Investigation of Pulp Pressure Dynamics by Modeling the Topical Application of 50% Lidocaine HCl in the Human Premolar

BEE 4530, Computer-Aided Engineering: Applications to Biological Processes

Aaron K. LaViolette
Samuel P. Furness
Alexander J. Rodriguez
Ashab S. Alamgir

Submitted: May 10, 2018

Contents

1.0 Executive Summary

The purpose of this research is to perform a time study on local anesthetics in dental surgery to provide insight on the inner workings pulp pressure dynamics. The dynamics of the pulp pressure when the dentin surface is exposed to atmospheric conditions are currently not understood. Verifying the ability of a high drug concentration to overpower the tooth's pressure gradient will provide evidence of a unique phenomenon in which diffusion overcomes fluid flow and uncover the physics of drug transport in the tooth. Quantifying this physics is the goal of this paper.

The time for a tooth to lose and regain sensitivity was measured with finite element modeling in COMSOL Multiphysics ® version 5.3. This model was built based on a clinical study which shows that the high concentration of lidocaine used (50% w/v or 500 mg/mL) was strong enough to overcome the natural pressure gradient from the pulp to the outside air. The clinical study reported that patients lost tooth sensitivity between 20 and 30 minutes and regained tooth sensitivity between 50 and 60 minutes. Within the tooth, there are three distinct layers: enamel, dentin, and pulp. Inside of the pulp, there are blood vessels which cause degradation of the lidocaine and nerve endings which lose sensation upon binding to lidocaine. In the clinical study, a 3 mm diameter hole was drilled 3 mm deep through the enamel exposing the dentin layer (modeled at the center to retain axisymmetric geometry). The model used the mass transport and Darcy's Law equations to model the physical situation. Drug application was modeled with 10 minutes of drug exposure in the hole followed by hydrated gauze. Pressure was modeled with an exponential pressure decay with varying time constants. The time constant was optimized to find which physical pressure situation produced results closest to the results of the clinical study. This was accomplished using an objective function which assigned penalties to each time constant based on whether the tooth was numb and sensitive at the appropriate times found during the clinical study. This gave a value for a time constant. Sensitivity analysis was run on parameters approximated from the literature. After sensitivity analysis, sensitive parameters were varied and new optimizations were run to produce a range of values for the time constant.

This report found that tooth pulp pressure can be modeled with first order decay upon dentin exposure to atmospheric conditions. The decay was found to be governed by a time constant of 7 minutes and 5 seconds. After

sensitivity analysis and variation of sensitive parameters, the time constant was found to fall in a range of 5 minutes and 15 seconds to 9 minutes and 25 seconds. The pressure dynamics were found to be particularly sensitive to hydraulic conductivity of pulpal fluid in dentin, and diffusivity of lidocaine in dentin.

This paper offers a glimpse into the poorly understood pressure dynamics in a tooth during dental surgery. It is reported that bulk fluid movement from pressure in human dentin produces solvent drag or the effect of slowing inward diffusive flux of exogenous solutes. The quantitative description of these pressure effects is important for future medical applications and understanding this evolutionary phenomenon. Future research directions include first finding exactly accurate parameters by experimentation to fine tune the model. Also, using a 3D geometry with different drilled hole placements could produce a more accurate description of the process.

Keywords: Lidocaine, Tooth Pulp Pressure, Dentin, Oral Surgery, Dentistry

2.0 Introduction

Use of local anesthetics such as lidocaine for numbing nerves is nothing new in dentistry. Lidocaine inactivates sodium channels of neurons, which prevents the neuron from depolarizing. As a result, the cell cannot be depolarized enough to fire an action potential, and thus sensory signals cannot propagate causing the patient to feel no pain [1].

Generally, lidocaine is administered by injection into the gum instead of topically. Topical administration is rarely used since tooth enamel is considered impermeable. However, in cases where the dentin, a porous layer of the tooth below the enamel, is already exposed, topical application of lidocaine becomes a viable treatment option [2],[3]. For example, dental cavities caused by acid generating bacteria on the enamel surface results in the decay of the enamel, exposing the dentin surface. Due to the dentin exposure, lidocaine may be applied topically to the tooth without any drilling.

While topical application may provide a new method of desensitizing a nerve, it also introduces a complication. Teeth with exposed dentin have a hard time allowing the lidocaine to diffuse because the tooth pulp is pressurized above atmospheric pressure creating outward flow. This impedes inwards diffusion [4]. The impedance that acts against diffusion is commonly referred to as solvent drag. It has been hypothesized that this outward flux creates a solvent drag against foreign chemicals diffusing into exposed teeth as a defense mechanism for the tooth [5]. In a clinical study by Rirattanapong et al, it was shown that topical application of 50% w/v (500 mg/mL) lidocaine HCl to exposed dentin in adult human premolars in vivo was able to desensitize the nerves. The applied concentration was much higher than the typical 2% w/v lidocaine injections given to overcome the outward flow [3].

It has been measured that the static pulpal pressure for human teeth is 14.1 cm of H_2O gauge [6]. This is measured by attaching a tube to a tooth with exposed dentin and inducing a pressure on one side and concluding the pressure where no flow exists to be equilibrium. However, it is not known how the pulp pressure may vary inside the tooth in a procedure such as this, where the dentin is exposed to atmospheric pressure. This is important for both topical applications in tooth surgery and understanding the basic defense mechanism in teeth. In an attempt to show that the static equilibrium found inside a canine tooth was the true equilibrium pressure and not an induced state, Brown and Yankowitz extracted and injected fluid to alter the pressure within the pulp. It was found that the pulp pressure returned to the initial equilibrium pressure with first order behavior. Thus, it is reasonable to believe that due to the outward flow of fluid, the pulp pressure will likely decrease with time and exhibit exponential decay governed by a certain time constant [7].

Since the data from the clinical study is available concerning the time it took to numb the tooth, this process can be modeled in COMSOL to provide a better understanding of how the pressure will vary with time. The model will mimic the clinical study and be optimized to produce similar results in order to find how the pulp pressure is changing with time namely through the definition of a time constant in first order decay. The information found can also be useful for patients who have cavities exposing the dentin, potentially providing an alternative treatment method.

2.1 Problem Statement

Lidocaine can be applied to a tooth topically by removing the impermeable enamel layer. However, since the pulp is pressurized above atmospheric conditions, pressurized fluid flow

opposes lidocaine diffusion into the tooth. These pulp pressure dynamics are currently poorly understood. The goal of this project is to find a reasonable way to model these pressure dynamics upon exposure of the dentin surface to atmospheric conditions. This specifically involves quantifying the time constant for pressure decay.

2.2 Design Objectives

This study's primary objective was to determine how pressure in the tooth pulp would vary over time due to exposure of the dentin surface to atmospheric pressure. This was complicated by several tooth properties being unavailable, and the need for reasonable approximations. As a result, this model had the following objectives.

1. Investigate the time constant, as tooth pulp pressure is believed to follow first order decay [7]. The time constant is determined by comparison with Rirattanapong et al.
2. Determine a range of possible pressure time constants by varying certain parameters one at a time and in combination.

3.0 Methods

Modeling of drug diffusion against pressure driven fluid flow is accomplished using the following geometry, governing equations, boundary conditions, and initial conditions. The model mimics a clinical study done by Rirattanapong et al.

3.1 Premolar Morphology

The geometry of a human second maxillary premolar was considered in order to determine a simplified model to simulate transport processes in. Figure 1 displays the cross sectional geometry of a human premolar. This is the exact type of tooth modeled in this report.

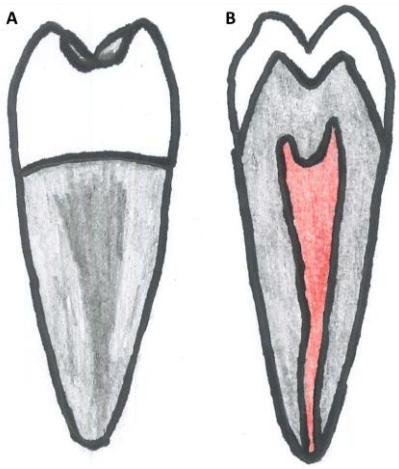

Figure 1: Drawing of a second maxillary right premolar. Views are shown from (**A**) the side view showing the exterior of the tooth and (**B**) a cross sectional view with enamel (white), dentin (grey), and pulp (red). The outer layer of the dentin is an impermeable layer made mostly of enamel (referred to simply as enamel) [8]. The single root of this tooth is compatible with axisymmetric modeling. The drawing is adapted from actual recorded tooth morphologies [9], [10]. This diagram was used with relevant dimensions to create a 2D geometry in Solidworks ® 2017.

As shown in figure 1 the cross section contains three distinct layers: the pulp (red), dentin (grey), and enamel (white). The outer layer of the tooth is covered by enamel or an enamel like surface that is considered to be impermeable [8]. This is referred to simply as the enamel going forward to avoid confusion. Using the true geometry of a tooth, a 2D Solidworks ® 2017 sketch was created and later imported into COMSOL for modeling. A 2D axisymmetric assumption for the model was appropriate due to the single root of the actual tooth. This assumption creates discrepancies between the model and the actual tooth mostly with respect to the cusps. This approximation is reasonable because no significant differences are observed between the model and a real tooth besides the fact that teeth are not perfectly symmetrical as in this model. It is also worth noting that this model assumed a centered hole drilled into the top of the tooth. The clinical study this model follows drilled in the cusp (top ridges) of the tooth. This approximation is reasonable considering the distance from the dentin surface to the pulp is mostly conserved no matter the hole location.

3.2 Model Methods and Schematic

This model directly follows the procedure of Rirattanapong et al. In the procedure, the concentration in the drilled hole was 50% (500 mg/mL) lidocaine solution for 10 minutes and then zero concentration afterwards due to drug removal and replacement by gauze containing water [3]. A very high concentration of drug was used to overcome the pressure in the pulp that acts against drug diffusion [3], [4]. Lidocaine is also degraded by the vasculature within the pulp accordant with first order decay [11].

The main process occurring is diffusion of lidocaine into the tooth. However, upon atmospheric exposure at the drilled hole boundary, pressure driven flow against diffusion begins and will decay as the pulpal pressure begins to decay. In a study done by Brown and Yankowitz, first order exponential decay was observed after inducing pressure in the tooth so we have decided to model with this type of pressure decay [7]. The pulp dentin boundary was thus modeled with a pressure boundary condition of first order pressure decay. The adoption of this approximation is reasonable because in both cases pressure is moving towards an equilibrium.

We used average pulp concentration to quantify when the nerves in the dentin lose and regain sensation in accordance with the numbing concentration. This numbing concentration of 1% (10 mg/mL) was found by interpolation between ropivacaine numbing values from Vreeland and El-Sharraway [12], [13]. Ropivacaine is similar to lidocaine in structure as they are in the same drug family.

