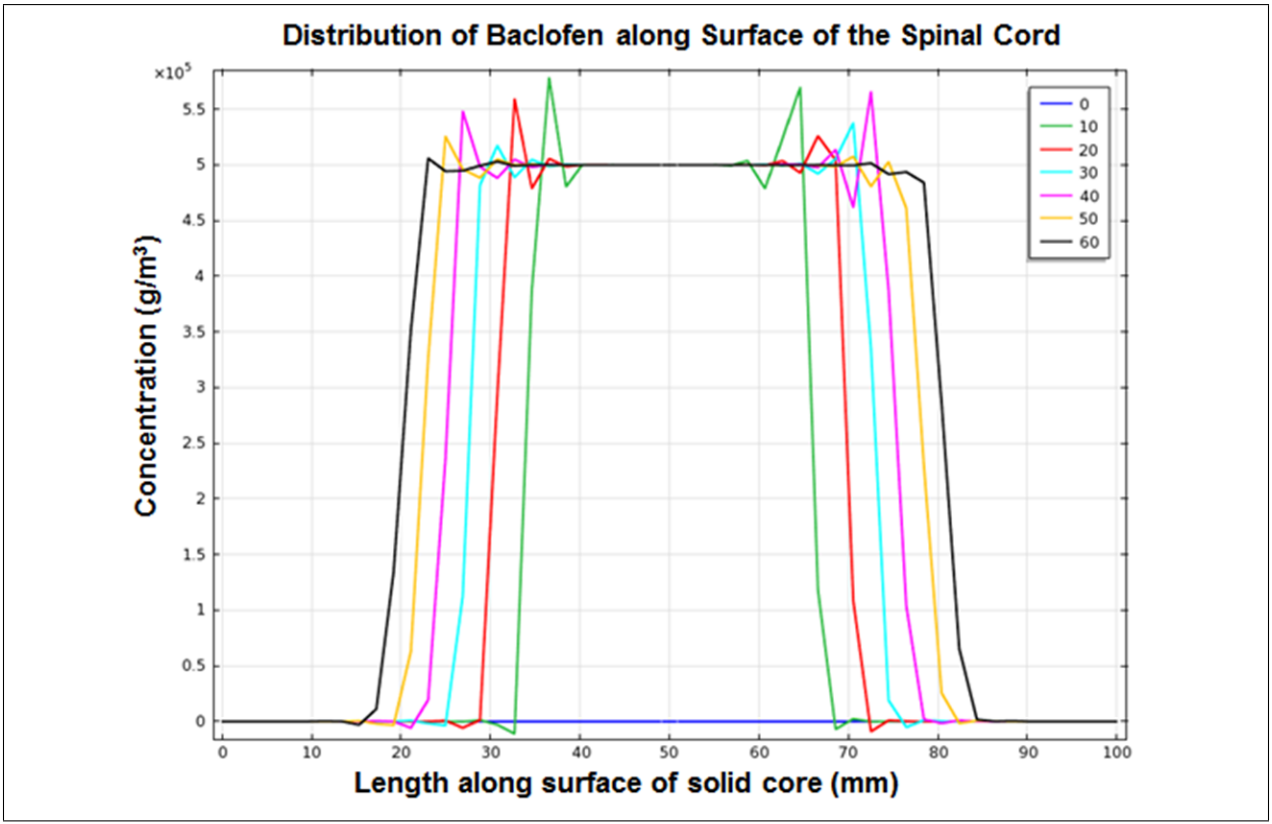


Figure 6: Distribution of Baclofen along the Surface of the Spinal Cord in intervals of 10 seconds for a duration of 60 seconds.

Interestingly, the concentration profile, in Figure 6, indicates rapid saturation of the spinal column within the 60 second run-time that resembled an injection of a single, large bolus of baclofen. While a clear departure from the desired chronic treatment protocol, whereby the concentration of Baclofen in the intrathecal space would level off in a much longer time-scale (out to days), the concentration profile demonstrates that the 500 g/m^3 doses utilized by Medtronic SynchroMed pumps (Saval and Chiado (2008)) will bring the average concentration of the 10 cm column of interest to the pump concentration within minutes of treatment.

In Figure 7, the concentration profile depicts the spread of the drug along two curved advancing fronts, headed towards the top and the bottom of the two cylinder model. Within these fronts, which traveled along the length of the 2-cylinder model at a velocity of approximately 4 mm/s, the entire intrathecal space and spinal cord was saturated with Baclofen.

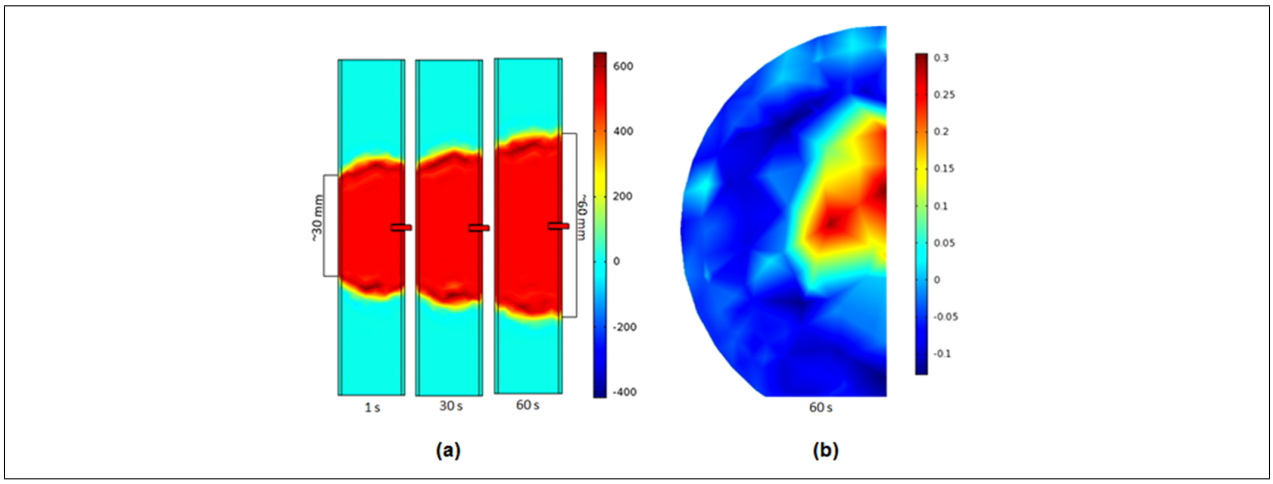


Figure 7: The concentration profile throughout the 60 second duration. Part (a) demonstrates the spread of the drug from the spinal column view at 1 second, 30 seconds, and 60 seconds. Note that at 1 second, the spread of the drug is witin 15 mm from the injection needle while at 60 seconds, the spread of the drug has increased to being within 60 mm from the injection needle. Part (b) demonstrates a top view of the cross section of the spinal column at 60 seconds.

