Maintaining Caffeine Concentration during Exercise in Quadriceps via Injection of Caffeine into the Femoral Artery

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EXECUTIVE SUMMARY

Caffeine is a performance enhancer. Despite being famous (or infamous) for its stimulatory effect on the brain, caffeine is also known to cause muscle contracture. This study aims to investigate the effects of caffeine on sports performance by modeling the concentration profile in a portion of the quadriceps of an athlete injected with caffeine via the femoral artery. Obtaining a working model of the diffusion and degradation of caffeine within the muscle, we were able to replicate the concentration profile of the optimal caffeine dose for performance (45 μM) while the body is at rest. During exercise, the concentration levels in the muscle deviate from this profile due to the more acidic pH and higher blood velocity. Using our model, we were able to determine which of two methods is preferable to maintain the concentration profile during exercise: (1) one injection at time t= 0 s of 180 μM or (2) five injections of 60 μM doses or four injections of 75 μM, with the first at time t= 0 s. Our results indicated that a single dose of 180 μM fell within ± 15% of the optimal concentration profile only at t= 12000 s to t= 19800 s. The smaller 60 μM or 75 μM doses taken a total of 4 or 5 times, respectively, stayed within the bounds of the optimal concentration profile throughout the 10-hour duration of the study.

INTRODUCTION

Background

Although it has been the object of study since before 1860, caffeine and its effects on muscle are still unclear today. In 1911, scientist Fred Ransom determined that caffeine generated "rigor" in frog muscle (Ransom, 1911); more recently, researchers at the University of Sydney have shown that caffeine consumption increases resting Ca^{2+}levels in muscle fiber, thereby increasing the sensitivity of muscle's sarcoplasmic reticulum (SR) to Ca^{2+} levels as well as increasing the force of muscle contraction (Allen & Westerblad, 1995). Although researchers hypothesize that increased sensitivity of the SR Ca^{2+} channels in muscle fibers increase performance, it is unclear to what extent this improvement is due to caffeine's direct effect on muscle.

When caffeine is ingested, it is directed through the gastrointestinal tract to the stomach and small intestine, where a large portion is absorbed into the blood stream. Once in the blood, caffeine flows to the capillaries where it easily diffuses through capillary pores into the interstitial fluid, and finally to the cells themselves. Recently, new techniques to increase alertness have been introduced, including the caffeine patch. In this case, caffeine diffuses through the dermal and epidermal layers to capillaries, where it is then transported to the rest of the body via the blood (Guyton, 2011). The caffeine in blood induces a stimulatory effect on the adrenergic receptors in the brain, increasing the heart rate. The increased heart rate induces an increase in oxygen in the muscle, increasing muscle function. Caffeine has, therefore, long been known to enhance performance for athletes in endurance sports.

Though the ergogenic effects of caffeine can be attributed mostly to the stimulation of the nervous system, the direct effect of caffeine in muscle has been shown; however, the extent of the role caffeine plays in muscular performance is still uncertain. To develop more of an understanding of caffeine's role in muscle performance and to analyze the physiological consequences, the optimal concentration of caffeine in the muscle must be maintained. Nevertheless, studying the effects of caffeine in muscle by maintaining caffeine concentration is further complicated by the effects of pH and blood velocity changes during exercise. During increased physical activity, there is a buildup of lactate, which causes a decrease in pH (Robergs, Ghiasvand, & and Parke, 2004). This leads to a

subsequent increase in the degradation of caffeine in the muscle. Additionally, increased exercise will lead to a higher blood velocity in the capillaries, leading to decreased diffusion of caffeine into the muscle. The study of the caffeine concentrations in the muscle is, therefore, modeled using COMSOL in order to visualize and understand the diffusion of caffeine, particularly in situations of increased exercise.

The COMSOL model provides a quantified analysis of the diffusion of caffeine from the well-mixed capillary, into the quadriceps after direct injection into the blood stream. More specifically, the model will aid in determining the method to maintain optimal concentration during decreased pH and blood velocity as a result of physical exertion. Using the COMSOL model the dosage and time intervals of caffeine injection in each of these conditions in order to maintain an optimal concentration in the tissue will be determined. The two methods tested using the model will be either the injection of a single large dose of caffeine into the muscle before exercise or the injection of smaller doses taken at 5 time points during exercise.

Design Objectives

The primary objective of this project is to determine the dosage of caffeine required to maintain an optimum concentration in the tissue when the subject being injected is undertaking physical activity and at what time intervals the dosage of caffeine should be injected. In order to do this, we will first develop an experimentally validated model to study the diffusion of caffeine after injection directly into the blood stream, bypassing any gastrointestinal effects. As a model, this delivery mechanism of caffeine allows better surveillance of reactions and degradation in muscle fibers. By modeling the diffusion, degradation, and removal of caffeine over time in COMSOL, we can determine whether the levels of caffeine in muscle remain significant over a period of 10 hours. Once this model is developed, we will vary specific parameters—mainly time of injection, degradation rates, and blood velocity in the capillary—to determine the concentration profiles in the tissue during a state of rest and a state of physical activity. By varying these parameters, we will successfully be able to find an optimal dosage to inject and be able to find what time interval, whether it is initially or at successive intervals for an individual who is exercising.

Problem Schematic

Previous studies of competitive athlete endurance during prolonged exercise at 85% of maximal oxygen consumption show that the optimal caffeine dose is 3 to 6 mg/kg (Graham & Spriet, 1995). This model assumes a male test subject weighing 70 kg and a caffeine dose of 6mg/kg, which consists of 420 mg of caffeine. To obtain this dosage, the subject is required to consume 5 Red Bull energy drinks, containing 80 mg each (Wilson, 2010). Thus, 45 μM will be injected into the femoral artery to bypass any unwanted effects of other organs on caffeine concentration at the site of interest (Graham & Spriet, 1995). After injection, 100% of the caffeine dose will be deposited in the circulatory system near the quadriceps, where it will travel through the artery and arterioles to the capillaries where it will then diffuse into the quadriceps.

By modeling a typical athlete's capillary and surrounding quadriceps muscle in COMSOL, we can generate a concentration profile of caffeine in the muscle dependent on the influx of caffeine from a nearby arteriole into the capillary and tissue and the elimination of caffeine through the nearby venule and degradation in the blood and tissue [See Figure 1].