These processes and geometries are illustrated in the schematic of figure 2. This schematic was recreated in Solidworks and imported into COMSOL for modeling. COMSOL was used to model the effects of the diffusion of 50% lidocaine in the second maxillary human premolar. The clinical study drilled a 3mm diameter holed into the tooth and our model placed this hole at the center so that the entire geometry would be axisymmetric [3].

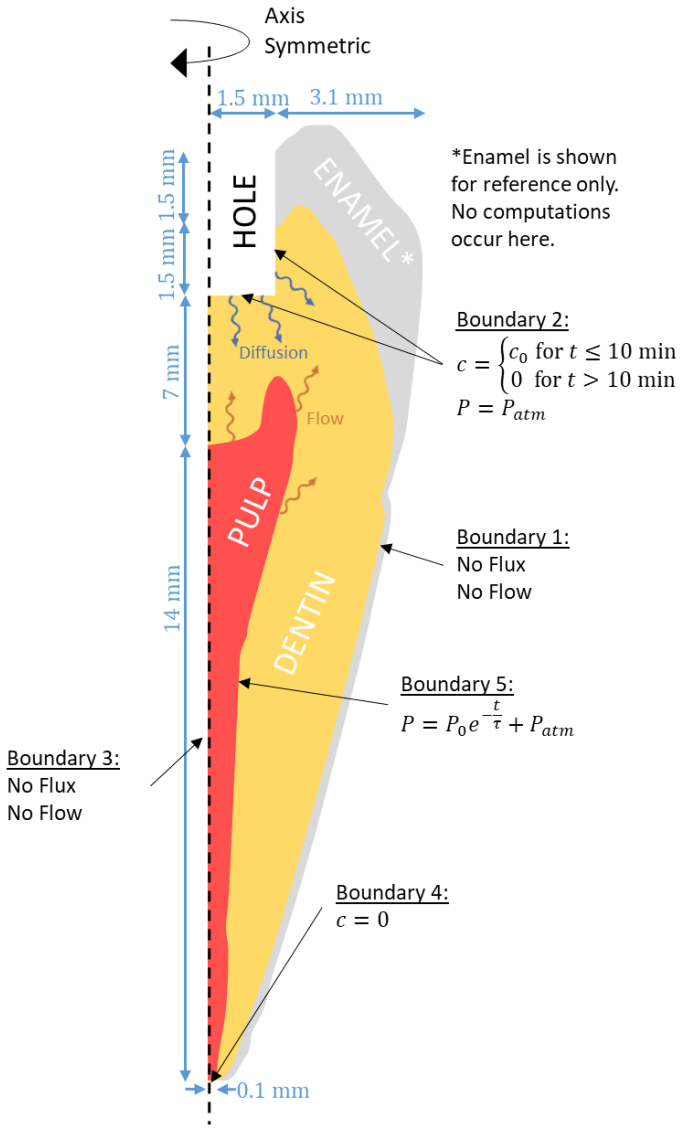

Figure 2: Schematic of the tooth used for modeling. The schematic includes the dimensions, and boundary conditions, and an illustration of the physics [14]–[18]. The enamel is shown purely for reference and no computations exist here. Here P_0 refers to the static equilibrium pressure (gauge) inside the pulp, and c_0 refers to the 50% lidocaine solution used. All computations deal with absolute pressure hence the inclusion of the P_{atm} terms in the schematic.

3.3 Governing Equations

Both mass transport and pressurized flow exist in this situation. The mass transport equation will be used in both the dentin and pulp domains. For the pulp the following equation is used.

$$\frac{\partial c}{\partial t} = \nabla \cdot (D_P \nabla c) - k'' c \tag{1}$$

where, c is the lidocaine concentration, D_P is the diffusivity of lidocaine in the pulp, and k'' is the rate constant for first order degradation of lidocaine.

In the dentin layer the following equation is used.

$$\frac{\partial c}{\partial t} + \boldsymbol{u} \cdot \nabla c = \nabla \cdot (D_D \nabla c) \tag{2}$$

where, D_D is the diffusivity of lidocaine in the dentin, and $\boldsymbol{u}$ is the velocity in the dentin.

The velocity field present in the dentin domain is solved for using Darcy's Law and the continuity equation, which are given below.

$$\boldsymbol{u} = -K \nabla P \tag{3}$$

where, K is the hydraulic conductivity of pulpal fluid in dentin, and P is pressure.

$$\nabla \cdot \boldsymbol{u} = 0 \tag{4}$$

The porosity and density terms drop out of the continuity equation because they do not vary temporally. It is assumed that pressure is the same spatially in the pulp and on the pulp dentin boundary. All calculations will be done using absolute pressure.

During COMSOL implementation the velocity from pressure was solved first and then entered into the mass transport equation (one way coupling). All values input into COMSOL are defined in table 3 of appendix B.

3.4 Boundary and Initial Conditions

The boundary conditions used in this formulation are given in table 1. A short basis for each condition is included. A more detailed discussion follows.

For mass transport, a no flux boundary condition is implemented at the dentin enamel interface as enamel is largely impermeable to lidocaine [8]. At the drilled hole surface at times less than 10 minutes the concentration of lidocaine is 500 mg/mL and 0 mg/mL after 10 minutes. This is done in accordance with the experimental study where a 500 mg/mL solution is left in the hole for 10 minutes and replaced with hydrated gauze after this time. No partition coefficient is assigned to this boundary because dentin is very porous and full of liquid so both regions will have roughly the same concentration at the boundary [15]. This is also true at the pulp and dentin boundary because the pulp is mostly liquid having a very high water content at 75 to 80% and thus has roughly the same concentration as the dentin at the interface [19]. Due to the axisymmetric geometry a no flux boundary condition is applied along the axis of symmetry. Along the pulp gum interface a concentration of 0 mg/mL is used since the large blood vessels present at the bottom of the tooth remove any lidocaine that reaches this boundary [20].

For fluid flow, a no flow boundary condition is set at the interface between dentin and enamel since the enamel is largely impermeable to pulpal fluid [8]. At the interface between the drilled hole and the atmosphere the pressure is set to atmospheric since it is exposed. Due to the axisymmetric geometry a no flow boundary condition is applied along the axis of symmetry. At

the pulp and dentin interface, exposure of the dentin surface to the atmosphere results in first order pressure decay given by the following equation.

$$P(t) = P_{atm} + P_0 e^{-\frac{t}{\tau}} \tag{5}$$

where P_{atm} is atmospheric and P_0 is the static pulpal pressure.

Here the static pulpal pressure, P_0, is 14.1 cmH_2O, which is equivalent to 1382.74 Pa [6]. This exponential decay was chosen based on a study done by Brown and Yankowitz [7]. Ultimately the time constant parameter is optimized for.

Table 1. Boundary conditions.

Boundary	Boundary No.	Condition	Basis
		Mass Transport	
Dentin/Enamel	1	No Flux	Enamel is treated as impermeable to lidocaine [8]
Hole/Dentin	2	$c = \begin{cases} c_0 \text{ for } t \leq 10 \text{ min} \\ 0 \text{ for } t > 10 \text{ min} \end{cases}$ where $c_0 = 500$ mg/mL	Conditions examined in the experimental study [3]
Axis of Symmetry	3	No Flux	Axisymmetric boundary
Pulp/Gum	4	$c = 0$	Large blood vessels at base of tooth act as a perfect sink to Lidocaine [20]
		Fluid Flow	
Dentin/Enamel	1	No Flow	Enamel is treated as impermeable to pulpal fluid [8]
Hole/Dentin	2	$P = P_{atm} = 101325$ Pa	Dentin is exposed to atmospheric conditions
Axis of Symmetry	3	No Flow	Axisymmetric boundary
Pulp/Dentin	5	$P = P_{atm} + P_0 exp(-t/\tau)$ where $P_0 = 1382.74$ Pa	Assumed dynamics based on studies by Brown and Yankowitz [7]

This is broken into two sections: one for mass transport and one for fluid flow. Boundary numbers correspond with the numbers in figure 2. All pressures in this table are absolute pressures.

The initial conditions used in this formulation are given in table 2. Initially there is no lidocaine present in any domains in accordance with the experimental study [3]. Initially the pressure in the dentin is 14.1 cmH_2O, equivalent to 1382.74 Pa (gauge) since before drilling the hole there is no flow present in the dentin [6].

Table 2. Initial conditions.

Domain	Condition	Basis
	Mass Transport	
All Domains	$c = 0$	No lidocaine was present in the tooth before the experimental study began [3]
	Fluid Flow	
Dentin	$P = 102707.75$ Pa	Pulp is initially pressurized above atmospheric and there is no flow in the dentin initially meaning it must also be pressurized above atmospheric conditions. Value from human tooth in Ciucchi et al. [6]

This is broken into two sections one for mass transport and one for fluid flow. All pressures in this table are absolute pressures.

All of the above boundary conditions, initial conditions, and input parameters were then taken to COMSOL to compute. Details on the numerical implementation are in appendix C. The mesh used had a maximum element size of 100 μm. Details on meshing are in appendix A.

4.0 Results

The following section outlines how an optimized time constant was obtained, and how a range of reasonable time constants was obtained to account for variations in parameters and geometry.

4.1 Optimization function

In order to find the pressure equation's time constant, the solution was run over many time constants. To compare time constants, the average concentration of lidocaine in the pulp was analyzed over an interval of 0 to 90 minutes. Average pulp concentration was used to quantify numbing and sensation times since innervation is distributed throughout the pulp rather than at a certain point in the tooth [21]. In order to quantify which time constant best fit the observed experimental results, an optimization function was made. This function was created to mimic the results found in the study by Rirattanapong et al [3].

In the experimental study a sample was taken every 10 minutes to determine if the patient could feel external stimuli on their tooth. It was found that the patients could feel stimuli at 10 minutes, 20 minutes, 60 minutes, and any interval after 60 minutes. However, the patients could not feel stimuli at 30 minutes, 40 minutes, and 50 minutes. Thus, the tooth lost sensation at a time between 20 and 30 minutes and regained sensitivity sometime between 50 and 60 minutes.

An average pulp concentration of 10 mg/mL of lidocaine was determined to be the threshold for numbing.

In our computation we computed the average pulp concentration every minute and for each i^{th} minute assigned a penalty, F, given by the following equation.

$$F_i = \begin{cases} C_{av,i} - 10 & \text{if } C_{av,i} > 10 \text{ mg/mL and } t < 20 \text{ min} \\ 10 - C_{av,i} & \text{if } C_{av,i} < 10 \text{ mg/mL and } 30 \text{ min} < t < 50 \text{ min} \\ C_{av,i} - 10 & \text{if } C_{av,i} > 10 \text{ mg/mL and } t > 60 \text{ min} \\ 0 & \text{otherwise} \end{cases} \quad (6)$$

From equation 6 it can be seen that no penalty is to be assigned if the time is between 20 and 30 minutes and between 50 and 60 minutes. This is a result of the method used by Rirattanapong et al. in their experimental study. Since sensation was observed at 20 minutes but not 30, numbing could happen at an arbitrary time between 20 and 30 minutes since it is unknown at what specific moment sensation was lost. The same case exists for the window between 50 and 60 minutes for return of sensation. Hence no penalty can be assigned in this time interval because there is no information about the time when numbing or return of sensation occurred. The overall penalty is thus a measure of the model's deviance from the experimental findings by Rirattanapong et al. [3].