As shown in Figure 7, the drugs spread was confined to a region within 15 mm from the injection site after simulation of one second of treatment. At the end of the 60-s runtime, the spread was confined to a region a little more than 30 mm from the injection site. A cross-section of the spinal column shown in Figure 7, taken at the top of the region of interest in order to view concentration distribution in unsaturated regions of the spine, indicates that the concentration fronts are largely localized in the solid core before saturating outlying regions in the intrathecal space. This, again, points to rapid therapeutic potential of a single bolus treatment and suggests possible drawbacks to the treatment scheme, as the distribution of Baclofen implies that the solid core bears the brunt of the Baclofen saturation and the most crucial(and easily damaged) tissue of the spinal canal could be easily impacted when over dosing.

5 Discussion

5.1 *Optimization*

The injection flow rate and injection concentration are optimized by doing an optimization of the Baclofen concentration both in the target area and in the rest of the spine. To solve this optimization problem, the target area concentration is calculated with a variety of injection flow rates and injection concentrations, and the best of each is chosen. The best result was determined by an equation that rewarded concentrations within the accepted range in the target region and rewarded low concentrations anywhere else. This was to minimize the adverse affects but maintain functionality. To determine the ideal location of the injection, this is done with the injection point in between several different vertebrae, and the best one is chosen.

Ideally, Baclofen should be delivered at efficient, sub-lethal concentrations directly on the dorsal nerve root core of the computational domain, and remain well below lethal concentrations throughout the entire spinal canal (i.e. the entire computational domain). Assuming minimum efficacy of a drug to be about 250 g/m^3, a concentration comparable to one that can be achieved through oral or systemic delivery of Baclofen (Penn 1988), and an overdose concentration of greater than 450 g/m^3, a set of objective functions could be attained to optimize the input concentrations of Baclofen delivered through the aperture of the computational domain:

$$\Sigma F_T = \Sigma F_{withininnercylinder} + \Sigma F_{withinoutercylinder}$$

$$\Sigma F_{withininnercylinder} = \begin{cases} (250\frac{g}{m^3 of CSF} - c) * 2, & \text{if } c < 250\frac{g}{m^3 of CSF} \\ (c - 450\frac{g}{m^3 of CSF}) * 3, & \text{if } c > 450\frac{g}{m^3 of CSF} \end{cases}$$

$$\Sigma F_{withinoutercylinder} = \begin{cases} (c - 450\frac{g}{m^3 of CSF}) * 1, & \text{if } c > 450\frac{g}{m^3 of CSF} \end{cases}$$

Starting from a concentration of Baclofen delivered clinically in market standard intrathecal devices, a range of lower input concentrations at varying inlet velocities were tested to determine optimum input concentration setting for delivery in a one minute treatment session in Figure 8.