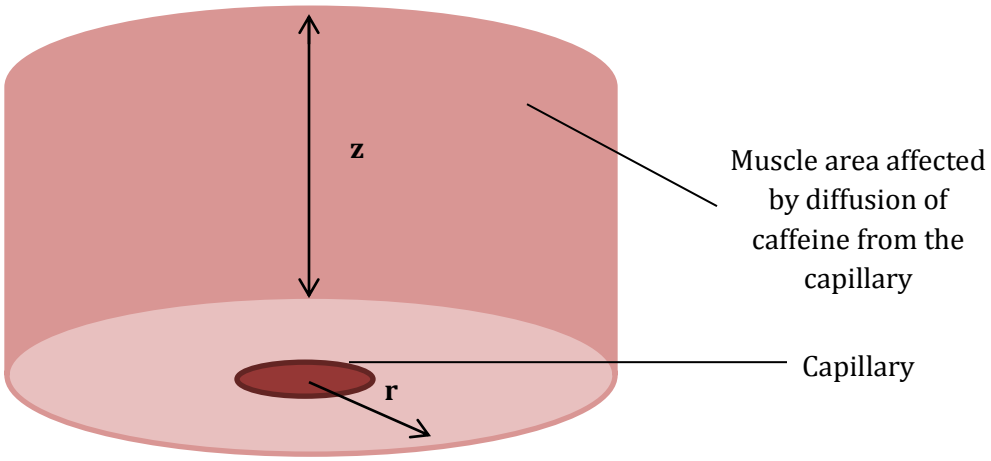


Figure 1. *3-D representation of capillary in affected surrounding muscle tissue. This diagram represents the small portion of the quadriceps that receives nutrients from the chosen capillary.*

Thus, the level of caffeine in the site of interest is modeled using the governing equation for mass transfer with convection, conduction, and generation terms. The Navier-Stokes equation is applied to the blood stream domain to determine the velocity of blood flowing past the tissue, while the mass transfer applies to both the blood stream and the muscle [See Appendix A for derivation]. By inputting the density and viscosity of blood into COMSOL, the model can give an accurate velocity for blood. The inlet boundary condition is set at a velocity of 470 x 10^{-6} m/s and the capillary wall is set as no slip. COMSOL then solves the mass transfer equation in the blood stream, using input parameters listed in Appendix A. Figure 2 details the corresponding schematic that is implemented in COMSOL.

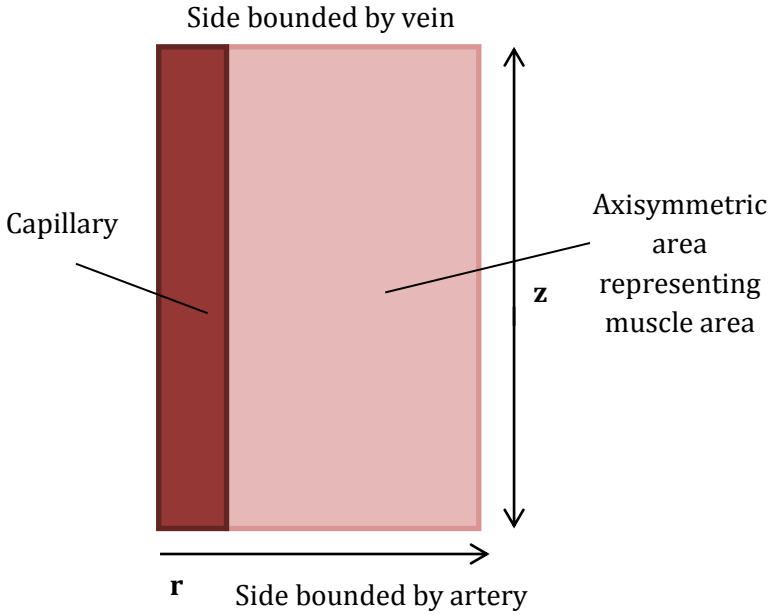


Figure 2. *Due to axisymmetric conditions, the effected muscle area can be accurately represented by modeling a cross-section of half of the cylinder. In COMSOL, this is implemented by choosing 2-D Axial Symmetry geometry.*

Using this model, we will study two methods of caffeine injection at two states: (1) an at-rest state, in which the male subject is seated and is not participating in any rigorous activity, and (2) a during-exercise state, in which the male subject is exerting significant amounts of energy and his body's physiological conditions reflect the undertaking of the rigorous activity. Note that during exercise, the velocity of the blood flow and the degradation rates are varied [See Appendix A for property values] to account for the increased blood flow and the effects of increased pH.

Because exercise conditions will decrease the concentration of caffeine in the muscle due to an increased degradation term and an increased blood velocity, we will need to examine two different methods of caffeine administration. In the first method, a large single dose of caffeine will be injected at the initial time, and the resulting concentration profile will be determined. In the second method, multiple smaller doses will be injected at periodic time intervals and an overall concentration profile of the smaller doses will be determined. Then we can compare these concentration profiles of the two methods to the optimal concentration profile at rest to calculate which method results in a profile that stays within the range of the optimal profile.

RESULTS AND DISCUSSION

We modeled the levels of concentration of caffeine in the muscle using Equation 1 in conjunction with the above schematic. Properties derived from literature were corrected for physiological conditions [See Appendix A]. To test the accuracy of our model, we first modeled the velocity profile in the capillary. Figures 3 and 4 below show the velocity profile for well-mixed, non-plug flow in the capillary, consistent expected conditions *in vivo*. More importantly, Figures 3 and 4 represent the flow of caffeine in the capillary when the athlete exhibits at rest capillary blood flow and degradation constant values in the tissue.

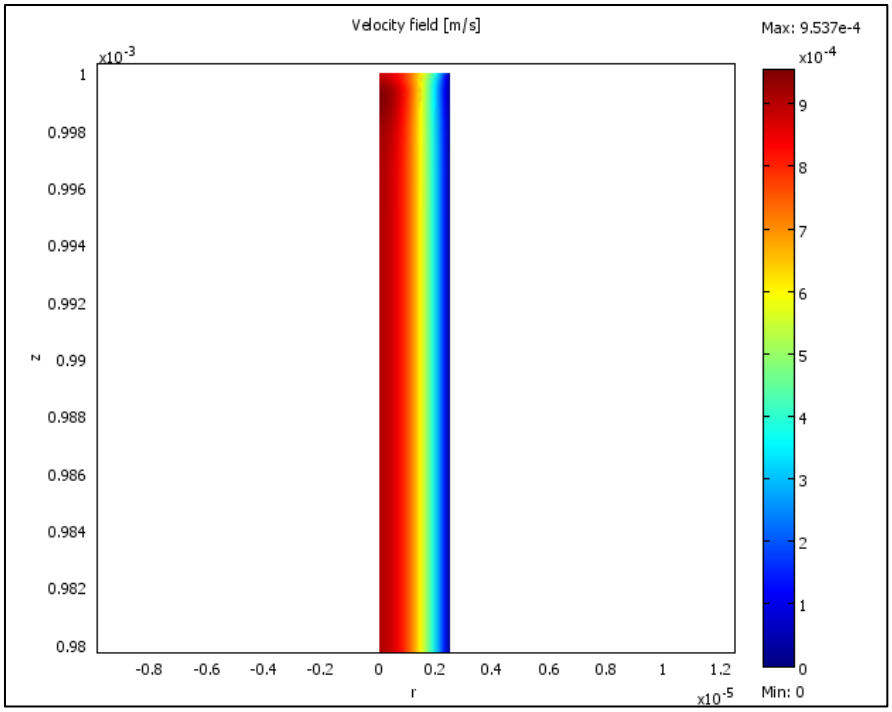


Figure 3.*Top view of velocity field of capillary. This velocity profile represents the flow of the caffeine in the blood when the athlete is at rest, assuming fully developed flow. The blood/caffeine molecules follow a Navier-Stokes velocity profile, where the center of the capillary has the maximum velocity and the wall of the capillary has a zero velocity (no slip).*

Fluid flow in the above figure illustrates a parabolic distribution of flow through blood vessels shown in literature surveys (Horng, Lin, & Liauh, 2007). Because the blood velocity profile obtained in a similar study is comparable to results obtained from velocity profile above, this model successfully describes the blood flow through the capillary.