The objective function, J, is given by summing all the penalties, F, for all the i^{th} times as shown by equation 7.

$$J = \sum_i F_i \quad (7)$$

We then computed this penalty and plotted the penalty against various time constants to find the optimized time constant (figure 3). Since the penalties are assigned in such a way that they are always positive as shown in equation 6, the minimum of this plot gives the optimized time constant.

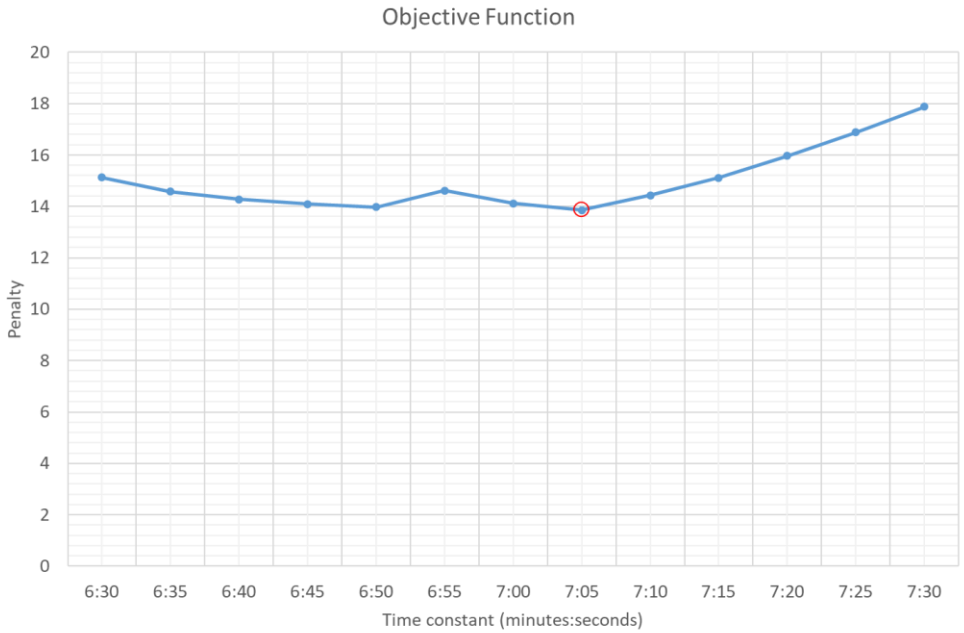

Figure 3: Graph of the objective function. Plotted is the penalty given by the objective functions for different time constants. Time constants are plotted at intervals of 5 seconds. The minimum penalty is the one that most closely represents the findings of Rirattanapong et al. as given by equations 6 and 7. The optimized time constant occurs at 7 minutes and 5 seconds.

It is determined from figure 3 that the optimized time constant occurs at 7 minutes and 5 seconds. To demonstrate this visually the average pulpal concentration over time was plotted for a handful of various time constants around the optimized value of 7 minutes and 5 seconds (figure 4).

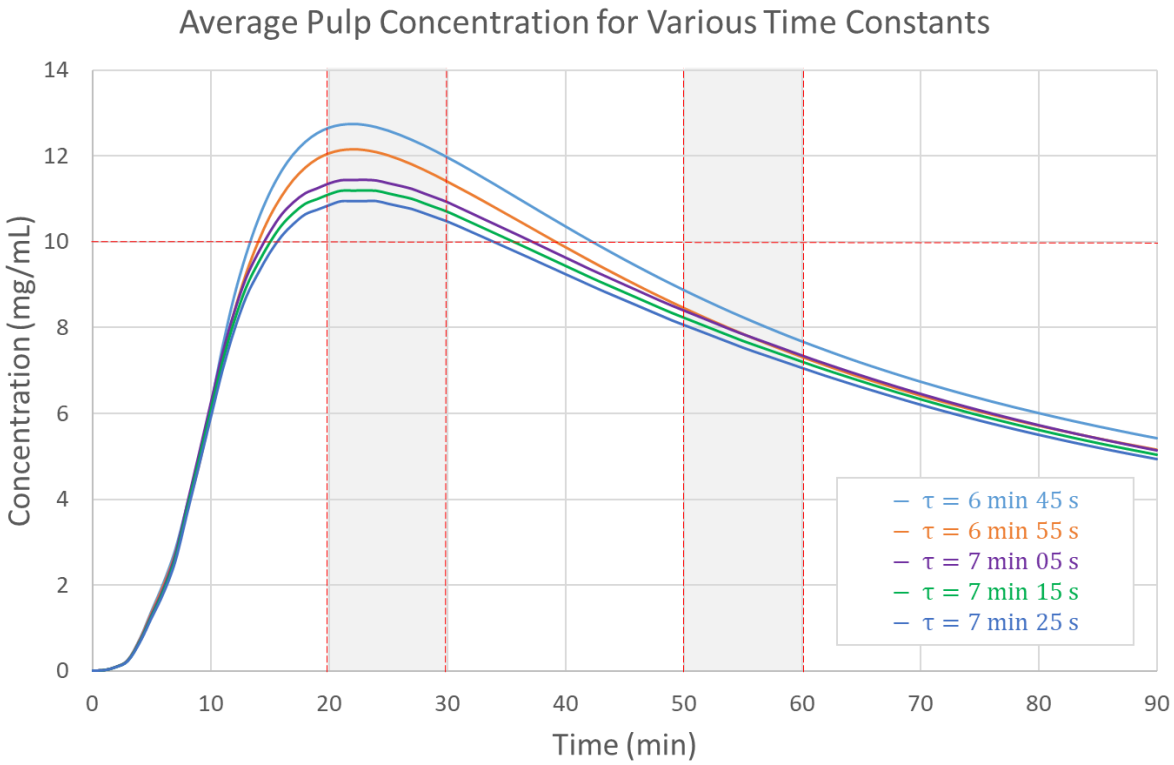

Figure 4: Average pulp concentration for various time constants. Plotted is the average pulp concentration of lidocaine for various time constants. The red horizontal dashed line at 10 mg/mL corresponds to the numbing concentration. The shaded regions bounded by the red vertical dashed lines between 20 and 30, and 50 and 60 minutes are regions where numbing should occur, and sensitivity should be regained respectively as reported by Rirattanapong et al. All of the peaks occur between 22 and 24 minutes.

From figure 4, it can be seen that the time constant does not have a major effect on shifting the numbing or sensation times because the concentration peaks do not shift significantly in time. They all peak closely between 22 and 24 minutes. However, the magnitude of the peak value of concentration does change significantly with the time constant. This is expected since if the pressure decays faster, then the lidocaine can more easily diffuse into the tooth from the hole in the first ten minutes allowing more lidocaine to ultimately enter the tooth and thus leading to higher concentration at lower time constants. In other words, the impedance by pressure driven flow is lower. As a result of the peak shifting up and down, smaller time constants have earlier intersections with the numbing concentration and regain sensitivity at a later time. This means that larger time constants aren't actually shifting both time to numbing and time to regain sensitivity later in time to better match the clinical study's window for numbing and regaining sensitivity.

To get a better idea of how the drug was moving through the tooth with the flow present several surface plots of concentration were constructed as shown in Figure 5.

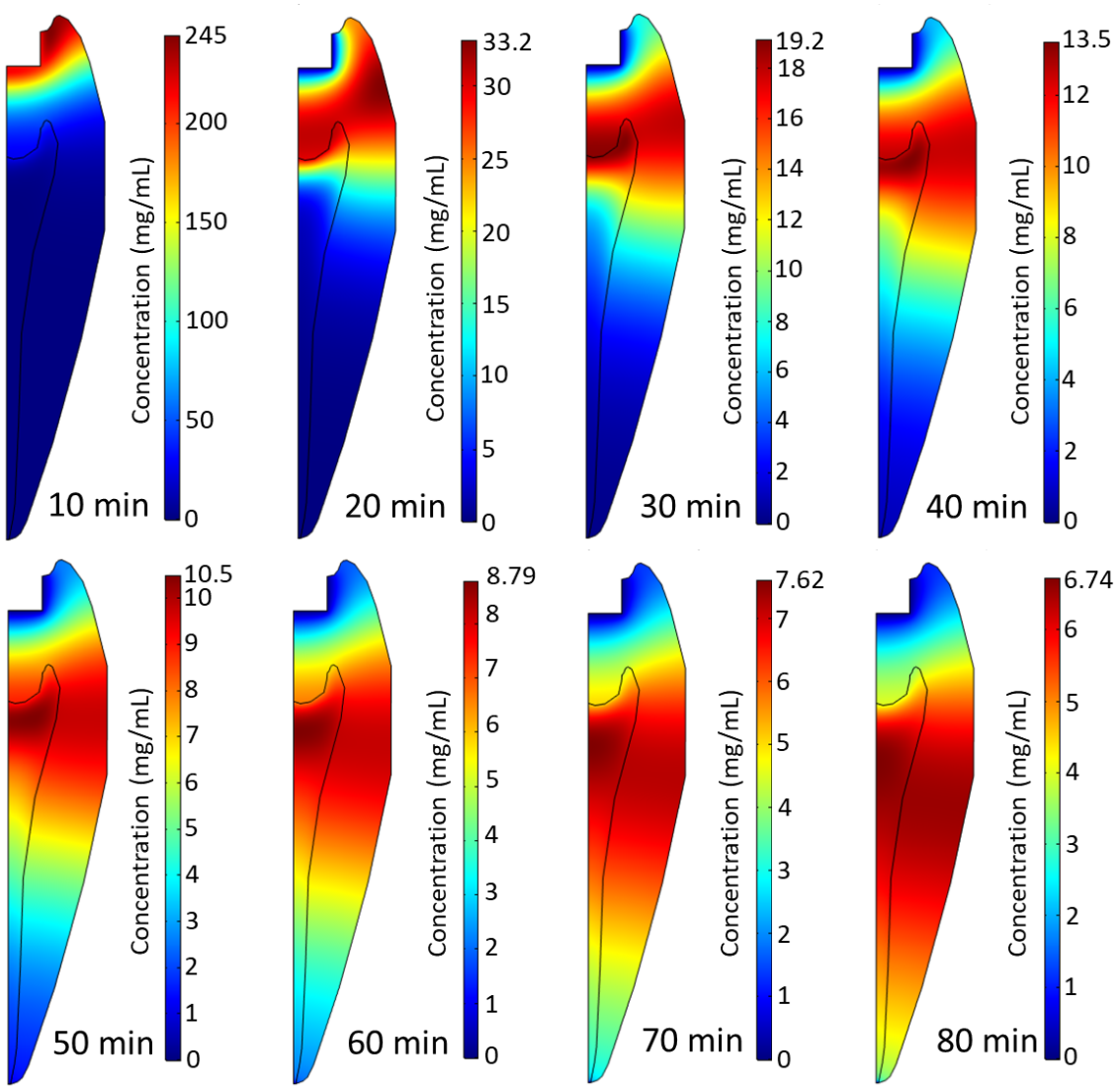

Figure 5: Surface concentration plots. Surface plots of the 2D axisymmetric geometry showing concentration of lidocaine are plotted every 10 minutes between 10 and 80 minutes for the optimized time constant of 7 minutes and 5 seconds. The plots show how the drug moves through the tooth with time. After 10 minutes the concentration of the hole is changed from 500 mg/mL to 0 mg/mL and the lidocaine can also exit from there as shown. As shown the drug moves faster through the dentin layer than the pulp as the dentin diffusivity is 2 orders of magnitude higher than diffusivity in the pulp.