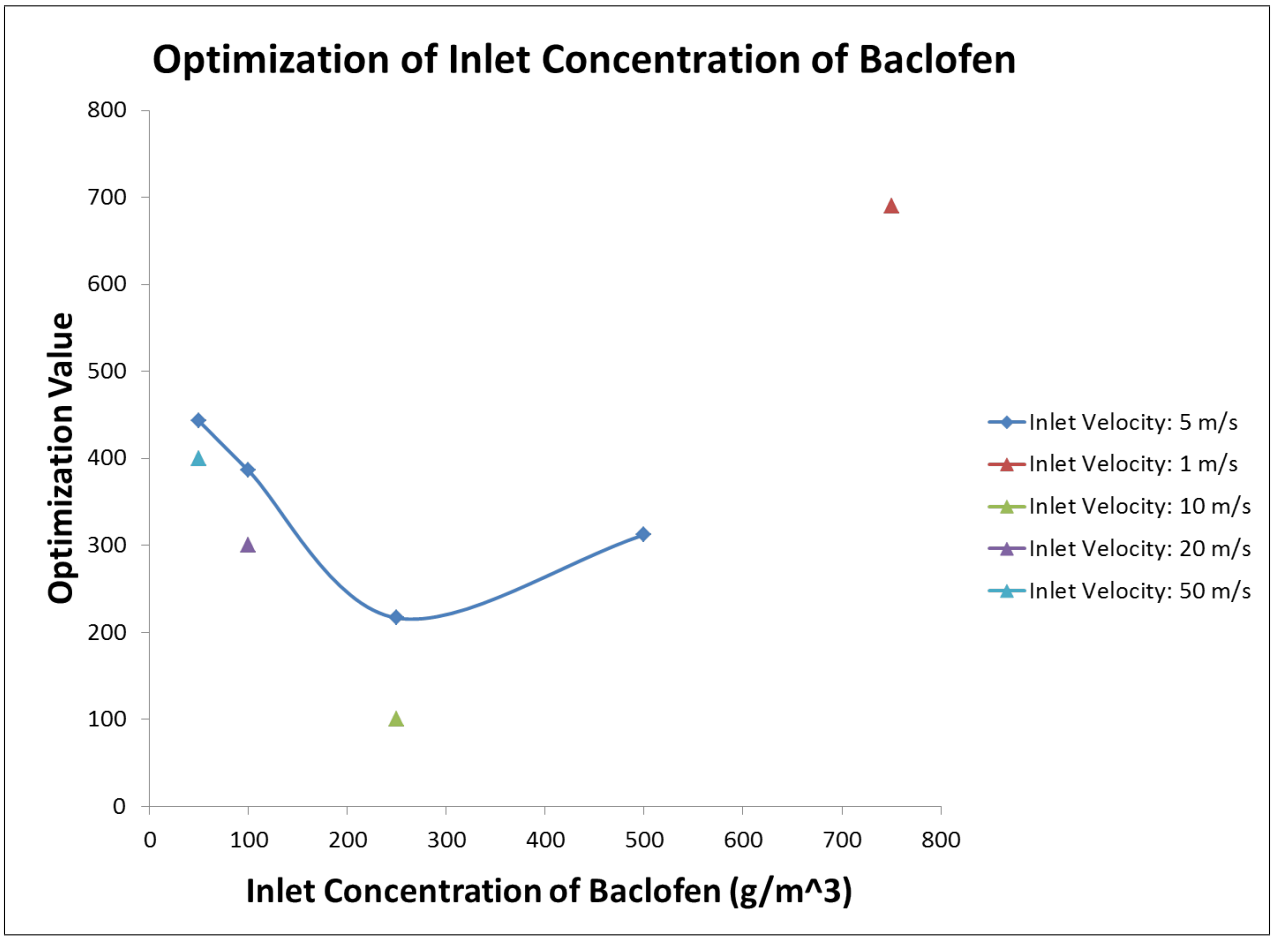


Figure 8: Values of the Optimization of the Concentration of Baclofen

In Figure 8, with the data that was run in COMSOL using the objective functions, it is determined that more concentration/inlet velocity trials must be done. This was not done due to lack of computational time. In Figure Figure 8, concentrations only one inlet velocity (5 m/s) were run. Independent parametric sweeps were not performed for velocities at each concentration. However, a velocity and an injection concentration were paired to attain a rough estimate of an ideal pump setting. Therefore, the optimal concentration for these trials is the lowest point on Figure 8: 250 g/m^3 at 10 m/s.

5.2 *Sensitivity Analysis*

While the focus of this study was assessing the optimal injection concentration of Baclofen and inlet velocity from the pump of the device, the sensitivity of the model to these input values should also be compared against the sensitivity to additional properties and parameters defining the function of the device. The sensitivity analysis done in this study is shown in Figure 9.

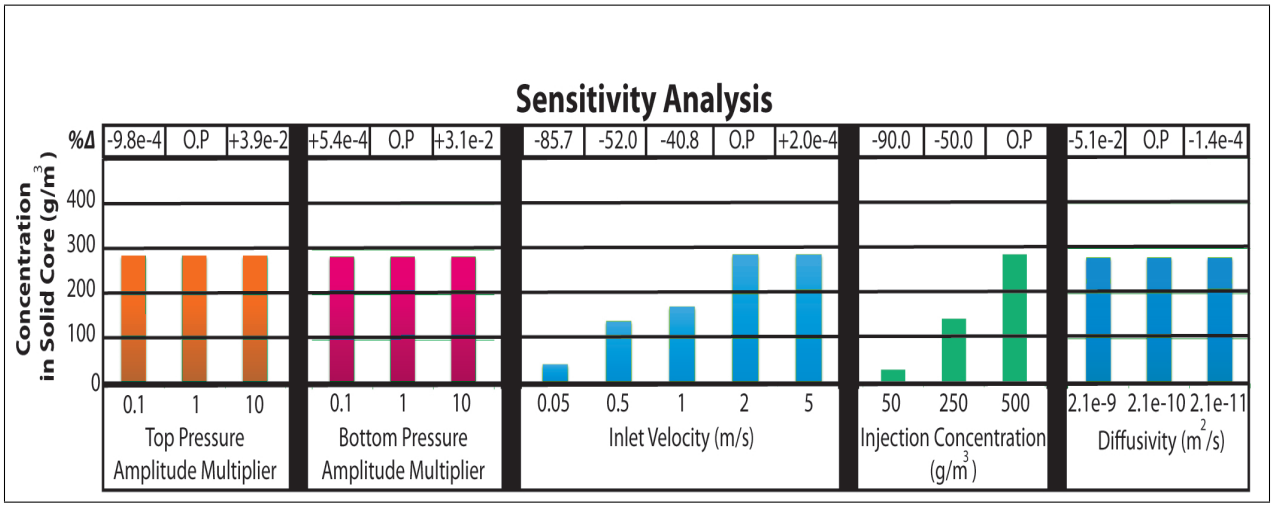


Figure 9: Sensitivity analysis was performed using a range of values for the amplitudes of the sinusoidal pressure profile defining the top and bottom conditions of the graph, the inlet velocity from the pump, the injection concentration, and the diffusivity of baclofen. Graphs indicate little variation in the concentration of baclofen in the solid core with variation with changing boundary conditions and diffusivity after a 60 second run time. Altering inlet velocity and concentration, however, caused significant changes to the concentration distributed in the solid core. (Concentration changes are indicated in upper row; O.P. indicates original parameter value)

For instance, one of the considerations being addressed in this study is the impact of cerebrospinal fluid flow within the spinal column on the distribution of the drug. One hypothesis was that the drug would reach a farther spread within the computational domain defined in this study; however, COMSOL solutions performed with 60-s run-times did not support this conjecture. Adjusting the amplitude of the sinusoidal functions defining the top and bottom boundary conditions altered the average concentration within the inner solid core of the spine by less than 0.04% even with order of magnitude variations. One possible rationale for this result was that fluctuating CSF pressure profiles would only play a strong role in drug distribution if diffusion played a significant role in the distribution of the drug from a pump-operated system.

The sensitivity analysis for diffusivity revealed that diffusivity did little to alter the concentration of baclofen in the solid core, with just a little more than 0.05% alteration when the diffusivity was considered one order of magnitude less than that of Baclofen in CSF. This suggests that this model can be generalized to other drugs.

As the model was sensitive to inlet velocity of the pump, with about 40% reductions in concentration when the velocity was halved, the COMSOL solutions suggest that convection predominates as the major component in the drug delivery system. Interestingly, increasing the inlet velocity did not alter the concentrations within the column, suggesting that the velocity used in a majority of the simulations ($2 \;\; m/s$) already caused saturation of the solid core. As expected, the solid core concentration varied most in response to increases in the injection concentration of the device, with the core concentration values almost scaling exactly with changes to the injection concentration, justifying the choice to optimize the injection concentration in this study.

5.3 *Accuracy Check*

Determining the accuracy of the model is an essential to creating a successful model. The best way to determine how the model compares with real data would be to run a parallel experiment with all of the same input parameters and conditions. This is the gold standard for determining the accuracy of a model and subsequently the legitimacy of its claims.

As part of this investigation, experimental data parallel to the simulation had not been gathered but there have been others who have performed similar experiments. The experiments Hettiarachchi et al had performed were highly similar to the ones that we are trying to model. In their experiments, they injected substances, such as flourescent dye that has a similar molecular weight to Baclofen, into a mechanical set up acting as a human spinal cord surrogate. When the results from this experiment, Figure 10a, and the experiments from literature, Figure 10b, are compared side by side, they are seen to be highly similar.