Figure 4 shows undeveloped flow near the artery side of the capillary, where the caffeine enters the capillary. Because of bio-fluid mechanics and the hindrance of the inlet of the capillary, we know that the fluid entering the capillary will not exhibit a parabolic distribution of flow, consistent with Figure 4. Therefore, the flow does not become fully developed until further down in the capillary. This is modeled in COMSOL using the Navier-Stokes equation.

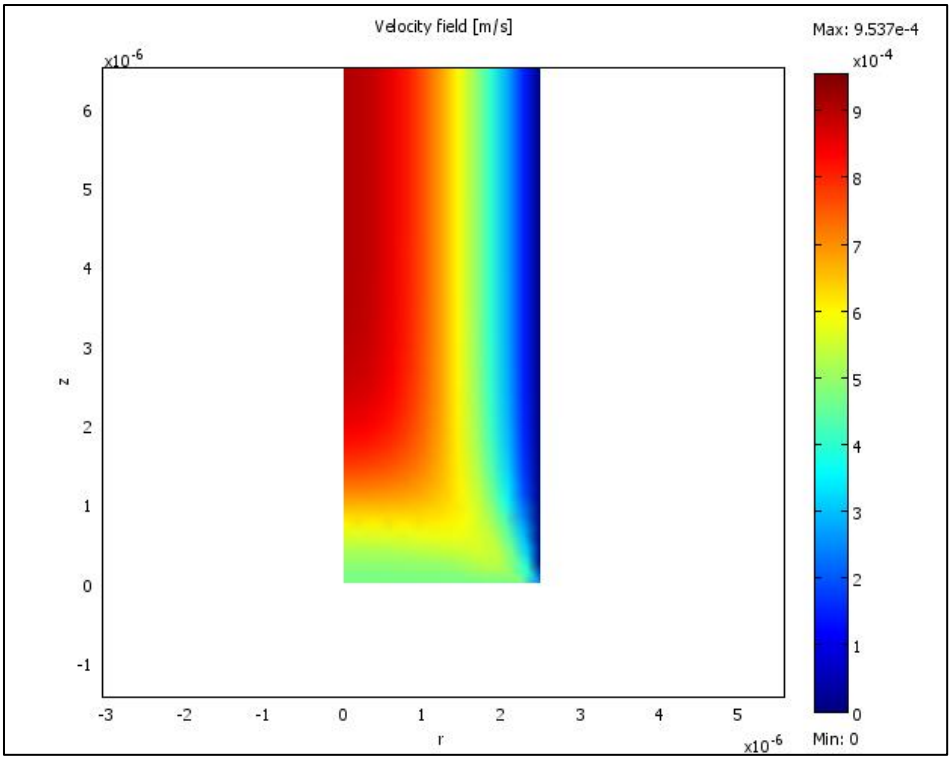


Figure 4.*Bottom view of velocity field of capillary at inlet. This surface plot depicts the velocity profile at the arteriole end of the capillary when the athlete is at rest. The flow is not fully developed at the inlet; therefore, the velocity profile is not parabolic at the inlet (as shown by a non-parabolic gradient of colors).*

After validating the velocity profile, the level of caffeine in the tissue was determined. Observing the surface plot in Figure 5, we can see the concentration profile of the optimal dose, 45 μM, of caffeine injected into the athlete. According to the figure, there is a larger gradient of caffeine in the muscle near the arteriole and a smaller gradient near the venule end, which is consistent with expectations. Intuitively, since caffeine first enters the capillary from the arteriole, the concentration at this end is expected to be greater than that at the venule end. Due to degradation of caffeine in the blood, there will be more caffeine at the arteriole end than near the venule. Also confirming our model, previous studies of caffeine levels in muscle show a similar gradient of caffeine levels from inlet to outlet (Datta & Rakesh, 2010).

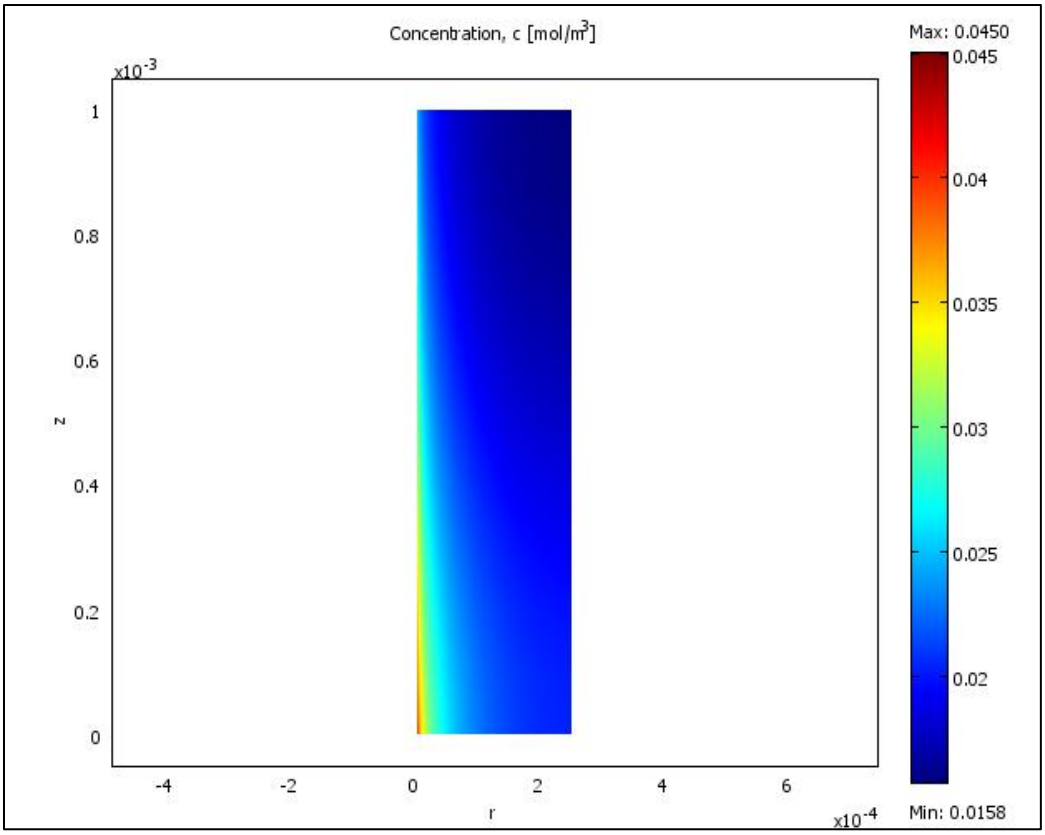


Figure 5.*Surface plot of solution10 hours after optimal dose administered. Concentration of caffeine as it flows from the inlet at the bottom to the outlet decreases with distance from the inlet. The concentration levels in the muscle also decrease with increasing z.*