These surface plots (figure 5) highlight the nature of figure 4. It can be seen how the average pulpal concentration rises to a maximum value and then decays with time as the band of concentration passes through the tooth. It can be seen that diffusion is slightly faster in the dentin layer than in the pulp in accordance with the dentin diffusivity, which is two orders of magnitude higher than the pulp (appendix B). As shown in figure 5, more of the lidocaine is moved up into the dentin cusp (top right point of the tooth in figure 5) at first before it moves down. This is compared to a smaller amount that moves straight down from the hole towards the pulp. It is

likely that this has to do with the effect of flow. Therefore, we also looked at how the flow behaves by looking at the velocity profiles in the tooth (figure 6).

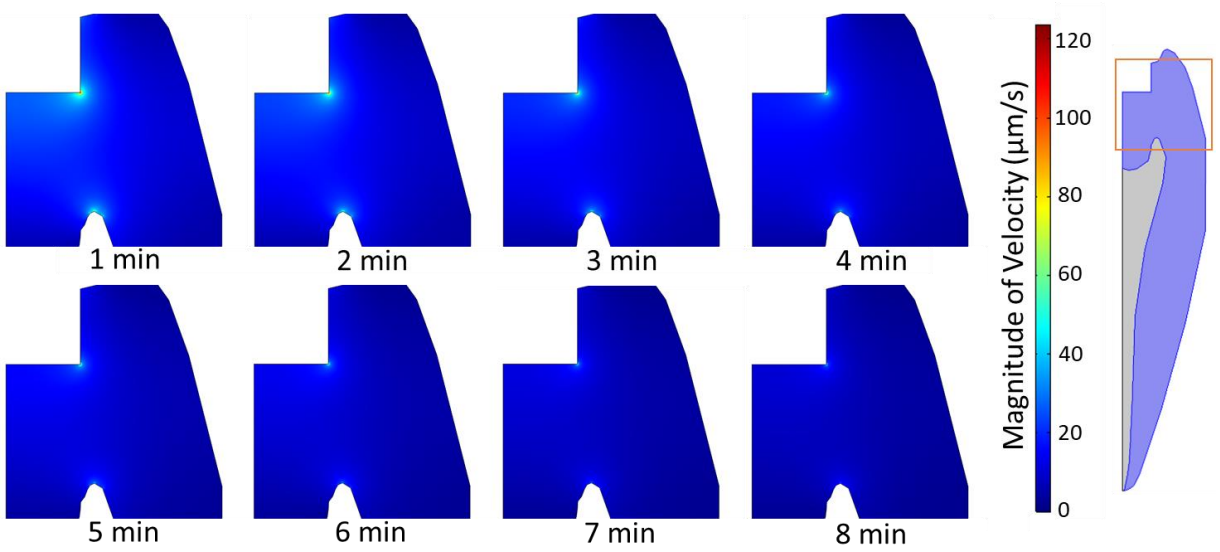

Figure 6: Surface velocity plots. Surface plots of a piece of the 2D axisymmetric geometry showing the magnitude of velocity of the fluid in the dentin between 1 and 8 minutes. The section shown was chosen because it is where there is flow. No flow (or at least very little) is present in the rest of the tooth. Where the flow set up corresponds with figure 5 where the concentration of drug is first pushed from the hole more to the right instead of uniformly out of the hole. The brighter regions at the pulp tip and hole vertex mean higher velocities.

As shown in figure 6, the major flow only exists in the region between the hole and top of the pulp. Predictably, the values for flow are zero far from this region since the pressure gradient is small in these regions. The path of the flow is also predictable due to the fact that the path between the drilled hole and pulp has the shortest distance between pulpal and atmospheric pressure giving it the highest pressure gradient. This results in the high flow velocities found in this region.

In accordance with figure 5, the flow existing in a mostly vertical path between the pulp and the hole at early times appears to influence the lidocaine to diffuse more where the flow isn't present. In this situation it means that more is going towards the cusp as opposed to straight down.

As an added means to confirm that this is what was happening, the model was run again without the flow present and the concentration profiles just after the lidocaine solution in the hole was removed (11 minutes) are compared (figure 7).

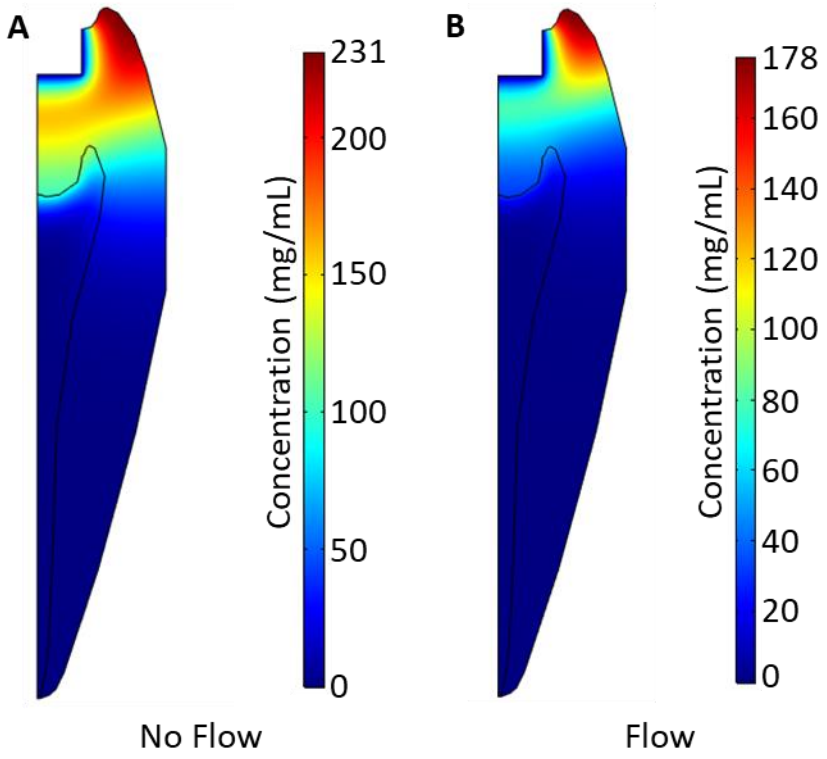

Figure 7: Surface concentration plot at of the tooth with (**A**) no flow and (**B**) flow. Both plots are taken at a time of 11 minutes, the first minute after the lidocaine solution has been removed. It can be seen that the flow impedes movement straight downward into the hole and more (as compared to the plot with flow) is forced sideways into the cusp.

As is evident by figure 7, at 11 minutes (one minute after the lidocaine solution had been removed), the model with flow absent allowed for more of the lidocaine to diffuse downward than into the cusp. This was predicted. In addition, more mass of lidocaine was allowed into the tooth without flow which is consistent with the fact that there is less overall impedance due to flow being removed completely.

4.2 Sensitivity Analysis

Sensitivity analysis was run over every parameter that was approximated from literature. This involved every parameter dealing with flow or lidocaine diffusion except the static equilibrium pressure in teeth since it is well reported in the literature at about 14.1 cmH_2O gauge and thus requires no sensitivity analysis (see input parameters in Appendix B, table 3). Accordingly, we choose to alter the following parameters:

1. Diffusivity of lidocaine in dentin: This value was approximated from experiments in trabecular bone and needs to be investigated to confirm the approximation's validity.
2. Time constant for the pressure decay: This value is researched in the model and sensitivity analysis will confirm its importance in pressure driven flow with solute transport.

3. Hydraulic conductivity: Due to the assumptions made to approximate hydraulic conductivity, it is necessary to confirm the extent of this parameter's effect on the solution.
4. Diffusivity of lidocaine in pulp: This value was approximated from silicone gels of similar water content as pulp and must be investigated to confirm the approximation's validity.
5. Degradation of lidocaine in pulp: The degradation constant likely varies from individual to individual, as a function of dental health, vasculature, and more. Further, this value was also taken from a study on arterial concentrations in injections.

We conducted our sensitivity analysis in figure 8 by varying each of the above parameters by ±10% and charting the percentage change on the average pulp concentration at the time of 24 minutes, which was approximately the peak magnitude of the average pulp concentration for the optimized time constant. This was done because there was the largest difference between curves of different time constants at this time (figure 4). This assures that the sensitivity analysis accounts for as much variability as possible.

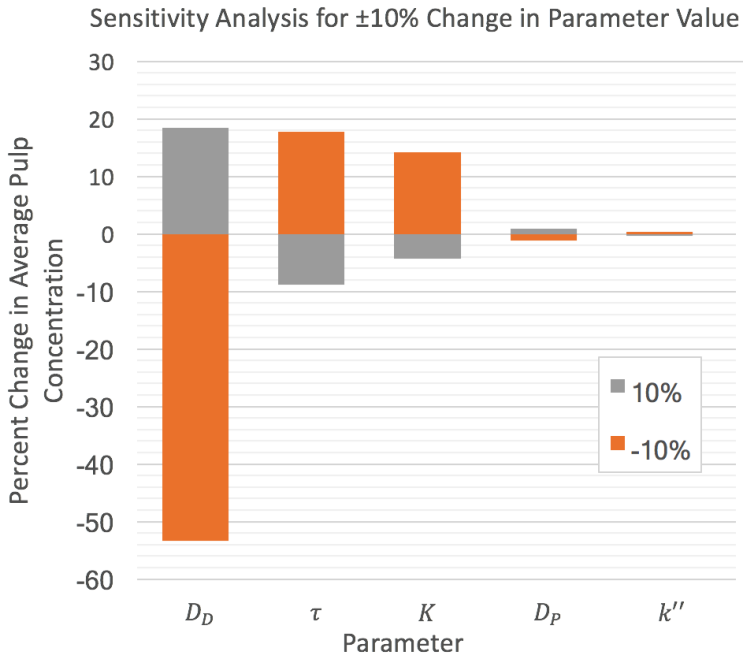

Figure 8: Sensitivity analysis. Displayed is the resulting change in average pulp concentration by changing the parameters of dentin diffusivity, the time constant, hydraulic conductivity of dentin, pulpal diffusivity, and the lidocaine degradation rate constant by ±10%. The two most sensitive parameters other than the time constant are diffusivity in the dentin and hydraulic conductivity. The pulp diffusivity and the degradation rate constant are fairly insensitive.