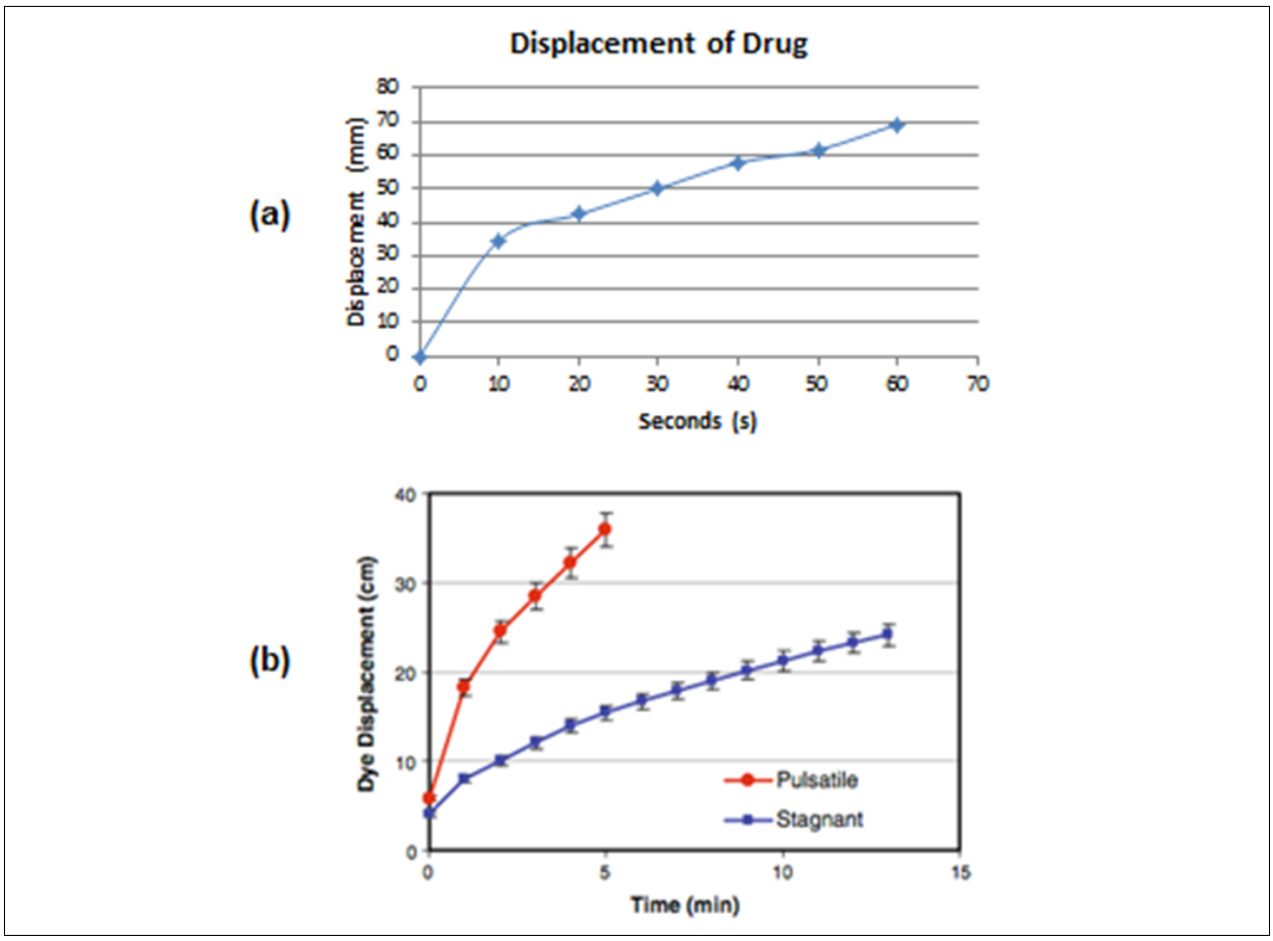


Figure 10: Side by side comparison of the displacement of Baclofen over time. Part (a) shows the results from this study. Part (b) shows a flourescent dye experiment done by Hettiarachchi et al. (2011).

It is important to note that, though the data do not have the exact corresponding time duration, the time that does apply to this model (time under 1 minute) does correspond nicely with the experiment shown here in the stagnant case. It is reasonable to compare our model to the stagnant case since we are modeling only the very lower section of the spinal cord. This section has the lowest rates of flow inside the spinal cord and hence flow rates would not be as high compared to in their experiment.

The striking discrepancy between the experimental setup and the set up of this simulation is the drug/molecule for injection. In the case of our model we had used Baclofen, a typical pain relieving drug, while in their experiments, they had used fluorescent dye (Figure 10b). The properties of the molecular dye should be similar to Baclofen since Hettiarachchi et al wanted to use the dye as a easily visualizable substitute for Baclofen in the experiment.

With the fluorescent dye experiment in Figure 10b, the value obtained at 1 minute is highly comparable to the value in the simulation suggesting that the solution obtained from COMSOL is a reasonable one.

6 Conclusion

6.1 *Future Aims and Design Recommendations*

Several significant simplifications were made to the original schematic of the intrathecal space and injection port to decrease computational time and memory allocation requirements. These changes, however, may have rendered much of this study nugatory, especially with respect to clinical applications of the intrathecal pump device. The catheter, for instance, should not be inserted into the gray and white matter of the spinal cord under any circumstance. Doing so will induce mechanical damage and possibly result in axotomy, or complete transection, of the nerves comprising the cord. A redesign of the device schematic would, therefore, be benefitted by a different angle of entry for the catheter and a much smaller needle gauge. This redesign will probably reflect a very different concentration distribution of baclofen, as the drug will have to travel from the cerebrospinal fluid-only space into the porous solid core.

The solution times for each simulation in COMSOL, 1-3 minutes, also reflected a dramatic departure from fundamental aims driving this study. The current generations of Baclofen pump devices are intended to be worn chronically, with a fully motile patient able to enjoy normal activities without worrying about drug dosing. This automation necessitates a much larger time-scale of study. At the very least, the protocol defining Baclofen delivery should have been tested out to a few days. Much slower injection velocities and smaller drug concentrations could have been used if the device was designed to distribute an effective concentration of Baclofen temporally averaged over a day rather than deliver a 1-3 minute single large bolus of the drug. At slower velocities, the effects of CSF flow may have been more noticeable, as well.