Based on literature, we know that the optimal levels of caffeine in the muscle are shown in Figure 6 below. The curve of blue curve in Figure 6 shows the concentration profile of a 45 μM dose of caffeine in muscle at rest. Previous experiments, such as Graham and Spriet, have shown that the optimal level of caffeine in the blood is 45 μM. Thus, this curve accurately represents this fact. The green curve in Figure 6 shows a dose of 45 μM during exercise, reflecting the data obtained in previous studies (Graham & Spriet, 1995). This data validates the model, because our output demonstrates a plateau in concentration after a substantial amount of time. Our data mimics the output that Graham and Spriet demonstrated in their study. Graham and Spriet's study looked at performance levels and determined an optimal concentration and concentration profile at 45 μM during rest and exercise (Graham & Spriet, 1995). Their experiment shows a plateau in the caffeine concentration in the plasma one hour after administration during exercise.

The green curve in Figure 6, representing the during-exercise condition, plateaus at around 4200 seconds—roughly 1.17 hours. After 1.17 hours, for the remaining time under study. The blue curve representing the concentration profile at rest is the optimal concentration profile, because under this at-rest condition none of the parameters are varied because there are no significant pH changes that effect parameters. It should be noted that concentration of caffeine is significantly diminished during physical activity due to increased velocity of blood flow and increased degradation rate in the tissue.

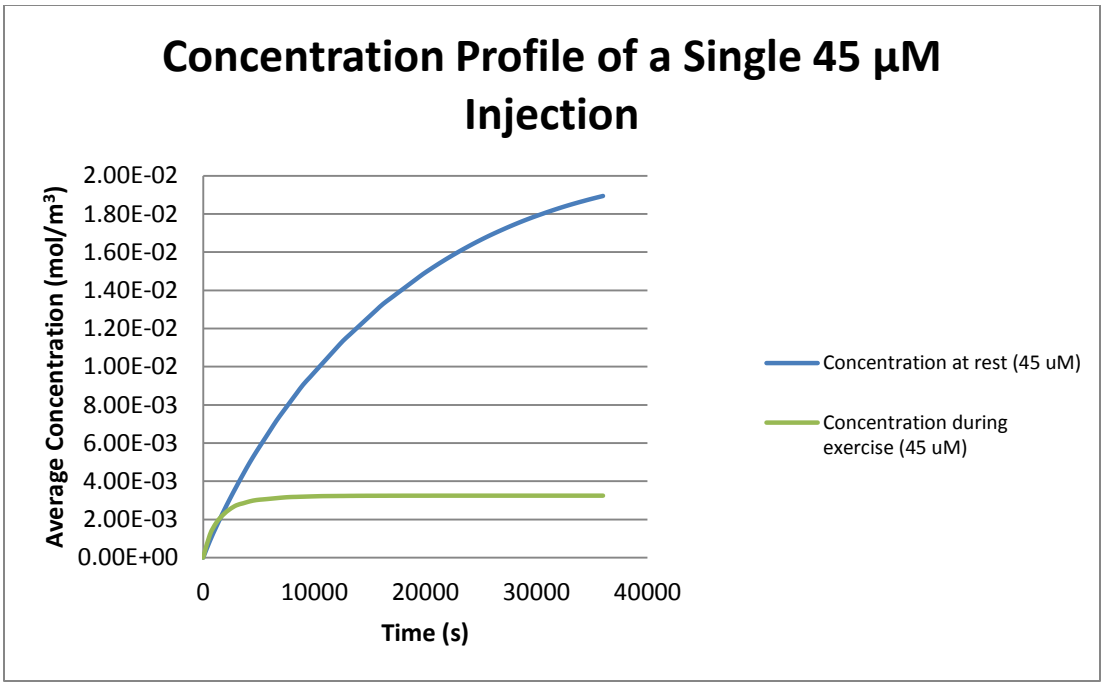


Figure 6: *Concentration profile over 10 hours of a single 45 µM injection at rest and during exercise. This shows that during exercise the average concentration in the quadriceps is decreased significantly due to the increased degradation rate and blood velocity.*

With our model validated, we can now determine the most advantageous method of caffeine administration. In order to maintain caffeine levels at the optimal concentration profile, we designed two methods with varying time intervals of caffeine administration.

In the first approach, the level of caffeine to be injected at time t=0 s in an athlete during exercise was determined. Most importantly, this level of caffeine had to be a quantity such that the concentration of caffeine in the muscle stays within a 15% range of the optimal caffeine concentration profile. This range provides an accurate approximation of the optimal concentration profile. The optimal concentration profile cannot be used as a lower limit to optimal caffeine concentration because no previous literature has found that a caffeine dosage greater than the optimal concentration profile has significant effect on performance (Graham & Spriet, 1995).

For a single injection dosage, three different concentrations were tested: 45 uM, 90 uM and 180 uM. The 45 uM and 90 uM dosages both plateaued before being able to reach the optimal concentration and the 180 uM dosage was the only one that was able to stay above the optimal. Figure 7 below shows the concentration profile of the 180 µM dose over time. Due to COMSOL limitations in calculation time, larger dosages could not studied, as computation time would increase significantly. Additionally, from the figure below, we can already see that a single injection dosage may not be a plausible solution for administering caffeine in order to maintain the optimal concentration profile. Using a smaller dosage may fit along the optimal curve, but for only a small period of time. Using a larger dosage will satisfy the optimal but more likely than not lie outside the 15% range.