From the sensitivity analysis, it is obvious that all parameters aside from diffusivity in the pulp and the pulp degradation rate are very sensitive because a ±10% variation in these parameters gives very large percent changes in average pulp concentration at 24 minutes. The parameters that need further analysis are dentin diffusivity and hydraulic conductivity. Although the time constant is sensitive, it is also what we are investigating and needs no further sensitivity

analysis. It is already known that changing how much pressure driven flow is present will affect the amount of drug transport.

It is interesting to see that the parameters had a disproportionate effect on the concentration. This phenomenon is very hard to explain and may be the subject of future research. We can however get an approximate feel for what is going on. This can be done by realizing that the three disproportionate parameters, namely the dentin diffusivity, hydraulic conductivity, and the time constant are all parameters that change impedance to drug transport. To get a better understanding the first thing that was done was to compare the model to one with no flow, which was done in figure 7.

From figure 7, it can be seen that the flow more or less creates an impedance in mostly the vertical direction between the pulp and hole. As a rough approximation we can think of this just being an impedance due to flow. We can also think about an impedance from the hole sideways towards the cusp being a second impedance mostly governed by the dentin diffusivity.

In the case of the hydraulic conductivity and time constant, which control the flow impedance, a lower value of these means less impedance downward and more drug is allowed to diffuse downward instead of sideways toward the cusp. Increasing either of these parameters leads to more impedance due to flow and means more lidocaine moves towards the cusp region. After 10 minutes, the drug is removed from the hole. If more lidocaine moves into the cusp, it is more likely to leave the way it came in and therefore less lidocaine is available to get to the pulp.

In the case of diffusivity, the lower this value gets, the higher the impedance of the sideways transport into the cusp area. If less lidocaine can get farther into the cusp, then less will get to the pulp as most will exit by the hole when the concentration is removed.

The best we can hypothesize is that the ability of the drug to exit the way it came and how much can get into different sections of the tooth leads to a nonlinear change in the average pulpal concentration due to a linear change in parameters (±10%).

4.3 Continued Optimization

Because the dentin diffusivity, D_D and hydraulic conductivity, K are both sensitive parameters and were approximated, their effect on the time constant was also investigated. A range of time constants was found for ±10% D_D and K. This was done with the same optimization function. Hydraulic conductivity produced a range of 6 minutes and 15 seconds to 7 minutes and 40 seconds. Dentin diffusivity produces a range of 5 minutes and 50 seconds to 8 minutes and 10 seconds. Plots of these optimizations are shown in figure 9.

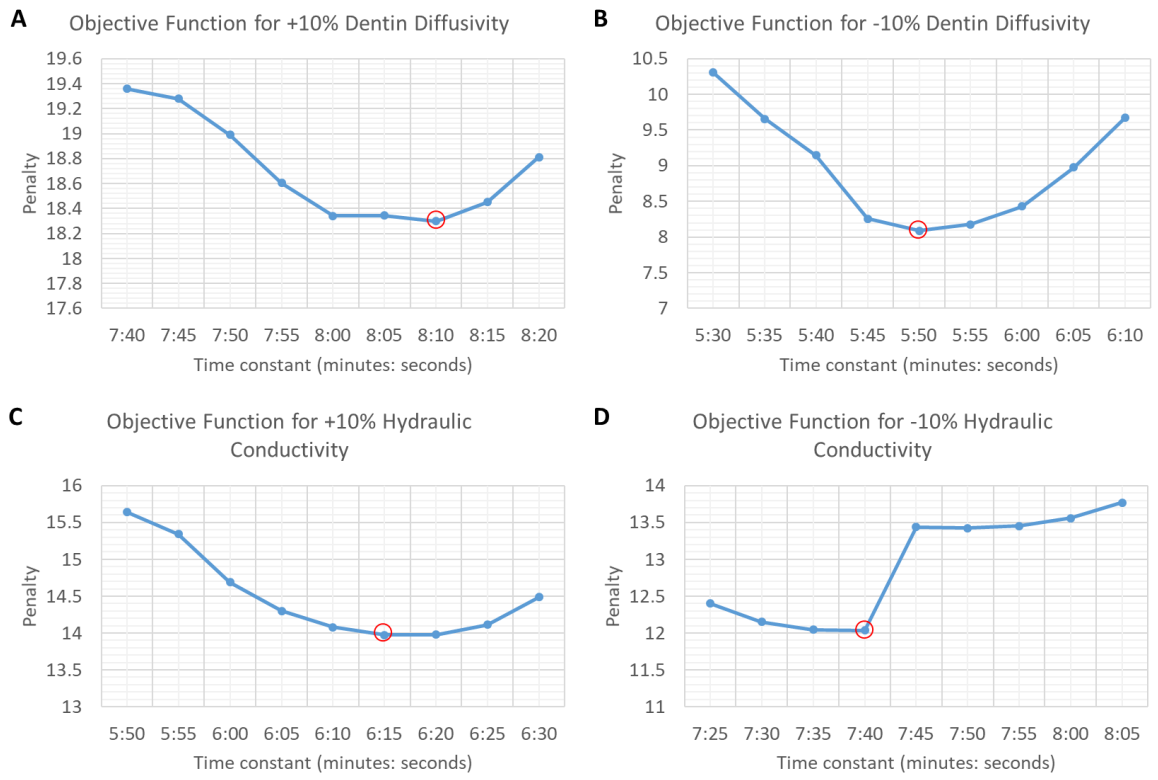

Figure 9: Graph of the objective function for (**A**) a +10% change in dentin diffusivity, (**B**) a -10% change in dentin diffusivity, (**C**) a +10% change in hydraulic conductivity, and (**D**) a -10% change in hydraulic conductivity. The minimum values (circled in red) of these plots give optimized time constants for the different situations in accordance with equations 6 and 7. Optimized time constants are 8 minutes and 10 seconds, 5 minutes and 50 seconds, 6 minutes and 15 seconds, and 7 minutes and 40 seconds for a +10% change in dentin diffusivity, a -10% change in dentin diffusivity, a +10% change in hydraulic conductivity, and a -10% change in hydraulic conductivity respectively.

Looking at these plots, it can be seen that increased hydraulic conductivity and decreased dentin diffusivity lead to a lower time constant. This helps us understand these parameters' effects on drug diffusion. If the hydraulic conductivity is greater (leading to larger velocities) or the dentin diffusivity smaller, then the lidocaine faces more impedance and the time constant must decrease to allow faster pressure decay to compensate for this difference. The opposite is true for the case of decreased hydraulic conductivity or increased diffusion. In this case the lidocaine faces less impedance and the time constant must increase to allow for a slower pressure decay to compensate for this difference.

After seeing these initial effects, we then optimized again with the cases that created the most impedance (a +10% change in K and a -10% change in D_D) and least impedance (a -10% change in K and a +10% change in D_D) (figure 10). This was done to find the range of time constants that could exist for the best and worst case scenarios of lidocaine impedance to give the best idea of ranges that could exist.

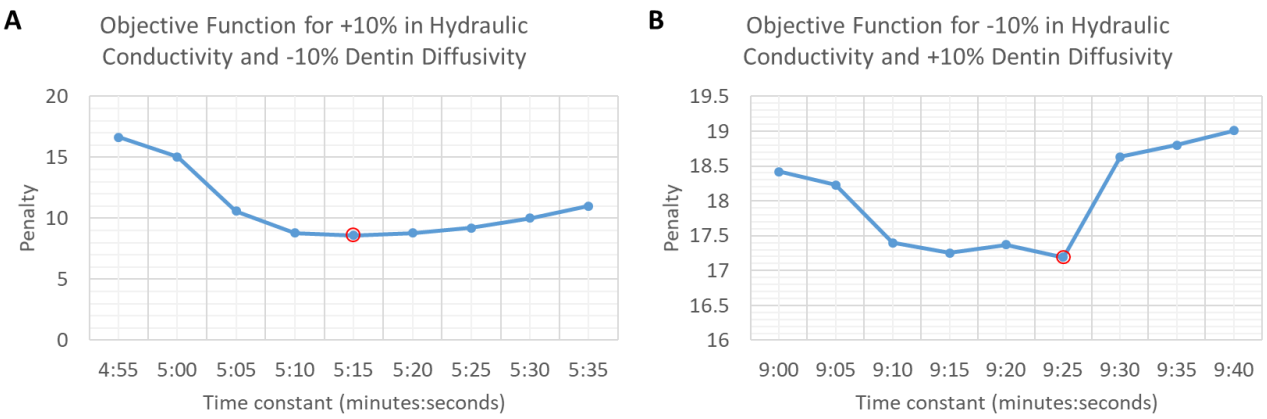

Figure 10: Graph of the objective function for (**A**) the most impedance (a +10% change in hydraulic conductivity and a -10% change in dentin diffusivity) and (**B**) the least impedance (a -10% change in hydraulic conductivity and a +10% change in dentin diffusivity). The results of combining these worst case scenarios give the ultimate range in the time constant for a combination of ±10% changes in dentin diffusivity and hydraulic conductivity. The minimum values (circled in red) of these plots give optimized time constants for the different situations in accordance with equations 6 and 7. The resulting range of time constants is 5 minutes and 15 seconds to 9 minutes and 25 seconds.

The final optimization produced a range of 5 minutes and 15 seconds to 9 minutes and 25 seconds. These optimizations present two situations. One where flow is harder and the time constant is thus smaller and one where flow is easier and the time constant is thus greater.

It is sensible to report a range in order to cover the morphological and parameter value differences that would exist from tooth to tooth as well as some of the error introduced from parameter estimation. The fact that these two parameters were so sensitive, not well-reported in the literature, and differ between people led us to calculate a range of time constants.

In the analysis of these secondary optimizations, as shown in figures 8, 9 and 10 the penalties that resulted are not all near the original penalty. To see why this was the case we plotted the average pulp concentration over time for the highest penalty situation (a +10% change in D_D), and lowest penalty situation (a +10% change in K and a -10% in D_D). Accordingly, the situations that allow for more impedance, move the peak to later times as it takes longer for lidocaine to reach the pulp. This is evident in figure 11.