Finally, the simplifications of the design necessitated the removal of important geometric factors and physiological considerations regarding operations within the intrathecal space and spinal cord. The spinal column is often difficult to access as entry must consider the discrete spacing of the vertebrae. Within the model used in this study, the site of entry was assumed to be directly over the target location in the spinal cord. A more realistic model would suggest a set number of discrete entry sites, with the optimization of the pump parameters focusing on arriving at an effective, safe concentration at a more distally placed region of interest. Moreover, the problem formulation for the computational simulation omitted the elimination component of the mass species equation. The drug must be metabolized to have an effect in tissue. Of course, this might not be relevant in the 1-3 minute time-scale prescribed in the solutions of the study; yet, at longer, clinically relevant time scales, drug metabolysis would actually be the main concern of the model. Otherwise, the implication is that baclofen simply aggregates at the region of interest and no chronic dosing would be necessary as the patient will always have the required amount of drug in his or her system.

To bring the model closer to physiological relevance, the exact geometry of the spinal canal could be rendered; however, given the difficulties encountered in simulating complex CSF flow and drug transport in the simplified two cylinder geometry of the model, this might be computationally impractical. At the very least, however, the study must consider a clinically relevant time-span of treatment, a safe and physiologically possible placement of the catheter in the spine, and the degradation and consumption of baclofen by the patient to be of any use to efforts directed at improving chronic management of spasticity.

6.2 *Evaluation of the Design Objectives*

In summary, the study was motivated by two major goals: characterizing the concentration distribution of the drug Baclofen given a treatment protocol similar to that of the current generation of Intrathecal pumps (such as those by Medtronic Inc) and identifying optimal injection concentration and pump flow settings to minimize risk of overdose and maximize therapeutic function. As far as the first goal was concerned, the study was successful in demonstrating the effects of treatment with the standard 500 g/m^3 injection concentration setting, indicating that a zone of saturation was established immediately after onset of treatment, with the spread of the drug nearly doubling over a one minute period. The simplifications to the design and delivery method (constant injection), however, manufactured a protocol that was more in line with what was expected of a single bolus injection, reducing the clinical relevance of the results. Moreover, the effects of the internal CSF flow were demonstrated to be trivial at these rapid delivery settings. The second goal was, therefore, only partially addressed, as ideal input concentration and velocities were determined (250 g/m^3 at 10 m/s), but only for the simplified protocol and for a 1-minute treatment span. While this might dampen the impact of the results from the study, especially with regards to chronic treatment of spasticity conditions, the simulations, at the very least, demonstrated that a simulation of the drug treatment can provide an understanding of the underlying importance of convection and diffusion on the transport of baclofen.

6.3 *Realistic Constraints*

6.3.1 *Economic Constraints*

While improved quality of life ought to be the primary concern for those suffering from spasticity conditions, the unfortunate reality is that there are some very real financial constraints influencing patient care. The 5-year coust of treatment with intrathecal baclofen therapy is about $\$\ 49,000$ (De Lissovoy and Matza (2007)). While a good value considering the surgical pricing and the cost of the drug involved in the therapy, the fact that the treatment manages often non-lethal issues, the therapy might not be insured. This study was designed to consider lowering concentration doses to provide safer, chronic treatment; however, creating a pump reservoir with a lower baclofen concentration would imply that the pump reservoir must be refilled more frequently, which requires reopening the surgical site. This would incur higher costs and may not be desired by doctors or patients attempting to manage the total cost of therapy.

6.3.2 *Health and Social Constraints*

While this study focused on a single-bolus approximation of pump delivery of baclofen, the focus was to attain an optimal low dose, rapid delivery system in a chronic treatment plan. For minor spastic conditions, the use of a chronic pump device poses several important constraints. The device, as modeled in this simulation, will still be fairly bulky, with a subdermal battery pack causing issues regarding motility and flexibility to patients. The device is unlikely to gain popularity among those suffering from minor spasticity conditions due to discomfort and possibly social aversion to such an intrusive device. Moreover, invasive treatments, such as feeding tubes and intrathecal delivery systems, are never considered socially responsible cosmetic options. This may limit the impetus to design more refined pump therapies, as often the market driving management therapies is guided by cosmetic appeal of devices.

7 Appendix A: Mathematical Statement of the Problem

7.1 *Schematic*

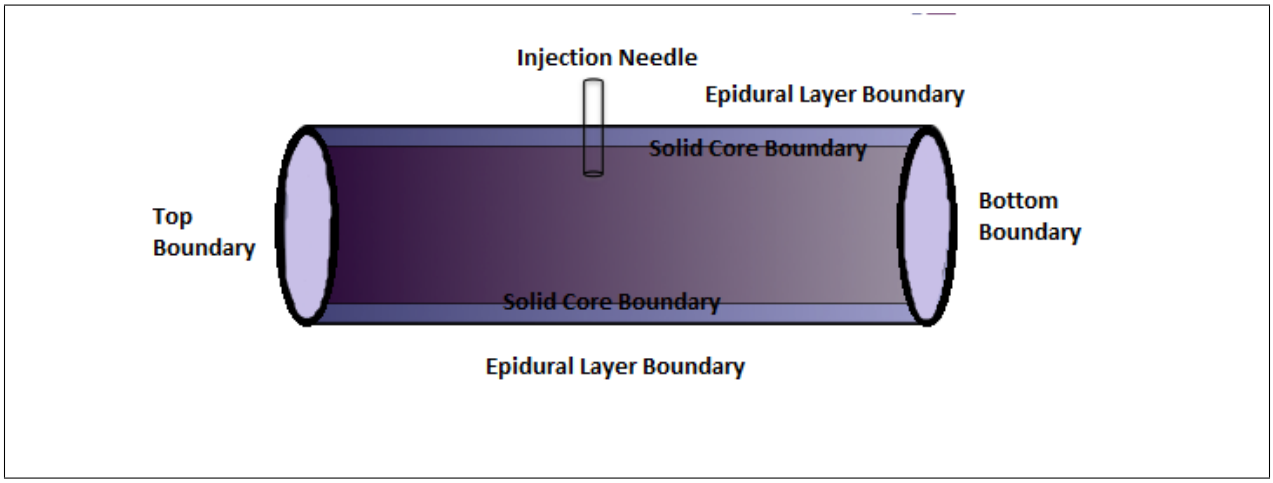


Figure 11: The 3D Schematic with labeled boundaries

7.2 *The Mass Species Equation*

THE MASS SPECIES EQUATION:

$$\frac{\partial C}{\partial t} + \vec{\nabla} \cdot (\vec{u}\,(t)\,C) = \vec{\nabla} \cdot \left(D\vec{\nabla}C\right) \tag{1}$$

7.3 *The Darcy's Law*

THE DARCY'S LAW:

$$\vec{q} = \frac{-k}{\mu}\vec{\nabla}P \tag{2}$$

The experimental data attained by Sweetman and Linninger can be used to estimate pressure differences induced within the computational domain in which the delivery of Baclofen is being modeled. The simulation will vary the pressure difference induced across the top and bottom boundaries of the computational domain over the duration of treatment, cycling through the pressure values every second (Table 1).