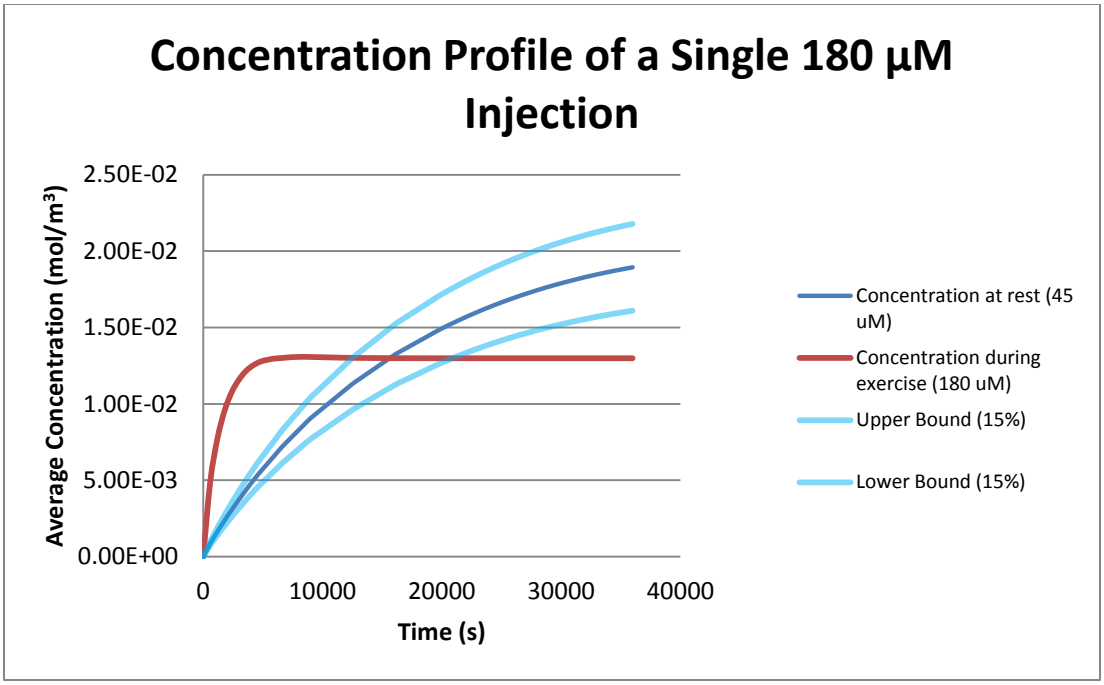


Figure 7: *Concentration profile over 10 hours of a single 180 µM injection during exercise compared to a single 45 µM injection at rest. The concentration profile at rest represents the optimal concentration profile of caffeine in the quadriceps. Because the initial dosage is increased to 180 µM, the concentration profile during exercise follows the optimal profile more closely than the concentration profile of 45 µM during exercise. This graph shows that the increased 180 µM injection is within ± 15% of the optimal profile.*

Instead of injecting one single dose at the initial time to satisfy a prolonged time constraint, our second method involved administering smaller dosages of caffeine to the athlete at smaller time intervals. This allowed for the concentration profile during exercise to be within the range of the optimal concentration profile. This method was tested with two different dosages: (1) dosages of 60 µM, consisting of approximately 533 mg of caffeine in each dose, and (2) dosages of 75µM, consisting of approximately 666 mg of caffeine in each dose.

Figure 8 shows the concentration profile of 60 µM injections administered at smaller time intervals. The first injection was given to the athlete at the initial time. The concentration in the tissue during exercise with the first injection of 60µM seemed to reach the optimal at 3600 s (1 hour), as seen in Figure 8. So after 1 hour we injected the athlete with another dose of caffeine at 60µM. In order to remain within the optimal range, the athlete was injected with an additional 60 µM dose of caffeine every time the concentration profile in the muscle began to plateau. A total of five injections was administered for the duration of the 10 hours. The concentration profiles of each injection remain relatively within the optimal range for the majority of their duration.

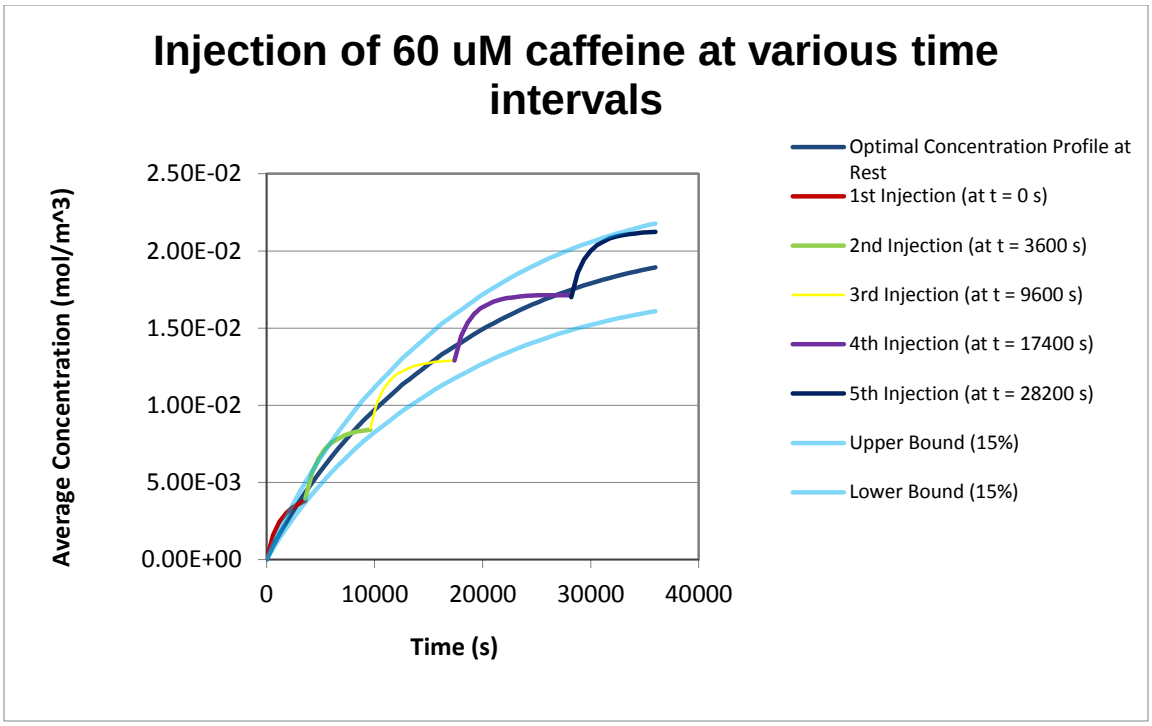


Figure 8: *Concentration profile over 10 hours of five 60µMinjections during exercise compared to a single 45 µM injection at rest with a 15% upper and lower bound. The injections were given at various time intervals that would have allowed for the optimal caffeine concentrations in the muscle.*

The simulation was performed again with a dosage of 75 µM rather than 60 µM. The concentration profiles of the 75 µM injections are shown in Figure 9. The first injection of 75 µM lasted till approximately t = 4800 s (1.33 hours). The muscle was then injected with an additional dose of 75 µM each time the concentration profile of the previous injection began to plateau and move outside the optimal concentration profile range. A total of only four injections were required for this dosage as seen in Figure 9. With this higher concentrated dosage, after the 3rd injection, the muscle maintains approximately optimal performance for 4 hours before requiring another dose.