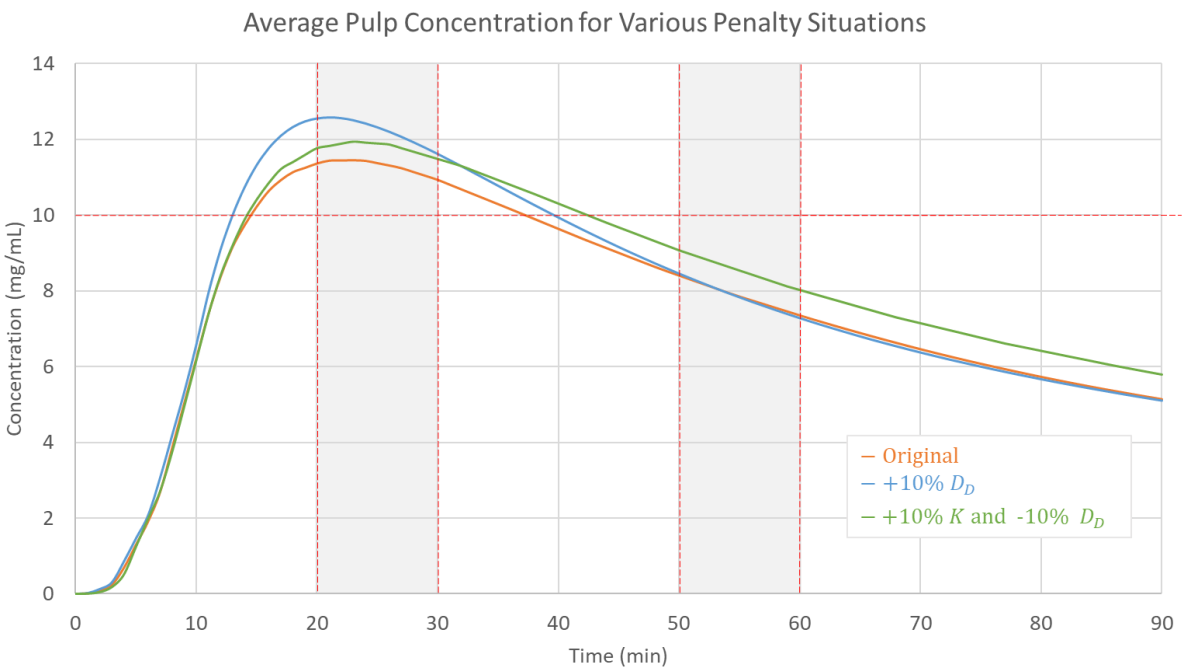

Figure 11: Average pulp concentration for the original solution, a +10% change in dentin diffusivity, and a +10% change in hydraulic conductivity and a -10% change in dentin diffusivity. Plotted is the average pulp concentration for the original solution, largest penalty (+10% change in dentin diffusivity), and smallest penalty (+10% change in hydraulic conductivity and a -10% change in dentin diffusivity). Plots were generated of these to see how the best and worst penalty situations affected the curve.

As shown in figure 11, the lowest penalty situation (a +10% change in K and a -10% in D_D) did indeed record curves that better fit the procedure modeled as that curve numbs and regains sensitivity later than the original, better fitting the data found in the clinical study. This explains why it had a significantly lower penalty than the original solution.

This ends up showing the effect that changing sensitive parameters can have on this model. By using an extreme of a sensitive parameter we get data that better fits with the clinical study performed. On the other hand another combination could generate a worse penalty when optimized. This shows that a sensitive parameter can have a significant effect on how well an optimized time constant will actually fit the data.

5.0 Validation

If we consider the range for time constants, they begin to make sense in the context of the clinical study. The decaying exponential function for pressure came from a study by Brown and Yankowitz. In this study the response of the static pressure in the tooth was measured by inducing an external pressure below and above the natural pressure monitoring its return back to the static equilibrium pressure. Based on their graphs of pressure over time, a first order approximation was reasonable for assuming that the pulpal pressure would behave as a decaying exponential [7].

However, it is also thought that the pulpal pressure in a situation such as the one being modeled could very well increase in time due to inflammation [6]–[8]. At the same time though, the fluid is flowing out of the tooth so there is likely a decrease in pressure with time. For the

controlled situation measured by Brown and Yankowitz, a time constant of about 1 minute was backed out of the graphs. However, it has been shown that with this measurement technique, there is little inflammation that occurs [6]. Therefore, it's reasonable that the time constant of our pressure function should be larger than what was found since the procedure would cause inflammation (but a decay of pressure should still exist because the fluid is still flowing out in addition to this). With this study we were able to find a time constant that was 7 minutes and 5 seconds.

It has been shown that a 2% lidocaine solution applied to the tooth instead of a 50% solution does not numb the tooth [3]. To verify this, the calculation was carried out in COMSOL using a 2% solution. The computation showed a maximum value in average pulp concentration of 0.344 mg/mL which is far below the 10 mg/mL threshold value for numbing, consistent with the clinical study.

Finally, since the concentration plots showed a curve that breached above and below the 10 mg/mL threshold along the same time scale as the study (30 to 60 minutes), means the model reasonably mimics the real physical process. Although it is not perfect, with the parameters that were sensitive and had to be approximated this model still gives a reasonable repetition of the clinical results.

To further validate the model was working we recomputed the solution using the optimized time constant, but without any fluid flow. As expected, as shown in figure 12A, the average pulpal concentration is much lower when there's flow resisting diffusion of lidocaine, verifying the model is working.

We also expected to see that the pressure driven flow in our model has the effect of delaying the time of numbing as predicted by Pashley et al. [5]. They predicted that pressure should create a solvent drag and hinder diffusion which translates to later numbing times. Figure 12A shows that the maximum concentration shifts marginally from 19 minutes to 23 minutes.

As an extra precaution to ensure that the peak of the average pulpal concentration can be pushed later in time the static pressure was increased ten times higher to an unphysical pressure. The same shifting occurs when unphysically large pressures are used as figure 12B shows. This confirms that the marginal time to numbing shift actually occurs in our model.

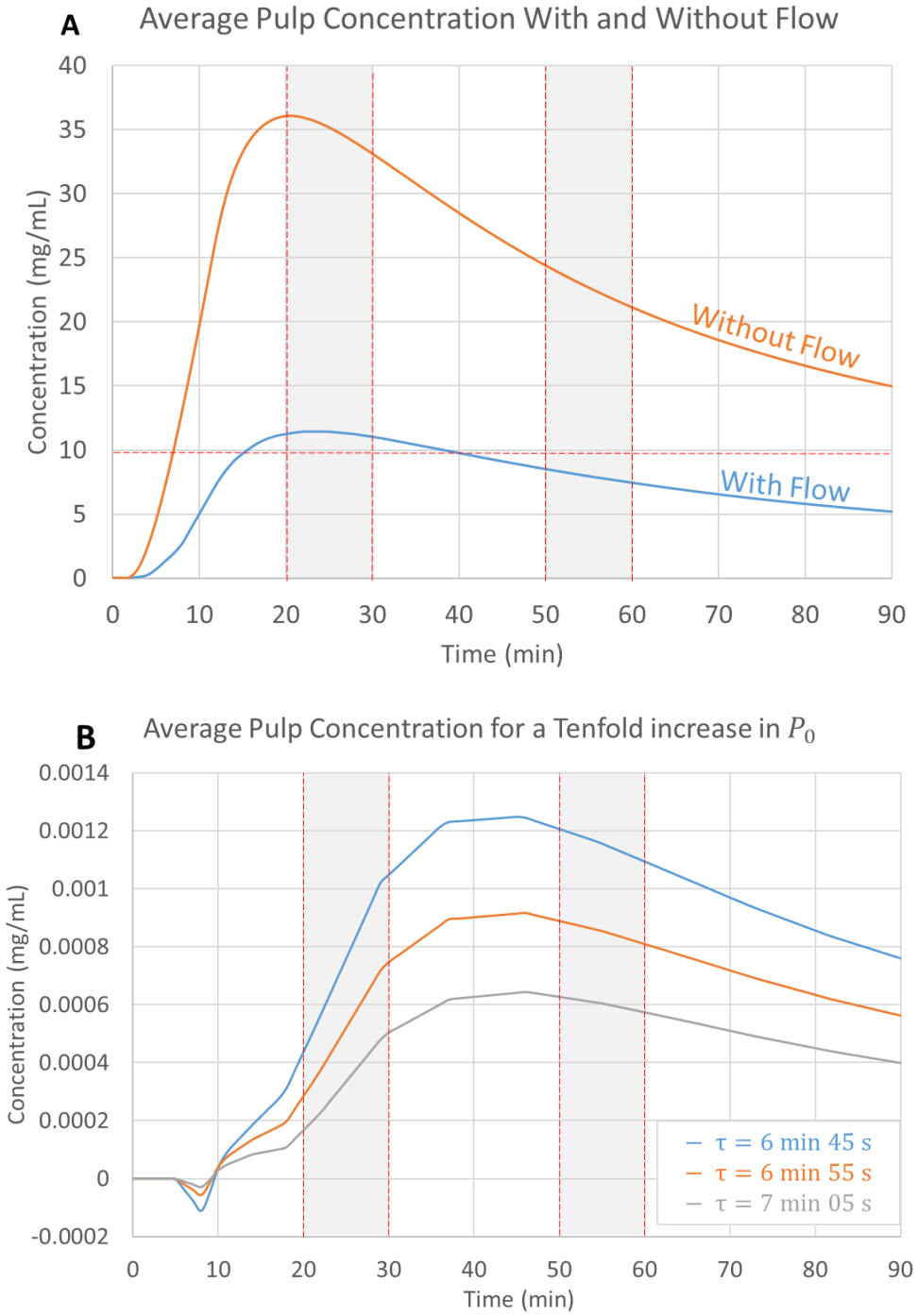

Figure 12: (A) Plot of average pulp concentration for existence of flow and no existence of flow. A larger concentration exists for the no flow situation than the with flow situation as expected since there is less impedance. Existence of flow shows a subtle shift of the peak to latter in time than without flow. This is expected due to the impedance with flow. **(B)** Plot of average pulp concentration for three arbitrary time constants with a tenfold increase in the static pressure. Existence of the tenfold increase is able to shift the peak latter in time. The plots show unphysical values which doesn't matter since all the information needed is about the peak behavior with time.

Both of these plots show that the concentration versus time plots shift left and right due to pressure changes. This is expected because a higher pressure will increase solvent drag on the lidocaine diffusing into the tooth. It thus takes more time to get to the tooth. With this unphysical increase in the pressure, the plot seems to peak in the correct zone (between 30 and 60 minutes). However, expectedly, the high pressure stops drug from reaching the numbing concentration in the pulp. Despite this it proves the point that the model is working as expected.

6.0 Concluding Remarks and Future Directions

The model completed its design objectives of defining pressure dynamics within the tooth by comparison to a clinical study. The model also concludes reasonably that pulp pressure can be modeled with first order decay with a time constant on the range of about 5 to 9 minutes, based on the validation analysis. Computing this range is especially relevant when person to person parameter values and tooth morphologies differ. This quantitative analysis of pulp dynamics is relevant to further investigation of topical procedures for teeth as well as mechanistic understanding of the tooth and particularly the pulpal pressure behavior.

Several design recommendations are presented here for future work. Due at least partly to the inflammation effects in the tooth, the pressure equation is likely not a perfect first order decay. Inflammation remains present even during diffusion and research into inflammation's effect would be beneficial to the model. Further, some values were estimated based off the literature leading to mathematical approximation error in the model. There is also continued complexity in the person to person morphological differences, differences in diffusivity throughout dentin, and the fact that the tooth hole was assumed to be drilled in the center even though the clinical study drilled on the cusp. This convenient 2D axisymmetric assumption could be dealt with by modeling in 3D. Perhaps editing a CT scan of a tooth would provide an exact geometry. Another further topic of research is investigation of why the sensitivity analysis had disproportionate effects.