7.4 *The Navier Stokes Equations*

THE NAVIER–STOKES EQUATION:

$$\frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u} \cdot \nabla)\mathbf{u} = -\frac{1}{\rho}\nabla p + \gamma\nabla^2\mathbf{u} + \frac{1}{\rho}\mathbf{F} \tag{3}$$

7.5 *The Boundary and Initial Conditions*

Table 1: The Boundary and Initial Conditions for each General Equation with respect to Figure 11

Boundaries	**Mass Species Equation**	**The Darcy's Law Equation**	**The Navier-Stoke's Equation**
Top Boundary	Convective Flux	Pressure: $-10(2\sin(\frac{40(x+20)}{\pi})$ $-3\sin(\frac{20(x+20)}{\pi}+5)-56$	N/A/
Bottom Boundary	Convective Flux	Pressure: $555+42\sin(20\frac{x}{\pi})$	N/A/
Solid Core Boundary	Mass Continuity Condition: $\frac{\partial\rho}{\partial t}+\vec{\nabla}\cdot(\vec{u}\,(t)\,\rho)=0$	Continuity Condition: $\frac{\partial\rho}{\partial t}+\vec{\nabla}\cdot(\vec{u}\,(t)\,\rho)=0$	N/A/
Epidural Layer Boundary	Mass Flux = 0	Insulated Boundary	N/A/
Injection Needle Top	C = C_inj, (Table 3)	N/A/	Specified Inlet Velocity = 2 $\mathrm{m/s}$
Injection Needle Bottom	Continuity Condition: $\frac{\partial\rho}{\partial t}+\vec{\nabla}\cdot(\vec{u}\,(t)\,\rho)=0$	N/A/	Continuity Condition: $\frac{\partial\rho}{\partial t}+\vec{\nabla}\cdot(\vec{u}\,(t)\,\rho)=0$
Walls of the Injection Needle	Mass Flux = 0	N/A/	No-Slip Condition: $\partial\mathbf{u}\times\partial\mathbf{n}=\partial\mathbf{U}\times\partial\mathbf{n}$, where $\partial\mathbf{u}$ is the fluid velocity, $\partial\mathbf{U}$ is the wall velocity, and $\partial\mathbf{n}$ is the unit vector.
Initial Conditions	Initial Concentration = 0 $\mathrm{g/m^3}$	Initial Pressure = 101325 atm	Initial Velocity = 0 $\mathrm{m/s}$

8 Appendix B: Input Parameters

The dimensions of the injection needle created by the catheter of the intrathecal pump was simulated to represent dimensions of the apparatus created in studies evaluating the nature of CSF flow and the possibility of pulsatile delivery of Baclofen (Hettiarachchi et al. (2011)).

The same held true for the clinical values for injection velocity for the drug delivery and input concentrations, values that served as accuracy checks for optimum values attained in this simulation. As a continuous flow pump, as modeled by the computational model used in this study, there are no additional engineering requirements on the delivery route for Baclofen, and these dimensions were assumed to be clinically relevant. The dimensions of the intrathecal space and the nerve root core, similarly, were attained from the pulsatile delivery study by Hettiarachchi et al, using an average adult male spine as a measure for the physiological dimensions. Additional physiological properties of the spine and CSF, along with diffusivity and pharmaceutical information about Baclofen were attained from a variety of sources.

Table 2: **Schematic Dimensions. The schematic can be referenced in Figure 3**

Description	**Name**	**Value**	**Units**
Radius of the intrathecal space (including the core)	r_intra	0.01	m
Radius of the solid core	r_core	0.009	m
Height of observed spine	h	0.1	m
Needle Radius	r_needle	0.0008	m
SA of the needle injection point	SA_needle	$7.85398 \cdot 10^{-7}$	m^2

Table 3: **Input Parameters Pt. 1**

Description	**Name**	**Value**	**Units**
Pressure Boundary at the Top	p_top	$101325 + 100 \cdot sin(t)$	Pa
Pressure Boundary at the Bottom	p_bottom	$101325 - 100 \cdot sin(t)$	Pa
Normal Inflow Velocity of CSF (Hettiarachchi et al. (2011))	V_in	$0.002 \cdot sin(x)$	$\mathrm{m/s}$
Dynamic of Viscosity of CSF (Yetkin et al. (2010))	visc_CSF	$7.2 \cdot 10^{-4}$	$\mathrm{Pa} * \mathrm{s}$
Density of CSF-filled space (Hettiarachchi et al. (2011))	d_CSF	1000	$\mathrm{kg} \cdot \mathrm{m}^{-3}$
Inlet Velocity of Baclofen (Hettiarachchi et al. (2011))	V_inj	$\frac{\mathrm{inj\_mass\_flow/C\_inj}}{\mathrm{SA\ of\ the\ needle\ injection\ point}} = 84.03$	$\mathrm{m/s}$
Diffusivity of Baclofen (Hettiarachchi et al. (2011))	D_bac	$2.1 \cdot 10^{-10}$	$\mathrm{m}^2 \cdot \mathrm{s}^{-1}$
Molecular Weight of Baclofen (Hettiarachchi et al. (2011))	MW_bac	213.6	$\mathrm{kg} \cdot \mathrm{kmol}^{-1}$
Initial Concentration of Baclofen (Hettiarachchi et al. (2011))	C_inj	500	$\mathrm{g} \cdot \mathrm{m}^{-3}$

Table 4: **Input Parameters Pt. 2**

Description	**Name**	**Value**	**Units**
Permeability of Baclofen in CSF (Lal and Sukbuntherng (2009)) (Deguchi et al. (1995))	p_bac_CSF	$8.82 \cdot 10^{-11}$	m^2
Permeability of Baclofen in the solid core (Lal and Sukbuntherng (2009)) (Deguchi et al. (1995))	p_bac_core	$2.58 \cdot 10^{-13}$	m^2
Porosity of spinal cord (Hettiarachchi et al. (2011))	p_spinal	0.3	no units
Mean Viscous Resistance of Spinal Cord (Hettiarachchi et al. (2011))	mvr_spinal	$1 \cdot 10^{16}$	m^{-2}
Infusion Duration (Hettiarachchi et al. (2011))	t_infusion	30	s
Injection mass flow (Hettiarachchi et al. (2011))	inj_mass_flow	0.033	$\mathrm{g} \cdot \mathrm{s}^{-1}$