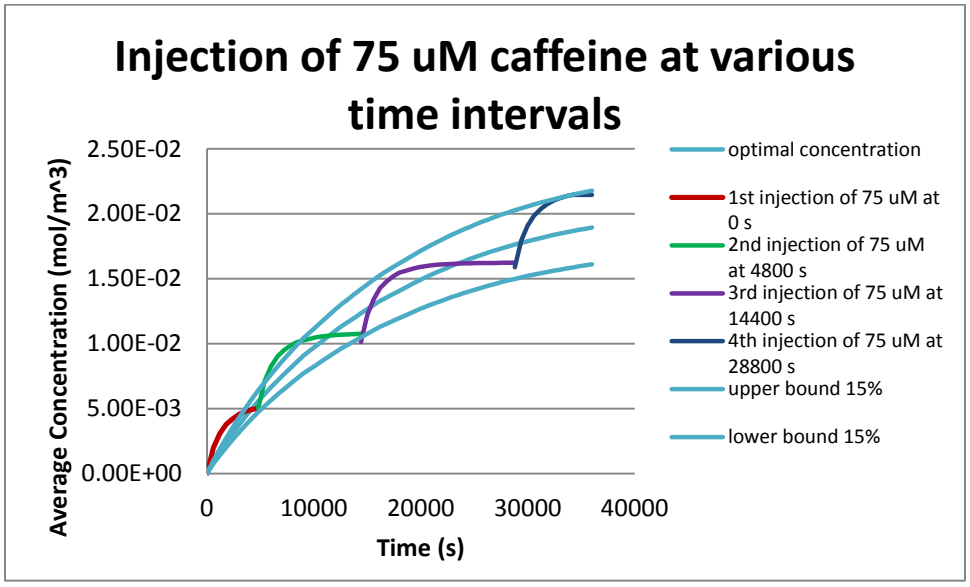


Figure 9: *Concentration profile over 10 hours of four 75 μM injections during exercise compared to a single 45 μM injection at rest with a 15% upper and lower bound. The injections were given at various time intervals that would have allowed for the optimal caffeine concentrations in the muscle.*

SENSITIVITY ANALYSIS

Several parameters that were derived from literature required interpolation to account for the physiological conditions in the muscle and the capillary: degradation rates of caffeine in the blood and the muscle. These parameters were tested to determine the responsiveness of the average concentration to the varying parameters. The parameters were varied first by 5% in both the positive and negative directions. Because no significant variability was observed in the calculation of the average concentration in the muscle, the parameters were then varied by 10% in both directions [See Table 1]. Additionally, the velocity of blood in the capillary was also tested in a similar fashion, by observing a range of ±10% of the velocity value, as there was large variation between sources in the numerical value of the velocity.

Table 1. *Parameters and ranges for sensitivity analysis.*

Varied Parameter	Determined Values	Range tested for Sensitivity Analysis (10% in each direction)
Degradation Constant of Caffeine in Blood At Rest	$3.50 \times 10^{-5} s^{-1}$	$3.15 \times 10^{-5} s^{-1} – 3.85 \times 10^{-5} s^{-1}$
Degradation Constant of Caffeine in Tissue At Rest	$3.50 \times 10^{-5} s^{-1}$	$3.15 \times 10^{-5} s^{-1} – 3.85 \times 10^{-5} s^{-1}$
Degradation Constant of Caffeine in Blood During Exercise	$3.50 \times 10^{-5} s^{-1}$	$3.15 \times 10^{-5} s^{-1} – 3.85 \times 10^{-5} s^{-1}$
Degradation Constant of Caffeine in Tissue During Exercise	$6.42 \times 10^{-4} s^{-1}$	$5.76 \times 10^{-4} s^{-1} – 7.04 \times 10^{-4} s^{-1}$
Blood Velocity in the Capillary At Rest	4.70×10^{-4} m/s	4.23×10^{-4} m/s - 5.16×10^{-4} m/s
Blood Velocity in the Capillary During Exercise	3.15×10^{-3} m/s	2.835×10^{-3} m/s - 3.465×10^{-3} m/s

The following Figures 10 and 11 display the results of the sensitivity analysis for the parameters listed in Table 1 [For analysis of each parameter individually, Appendix C]. The degradation constant in blood during exercise and the degradation constant in muscle at rest are insensitive to changes in the value indicating that the diffusion-degradation process of caffeine through the muscle is insensitive to these parameter values, as shown by Figure 10.

Also as seen in Figures 10 and 11, the results of this sensitivity analysis suggest linear relationships between degradation constant in muscle, blood velocity in capillary during exercise and average concentrations. The degradation constant in blood during exercise seems to have a higher order relationship with average concentration, as shown in Figure 10; also, the variability of this degradation constant seems to affect the solution the most, compared to the other sensitivity analysis.