This model does have a few limitations. Foremost, for all computations the average pulp concentration was used as a metric of analysis for whether the tooth was sensitive or numb. This is a sizeable assumption based on the innervation of the tooth pulp. It is possible that local anesthetic acting on the nerve tips closest to the dentin is enough for the tooth to lose sensitivity. If this is the case, then it would be inaccurate to use the average pulp concentration as a metric for whether the tooth is sensitive. Future studies could further consider the innervation architecture in the tooth pulp and how this affects the region of interest for determining if the pulp has reached numbing concentration. There is also the approximation of 10 mg/mL as the numbing concentration from ropivacaine and the assumption of no partition coefficients. These may not be true and along with other approximated parameters could be fixed with more experimental data on the matter. Nevertheless, our model gives a reasonable model to start understanding pulp pressure dynamics.

Appendix A: Mesh Convergence and Mesh

A mesh convergence was performed on the average pulp concentration at 24 minutes, using a time constant of 7 minutes and 5 seconds. The average pulp concentration was chosen since this is our most important parameter and the one used against the experimental study as a comparison to optimize the time constant. The optimized time constant was used because this is what was solved for. The time of 24 minutes was chosen because this was approximately the peak of the average concentration in the pulp and it appeared to vary the most between different mesh sizes.

6 free triangular meshes were ran in the convergence. We began by using some of the built in mesh sizes in COMSOL namely, Fine, Extra Fine, and Extremely Fine. We also went finer than the finest built in mesh with three more meshes we named Even Finer 1, Even Finer 2, and Even Finer 3, each more fine than the last. The characteristics of these meshes are given in table 3.

Table 3: Characteristics of meshes used in the mesh convergence analysis.

Mesh Size Name	Maximum Element Size (m)	Minimum Element Size (m)	Maximum Element Growth Rate	Curvature Factor	Resolution of Narrow Regions
Finer	8.60×10^{-4}	2.91×10^{-6}	1.25	0.25	1
Extra Fine	4.65×10^{-4}	1.74×10^{-6}	1.20	0.25	1
Extremely Fine	2.32×10^{-4}	4.65×10^{-7}	1.10	0.20	1
Even Finer 1	2.00×10^{-4}	4.00×10^{-7}	1.00	0.15	1
Even Finer 2	1.00×10^{-4}	3.50×10^{-7}	1.00	0.15	1
Even Finer 3	8.00×10^{-5}	1.00×10^{-7}	1.00	0.10	1

The first three mesh names refer to the built in meshes in COMSOL. The last three are not built in.

The 6 meshes were then computed and the maximum element size versus the average pulp concentration at 24 minutes was plotted (figure 13). The resulting plot shows that a convergence exists at maximum element size of 200 μm (corresponding to the mesh Even Finer 1) since the solution doesn't change at smaller meshes beyond this.

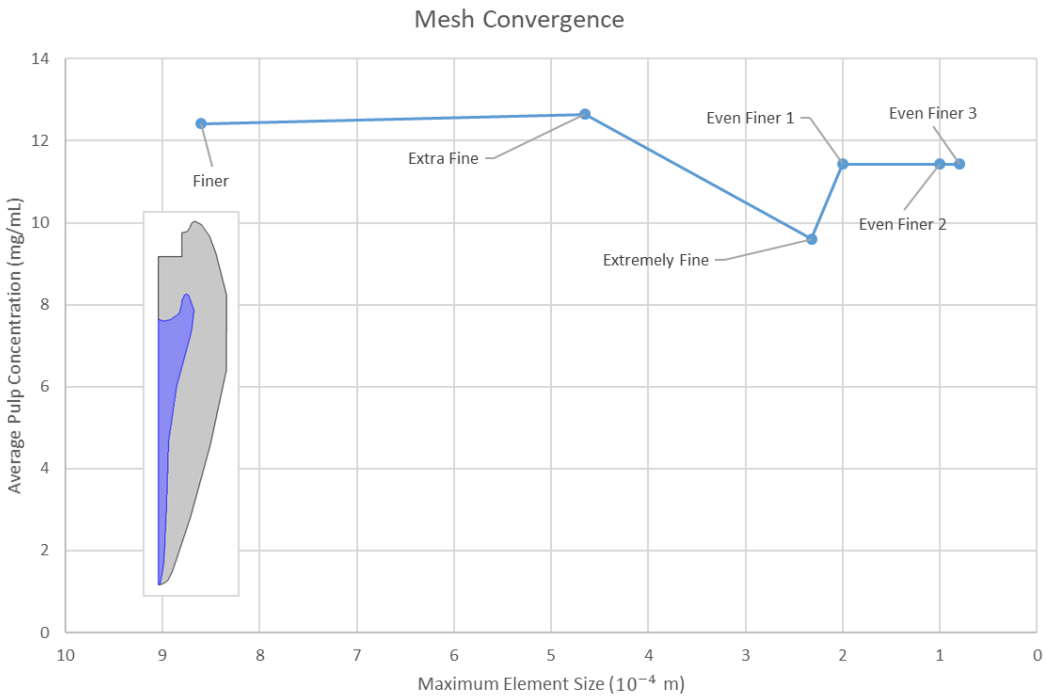

Figure 13: Mesh convergence. Mesh convergence was run by checking the average pulp concentration (domain shown in blue in the graphic) at 24 minutes (approximately the time of the peak of average pulpal concentration) using the optimized time constant of 7 minutes and 5 seconds. The mesh shows convergence with a maximum element size of 200 µm at size even finer 1. A 100 µm mesh at size even finer 2 was selected for all computations as the computation time was not much greater.

Despite the fact that figure 1 shows a convergence at a maximum element size of 200 µm, using a maximum element size of 100 µm had a computation time of about 1.5 minutes per time constant. Thus this smaller mesh, namely Even Finer 2, was used since the time to compute was not significant. A visual of the mesh is shown in figure 14.

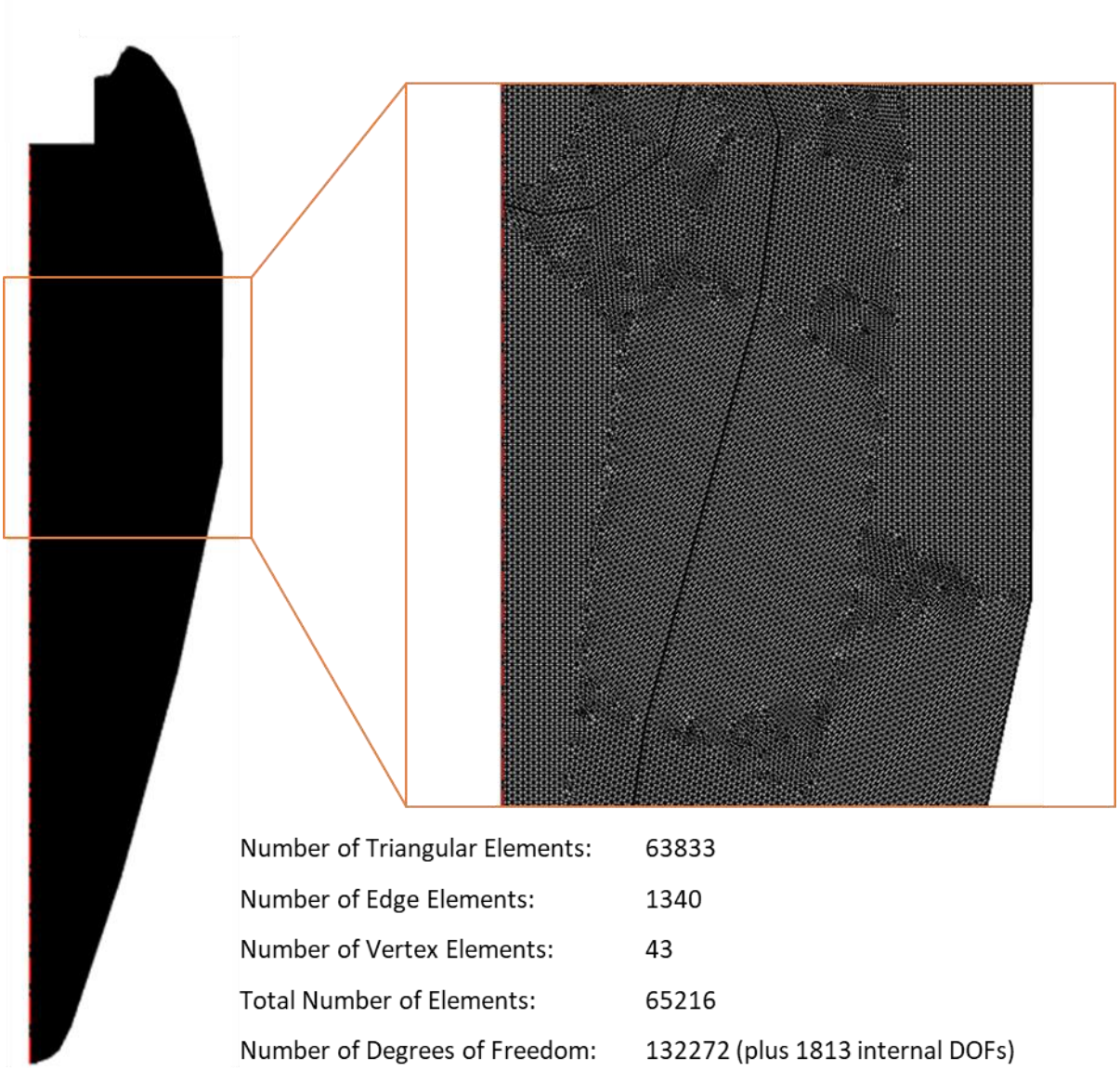

Figure 14: Mesh and mesh statistics. This was the mesh used to do computations. This mesh was size even finer 2 as given in table 4. The mesh had a maximum element size of 100 µm. Runtimes took approximately 1.5 minutes per time constant.

The resulting mesh used shown in figure 14 ended up having a total of 65216 elements and 132272 degrees of freedom.

Appendix B: Input Parameters

Input parameters used in the model are given in table 4 as well as a basis of how they were selected.

Table 4: Input parameters.

Description	Symbol	Value	Source/Methods
Static Equilibrium Pressure	P_0	1382.74 Pa (gauge)	Ciucchi et. al. [6]
Hole Boundary Concentration	c_0	500 mg/mL	50% (w/v) lidocaine value used in clinical study [3].
Diffusivity of Lidocaine in Dentin	D_D	1×10^{-8} m^2/s	From Mokhtarzadeh [22]. Diffusivity of generalized drug in trabecular bone (similar to dentin).
Diffusivity of Lidocaine in Pulp	D_P	7.82×10^{-10} m^2/s	Pjanovic et al. Based on lidocaine diffusion in hydrogel of similar water content as pulp [23].
Degradation of Lidocaine in Pulp	k''	1.20338×10^{-4} 1/s	Found from half-life in Local Anesthetics book, arterial blood concentrations after intravenous infusion of drug [24].
Hydraulic Conductivity of Dentin	K	5×10^{-11} m^2/Pa/s	Approximated from Bone, Rat Brain, Tumor tissue at 3.5×10^{-9}, 2×10^{-12}, and 5×10^{-12} m^2/Pa/s respectively. Dentin is porous like bone but also has tissue-like characteristics [25]–[27].
Initial Concentration of Lidocaine	N/A	0 mg/mL	No lidocaine was present in the patient before the study began [3].
Initial Pressure in Dentin	N/A	102707.75 Pa (absolute)	Ciucchi et. al. (Human tooth) [6].