9 Appendix C: Solution Strategy in COMSOL

9.1 *Modules Used*

Implementation of the mathematical statement of the problem was largely based on an example case found in COMSOL 4.2. The convection-diffusion equation was implemented using COMSOLs Diffusion and Convection Module for Mass Species Transport. In the cases where Fluid Flow is concerned, either the Darcys Law Module, or the Navier-Stokes Module for Incompressible Fluids was used. All of the subdomains implement the Diffusion and Convection Module, the subdomains representing the spinal cord in this model all have fluid flow modeled by Darcys Law and the needle subdomain is the only one that implements the Navier-Stokes Module.

9.2 *Time Considerations: Transient and Time Stepping*

9.2.1 *Transient*

Due to the nature of this problem, injection of drug into the body, a transient model would be most accurate and useful representation of the situation. A transient model allow us to look critically at the time dimension of the problem and study flow of drug over time (as opposed to steady state, in which the time dimension does not matter). In addition, time data gathered would be useful in understanding the spread of the drug and what forces dominate in the movement of the drug (see sensitivity analysis).

9.2.2 *Time Stepping*

Time steps Since there had been no reason to restrict the time-steps used by the solver in the solution process, the default COMSOL algorithm was used to automatically choose whatever time-steps would work best for the problem.

9.3 *Mesh*

9.3.1 *Design of Mesh*

The basic design of the mesh was constructed using a default method COMSOL implements for free unstructured M=meshes (Figure 12a).

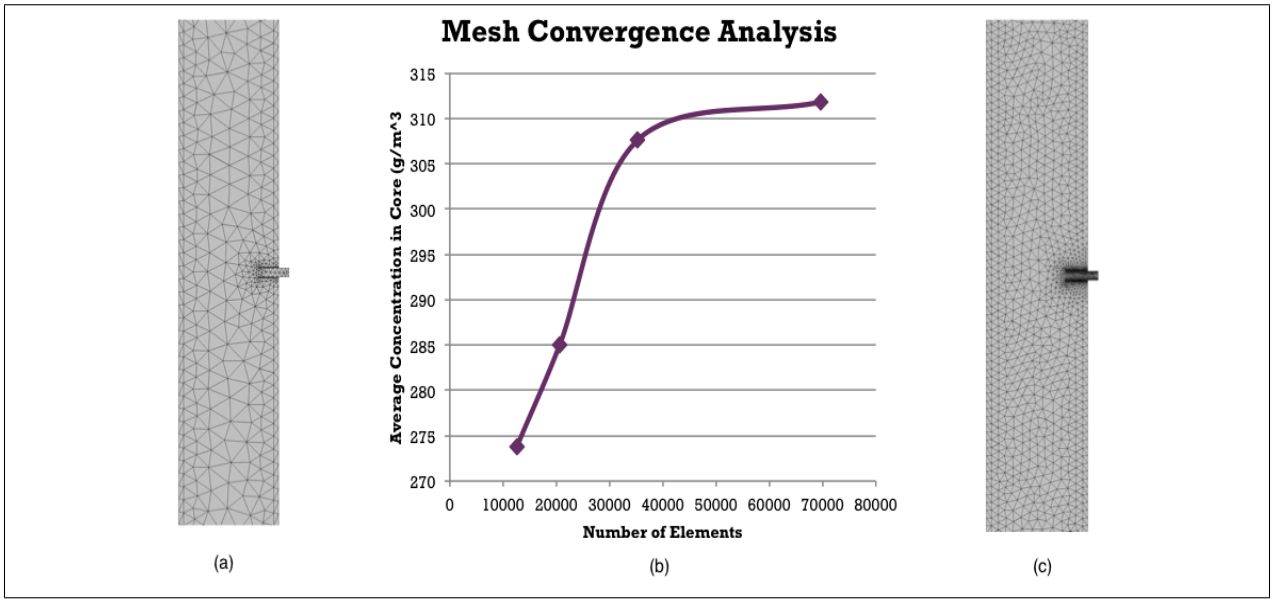


Figure 12: Mesh Convergence

The advancing front option allows for finer and smaller elements around the injection site, the location where the most and the largest of the changes in concentration were expected. Due to the fact that the mesh is unstructured and implemented by COMSOL algorithms, the elements specified by the algorithm are tetrahedrals.

9.3.2 *Mesh Convergence*

The choice of mesh should not theoretically affect the solution but due to discretization errors, it is still an issue. To make sure there is stability in the solution, regardless of the choice of mesh, the solution was calculated for a variety of different meshes of varying number of elements. This was done using the built-in setting COMSOL has for determining meshes. Meshes of 4 degrees of fineness were created to determine the the stability of the solution (In Figure 12). In Figure 12, it is evident that there is a significantly more stable solution with element size larger than 40 000. At closer inspection of the solution, it was determined that there is a lot of variation in the advancing front of the drug (Figure 13). The solution everywhere else in the solution is very stable. Since even in the finest mesh analyzed, there still exists the instability, the decision was made to save processing time and power. The mesh with 20615 elements was used for all of the sensitivity analysis and accuracy checks(Figure 12b).