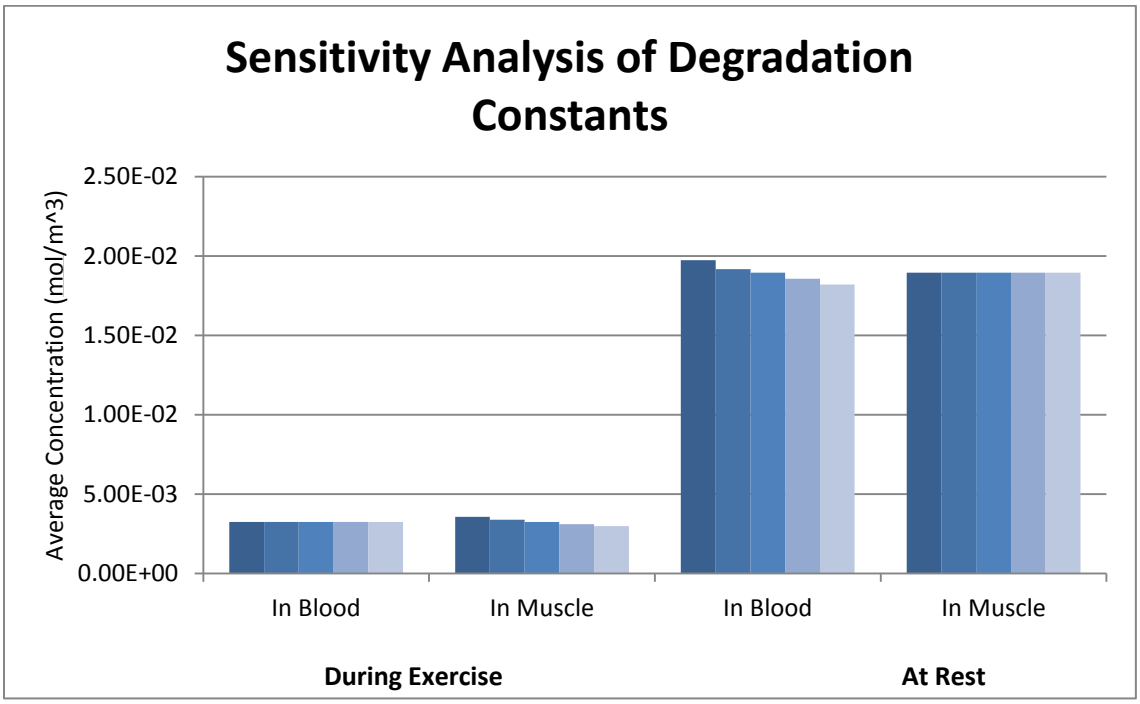


Figure 10: *Results for sensitivity analysis on values of the degradation constant under at rest and during exercise conditions in the blood and in muscle after an initial injection of 45 μM injection. Blood velocity was set to its during exercise value in the left hand portion of the graph, and its at rest value in the right hand portion. For analysis of each degradation constant value, values from left to right are 90% of original, 95%, 100%, 105%, 110%, respectively.*

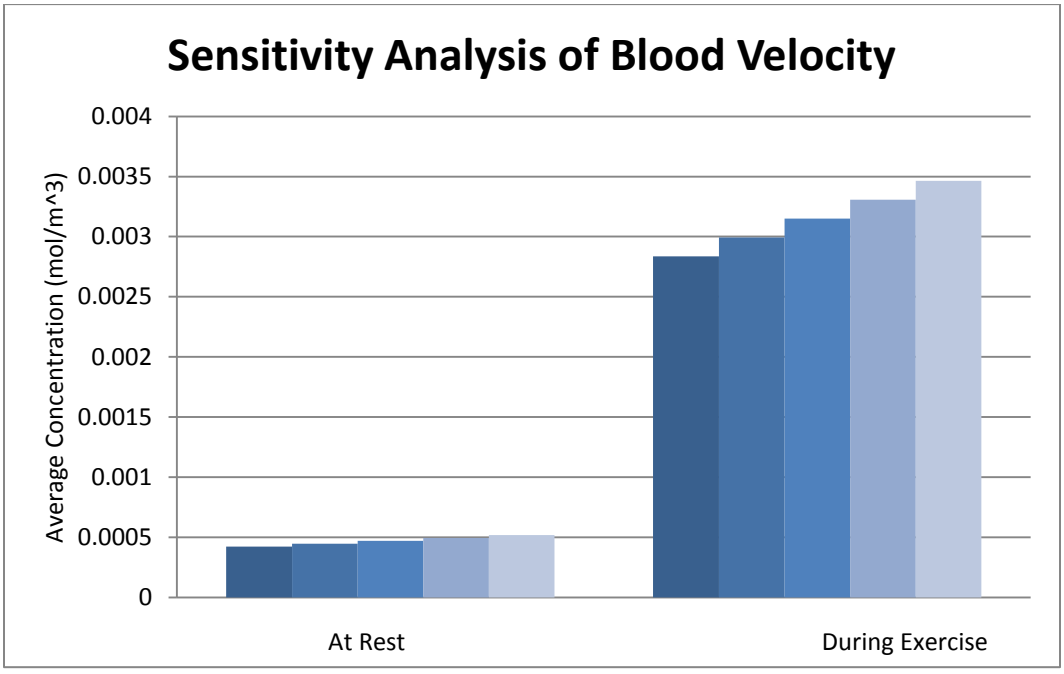


Figure 11: *Results for sensitivity analysis on the blood velocity in the capillary after an initial 45 μM Degradation value used was the during exercise value for the right hand portion of the graph and the at rest value for the left hand portion of the graph. For analysis of each degradation constant value, values from left to right are 90% of original, 95%, 100%, 105%, 110%, respectively.*

CONCLUSION:

Based on our results, we have determined that while a large, single dosage offers more convenience for the user, multiple smaller dosed injections at spaced time intervals work better in maintaining the optimal concentration of caffeine in the muscle. According to Figure 7, the large initial dosage of 180 μM increased the levels of caffeine in muscle tissue to well above ±15% of the optimal concentration profile between t= 0 and t= 12,000 s and well below optimal range at t≥ 19,800 s. Thus, a large, single dosage was not an efficient method for caffeine delivery based on our findings, since it was only within optimal at t= 12,000 s to 19,800 s. Multiple injections at smaller dosages between 45 μM and 75 μM, however, maintained concentration levels within ±15% of the optimal concentration profile easily. Concentrations that were significantly lower or higher than the 45 μM and 75 μM were outside the ±15% range.

For our comparison of multiple injections over time, we found that smaller dosages corresponded to more frequent injections. Because a new dose was given each time the caffeine levels fell below the optimal concentration profile, a smaller dose corresponded to a smaller change in concentration. Thus, injections must be administered more frequently in order to maintain the optimal concentration profile. Larger doses corresponded to larger changes from the optimal profile, requiring less frequent injections. These changes from the optimal profile are bounded by the upper limit—+15%. Above this point, caffeine concentrations are not as efficient, since it has not been proven that levels above the optimal concentration profile would result in increased muscle performance.

In conclusion, we looked at two different ways of maintaining the optimal concentration of caffeine in the muscle through a single, large initial dosage and through multiple, smaller dosages over spaced intervals. The frequent smaller dosages appeared to work better than the large initial dosage in maintaining the optimal concentration in the muscle. For shorter time intervals, the concentration administered was not important in maintaining the optimal concentration profile. This is because the concentration profile of each injection increased linearly in short time intervals. With this study on maintaining a caffeine concentration profile in muscle under various conditions, the direct effects of caffeine on muscle can be determined.

Design Recommendations:

Because the large, single dose method requires concentration levels far above and below the target range considered, this method is not ideal. Thus, we recommend multiple, small injections of caffeine to maintain levels near the optimal concentration profile. With this method of maintaining the concentration profile, we can expand this study to test the direct effects of caffeine on muscle. Once proven that there are direct effects of caffeine on muscle, our study of injections can be used to improve performance in athletes.

To create a more accurate model, we can introduce complications that will more closely follow physiological conditions. For example, since capillaries are often part of interconnected networks, we can study the effects of branched capillaries on caffeine diffusion throughout the tissue. Because capillaries are thin to allow greater diffusion between blood and interstitial fluid, capillaries are as wide as the diameter of an erythrocyte. Thus, there is often plug flow in capillaries. In this case, the blood velocity profile would not follow Navier-Stokes. Finally, the body's temperature would rise as a result of exercise, affecting the ease of diffusion through the muscle. To account for this, our exercise conditions would include a change in temperature of the tissue. This change in temperature would mean finding new values for the many of the parameters since this would cause an effect on diffusivities.