Table lists all relevant input parameters used in this model. Sources and methods for the numbers are also included. Numbers were converted from the units given in the sources to units used in this model.

Appendix C: Numerical Implementation

The equations were solved using a commercial finite elements package, COMSOL Multiphysics ® version 5.3 (COMSOL Inc., Stockholm Sweden). Two modules in this software were used: *Transport of Diluted Species*, and *Darcy's Law*. *Transport of Diluted Species* solved for the concentration of lidocaine HCl in the tooth (equations 1 and 2). *Darcy's Law* solved for the velocity of pulpal fluid in the dentin (equation 5). A backward time difference discretization with free steps and a maximum order of 2 was used. The relative tolerance value was set at 0.01 and the absolute tolerance set at 0.1. A free triangular mesh containing 63833 triangular elements, 1340 edge elements, and 43 vertex elements with max element size of 100 μm was constructed. This resulted in 132272 (plus 1813 internal) degrees of freedom. The equations were one way coupled where the velocity from the *Darcy's Law* module was used in the *Transport of Diluted Species* Module. A MUltifrontal Massively Parallel sparse direct Solver (MUMPS) was used. Run times took about 1 minute and 30 seconds per time constant with the optimized solution taking 1 minute and 29 seconds to compute. The optimized time constant used 1.38 GB of physical memory and 1.59 GB of virtual memory with a 3.4 GHz Intel ® Core™ i7-6700 CPU processor.

Two of the boundary conditions were time dependent. The first was the concentration being removed after 10 minutes. This was implemented into COMSOL by using an interpolation function where the concentration was left at 500 mg/mL for the first 600 seconds and 0 mg/mL from 601 seconds onward. The exponential decay of pressure was implemented by using an analytical function and entering the specified equation for exponential decay, equation 5.

Figure 15 show the typical log output shown after a run with the optimized time constant.

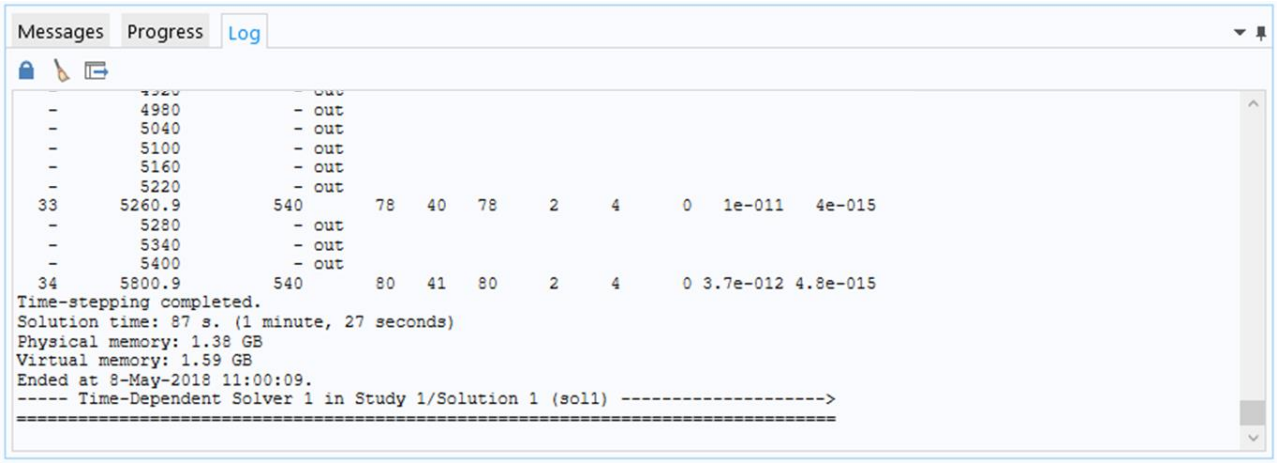

Figure 15: COMSOL log output window. This output shown is for a run on the optimized time constant 7 minutes 5 seconds. Run time is 1 minute and 27 seconds which is typical of the run time per time constant.

Appendix D: References

[1] M. P. M. Bear, B. Connors, “Local anesthesia: Lidocaine’s mechanism of action,” in *Neuroscience: Exploring the Brain*, 4th ed., Philadelphia, PA: Medknow Publications, 2016, p. 102.

[2] American Dental Association, “Tooth anatomy,” *Mouth Healthy*. [Online]. Available: https://www.mouthhealthy.org/en/az-topics/t/tooth. [Accessed: 28-Feb-2018].

[3] P. Rirattanapong, K. Vongsavan, P. Kraivaphan, N. Vongsavan, and B. Matthews, “Effect of the topical application of 50% lignocaine hydrochloride on the sensitivity of dentine in man,” *Arch. Oral Biol.*, vol. 58, no. 10, pp. 1549–1555, Oct. 2013.

[4] M. Ozawa, H. Ikeda, and H. Suda, “The effect of pulpward pressure on the response to 50% lidocaine (lignocaine) applied to exposed dentine in cats.,” *Arch. Oral Biol.*, vol. 47, no. 4, pp. 333–6, Apr. 2002.

[5] D. H. Pashley and W. G. Matthews, “The effects of outward forced convective flow on inward diffusion in human dentine in vitro,” *Arch. Oral Biol.*, vol. 38, no. 7, pp. 577–82, Jul. 1993.

[6] B. Ciucchi, S. Bouillaguet, J. Holz, and D. Pashley, “Dentinal fluid dynamics in human teeth, in vivo,” *J. Endod.*, vol. 21, no. 4, pp. 191–194, Apr. 1995.

[7] A. C. Brown and D. Yankowitz, “Tooth pulp tissue pressure and hydraulic permeability,” *Circ. Res.*, vol. 15, pp. 42–50, Jul. 1964.

[8] B. S. Manjunatha, *Textbook of Dental Anatomy and Oral Physiology : Jncluding Occlusion and Forensic Odontology*. Jaypee Brothers Medical Publishers, 2013.

[9] M. Zezo, “Permanent posterior teeth,” *Pocket Dentistry*. [Online]. Available: https://pocketdentistry.com/17-permanent-posterior-teeth/. [Accessed: 13-Feb-2018].

[10] S. Blausen, “Medical gallery of Blausen Medical 2014,” *WikiJournal Med.*, vol. 1, no. 2, p. 10, 2014.

[11] E. A. Naumova, T. Dierkes, J. Sprang, and W. H. Arnold, “The oral mucosal surface and blood vessels,” *Head Face Med.*, vol. 9, no. 1, p. 8, Dec. 2013.

[12] D. L. Vreeland, A. Reader, M. Beck, W. Meyers, and J. Weaver, “An evaluation of volumes and concentrations of lidocaine in human inferior alveolar nerve block,” *J. Endod.*, vol. 15, no. 1, pp. 6–12, Jan. 1989.

[13] E. El-Sharrawy and J. A. Yagiela, “Anesthetic efficacy of different ropivacaine concentrations for inferior alveolar nerve block.,” *Anesth. Prog.*, vol. 53, no. 1, pp. 3–7, 2006.

[14] C. G. Castro, F. R. Santana, M. G. Roscoe, P. C. Simamoto, P. C. F. Santos-Filho, and C. J. Soares, “Fracture resistance and mode of failure of various types of root filled teeth,” *Int. Endod. J.*, vol. 45, no. 9, pp. 840–847, Sep. 2012.

[15] F. B. C. Ghazali, “Permeability of dentine.,” *Malays. J. Med. Sci.*, vol. 10, no. 1, pp. 27–

36, Jan. 2003.

[16] V. D. Kumar, “A scanning electron microscope study of prevalence of accessory canals on the pulpal floor of deciduous molars.,” *J. Indian Soc. Pedod. Prev. Dent.*, vol. 27, no. 2, pp. 85–9, 2009.

[17] S.-Y. Kim, S.-H. Lim, S.-N. Gang, and H.-J. Kim, “Crown and root lengths of incisors, canines, and premolars measured by cone-beam computed tomography in patients with malocclusions,” *Korean J. Orthod.*, vol. 43, no. 6, p. 271, 2013.

[18] T. Al-Gunaid, M. Yamaki, and I. Saito, “Mesiodistal tooth width and tooth size discrepancies of Yemeni Arabians: A pilot study.,” *J. Orthod. Sci.*, vol. 1, no. 2, pp. 40–5, Apr. 2012.

[19] “Oral Histology: Dental Pulp Lecture,” *University of Kentucky*. [Online]. Available: http://www.uky.edu/~brmacp/oralhist/module4/lecture/oh4lect.htm. [Accessed: 28-Feb-2018].

[20] D. E. Cutright and S. N. Bhaskar, “Pulpal vasculature as demonstrated by a new method,” *Oral Surgery, Oral Med. Oral Pathol.*, vol. 27, no. 5, pp. 678–683, May 1969.

[21] T. Iijima and J.-Q. Zhang, “Three-dimensional wall structure and the innervation of dental pulp blood vessels,” *Microsc. Res. Tech.*, vol. 56, no. 1, pp. 32–41, Jan. 2002.

[22] H. Mokhtarzadeh, M. S. Aw, K. A. Khalid, K. Gulati, G. J. Atkins, D. M. Findlay, D. Losic, and P. Pivonka, “Computational and experimental model of nano-engineered drug delivery system for trabecular bone.”

[23] R. Pjanović, N. Bošković-Vragolović, J. Veljković-Giga, R. Garić-Grulović, S. Pejanović, and B. Bugarski, “Diffusion of drugs from hydrogels and liposomes as drug carriers,” *J. Chem. Technol. Biotechnol.*, vol. 85, no. 5, pp. 693–698, May 2010.

[24] G. R. Strichartz, *Local Anesthetics*. Springer Berlin Heidelberg, 1987.

[25] L. J. Liu and M. Schlesinger, “Interstitial hydraulic conductivity and interstitial fluid pressure for avascular or poorly vascularized tumors,” *J. Theor. Biol.*, vol. 380, pp. 1–8, Sep. 2015.

[26] T. L. Nobrega, “An infusion-pressure system to determine hydraulic conductivity of soft biological tissues and monitor clinical infusions,” *Thesis*, vol. 53, no. 9, pp. 1689–1699, 2010.

[27] J. Hwang, W. C. Bae, W. Shieu, C. W. Lewis, W. D. Bugbee, and R. L. Sah, “Increased hydraulic conductance of human articular cartilage and subchondral bone plate with progression of osteoarthritis,” *Arthritis Rheum.*, vol. 58, no. 12, pp. 3831–3842, Dec. 2008.