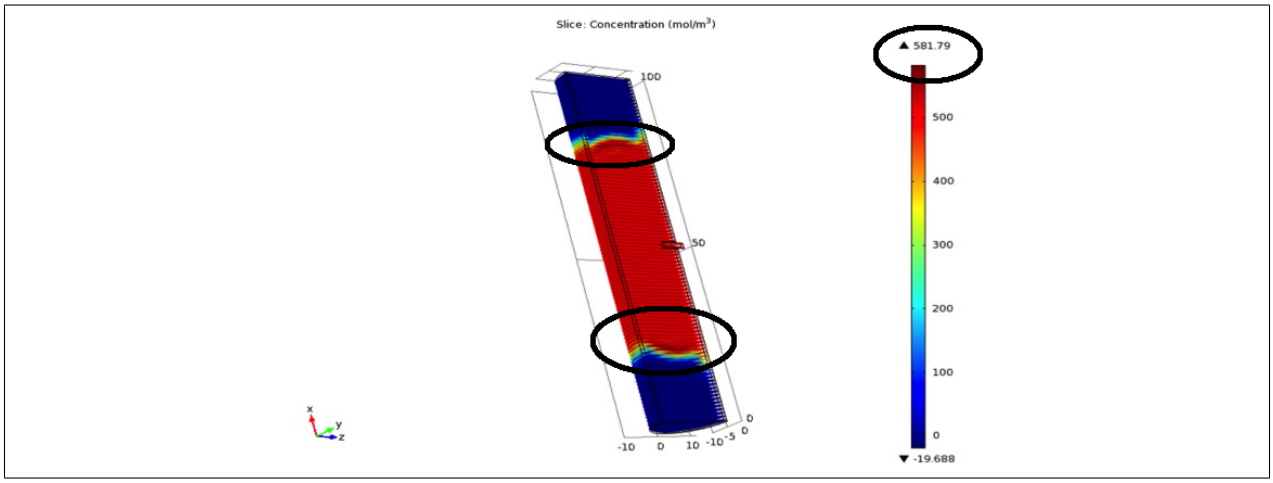


Figure 13: The 3D solution in COMSOL with labeled locations at which the average concentration of the solution changes with the number of elements in the mesh.

There is a significant difference in the average concentration of the solution below 40 000 elements. This is likely due to the instability of the convergence of the solution at the front of the spread of the drug as detailed in Figure 13.

9.4 *Solver*

To implement both the flow characteristics and the mass transport in COMSOL, an segregated iterative multigrid solver was used. Due to the unique nature of the problem where there flow characteristics and mass transport are coupled, a lot of computational power and memory needs to be used if the solution were to be determined all at once in both governing equations. Therefore the solver used breaks this large solution down into smaller parts. The solver first determines the flow patterns from the modules that determine velocity and pressure for the given time step. With this data in hand, it solves for the concentration at each point of the solution for the same time step. Afterwards, this repeats switching between solving for the flow and the mass transport until all of the timesteps have been taken. This lightens the load for the amount of memory required to solve the problem.

10 Appendix D: Additional Figures

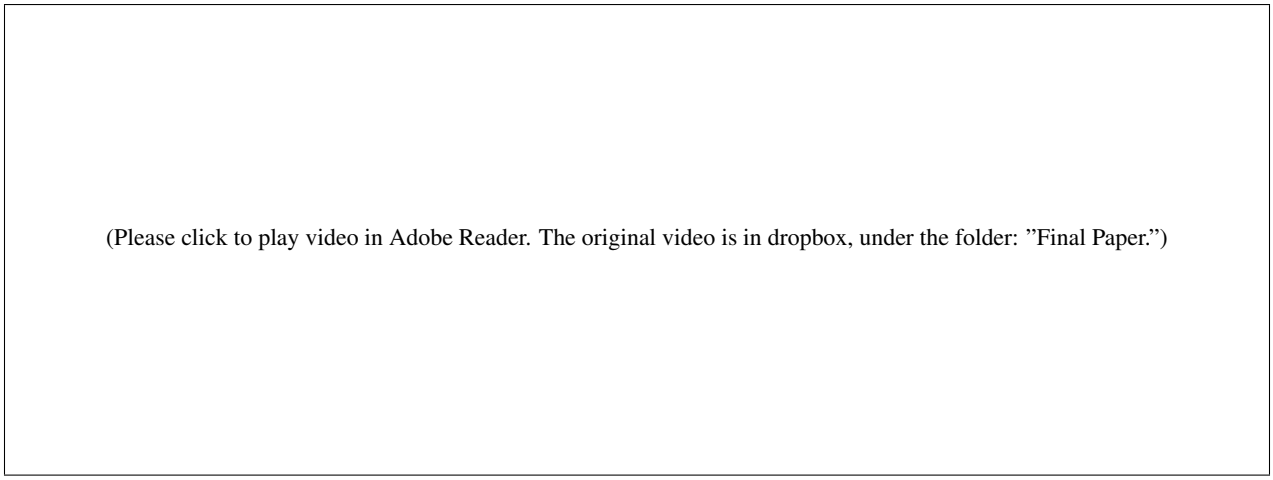


Figure 14: The changing concentration profile over 60 seconds seen from a side view. This is also shown in Figure 7.

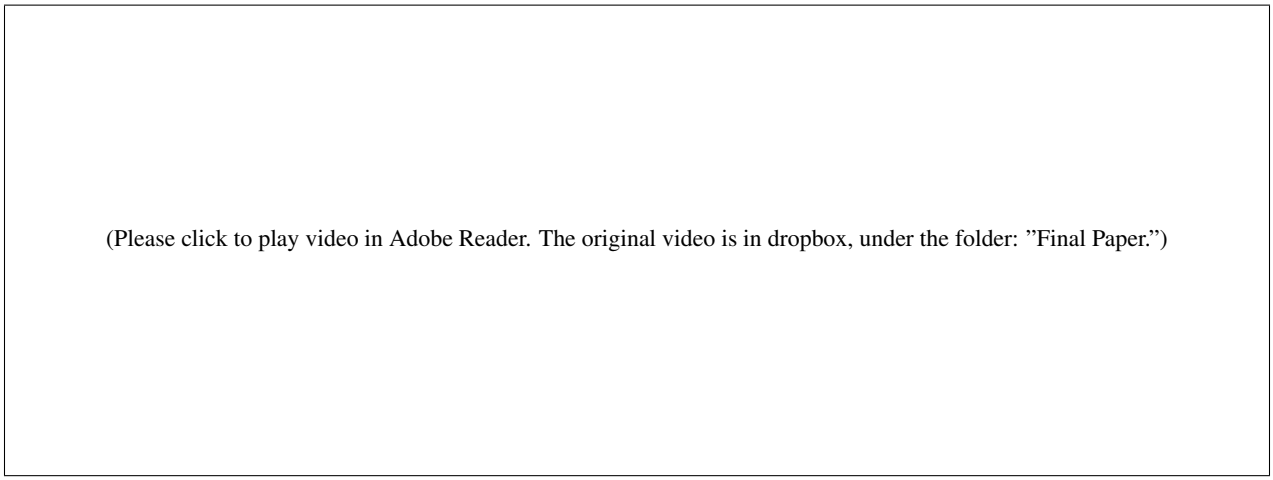


Figure 15: The changing concentration profile over 60 seconds seen from the top view.This is also shown in Figure 7.

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