Design Constraints:

The optimal concentration profile of caffeine in the muscle was determined via previous studies indicating the optimal dose for ingestion to be 3 – 6 mg/kg (Graham & Spriet, 1995). However, this study was performed by observing changes in performance level after ingestion of various doses of caffeine. From this data, we performed reverse calculations to determine the level of caffeine that would be present in the blood stream if an optimal dose of 3 – 6 mg/kg was ingested. Because this study was behavioral, it is possible that subjects in this previous study did not exhibit caffeine concentration profiles similar to the model. Due to unknown conditions of subjects (e.g. higher metabolism, altered diet, etc.) that could deviate caffeine levels in the muscle from our back calculations, our model could be somewhat inconsistent with experiments performed with real subjects.

Other possible conditions that could not be taken into consideration in our model include caffeine tolerance and a saturation point of caffeine in muscle. A regular intake of caffeine will result in a decrease in caffeine's effect over time. Caffeine's direct effect on muscle has yet to be studied in great detail, thus caffeine tolerance could occur in the brain or the muscle. Because the mechanism of caffeine tolerance is not well known, this parameter is not easily integrated into our model. This condition should be considered in future studies, however. The saturation point of caffeine could also impact results of performance enhancement. Because the mechanism of caffeine is still unclear, caffeine may have a point of saturation, at which an increase in concentration of caffeine will no longer cause a noticeable effect due to the complete saturation of all caffeine receptors or molecules interacting with caffeine in the muscle. Again, because caffeine's direct effect on muscle is still under investigation, a possible saturation point cannot yet be determined. This makes this condition another good candidate for future studies.

Another important consideration of the two methods is the amount of caffeine injected and its possible negative implications for an athlete. Because the large, single dose contains a relatively large amount of caffeine (equivalent to approximately 10 Red Bulls), it is potentially dangerous for athletes with pre-existing heart conditions. Thus we minimize any health risks associated with performance enhancement by recommending multiple, smaller doses that maintain lower and consistent levels of caffeine throughout the tissue.

APPENDIX A: MATHEMATICAL FORMULATION

To determine the concentration level of caffeine in the governing equation, we will model a system based on the mass transfer equation for cylindrical coordinates.

$$\frac{\partial c}{\partial t} = D\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial^2 c}{\partial x^2}\right) + \frac{1}{r^2}\frac{\partial^2 c}{\partial \varphi^2} + \frac{\partial^2 c}{\partial z^2}\right] + r_a$$

Because we will model our problem as Axial Symmetry (2D), the φ term drops out. The below equation is specifically for the muscle domain:

$$\frac{\partial c}{\partial t} = D\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial^2 c}{\partial x^2}\right) + \frac{\partial^2 c}{\partial z^2}\right] + r_a$$

We also have an equation for the bloodstream:

$$\frac{\partial c}{\partial t} + \left[v_r\frac{\partial c}{\partial r} + v_z\frac{\partial c}{\partial z}\right] = D_b\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial^2 c}{\partial x^2}\right) + \frac{\partial^2 c}{\partial z^2}\right] + r_b$$

The velocity of the blood in the capillary can be determined by the Navier-Stokes equation:

$$\rho\left(\frac{\partial v_z}{\partial t} + v_z\frac{\partial v_z}{\partial z}\right) = -\frac{\partial P}{\partial z} + \mu\left(\frac{\partial^2 v_z}{\partial z^2}\right) + \rho g_z$$

To achieve a model as close to physiological conditions as possible while maintaining model feasibility, we assume the following:

1. For implementation in COMSOL, we neglect the diameter difference between capillary and arteriole/venule in series.
2. Neglect possibility of plug flow in the capillary.
3. Assume the initial concentration of caffeine on the vein side of the capillary is 0 mole/m^3.
4. Assume the initial concentration of caffeine in the muscle is 0 mole/m^3.
5. Assume the diffusivity of caffeine in blood is that of caffeine in aqueous solutions.
6. Because the diffusivity of caffeine in the muscle could not be found, we adjusted the diffusivity of the caffeine in blood by a factor of 100 to accommodate for the muscle.
7. The degradation of caffeine is modeled as a first order kinetics rate equation.

Boundary conditions based on real conditions are:

1. Boundary of muscle along the artery and vein are insulated. Flux at these points must be zero.
2. Convective flux at the outlet of the capillary.

For implementation of the model given our calculated caffeine dosage, the initial condition is set to be:

1. $C_{Initial}$ at z=0 is 82.39 mole/m^3

Additional parameters needed to implement the model in COMSOL:
Capillary diameter: 5×10^{-6} m
Radius of capillary: 2.5×10^{-6} m
Radius of tissue: 2.525×10^{-4} m

Length: 1 x 10^{-3} m
Diffusivity of caffeine in blood: 7.78 x 10^{-12} m^2/s (Price, 1989)
Diffusivity of caffeine in muscle: 6.79 x 10^{-12} m^2/s (McCabe, 1972)
Density of blood: 1060 kg/m^3 (Datta & Rakesh, 2010)
Dynamic viscosity of blood: 3 x 10^{-3} Pa s (Datta & Rakesh, 2010)
Velocity of blood: 470E-06 m/s (Datta & Rakesh, 2010)
Velocity of blood after exercise: 315E-05 m/s (Shoemaker, 1996)
K in blood: 3.5E-05 /s
K in tissue: 3.5E-05 /s
K in tissue after exercise: 6.42E-04 /s
Molecular weight of caffeine: 194.2 g/mol
Duration time: 36000 sec = 10 hr

In COMSOL, degradation of caffeine in the blood and muscle will be assumed to be equal and first order, thus we input:

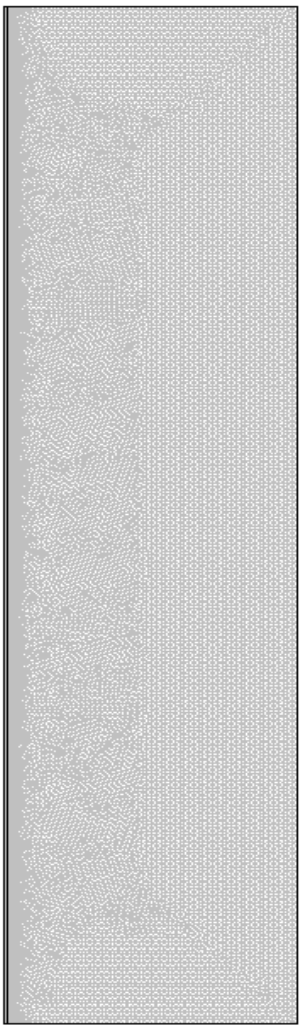
Constants:
kbl: 3.5 x 10^{-5} degradation term in blood and muscle (Holstege, Kurz, Weinbeck, & Gerok)
kti: 3.5 x 10^{-5} degradation term in muscle at rest
kti: 6.42 x 10^{-4} degradation term in muscle during exercise

Expressions:
Rbl_r: -kbl*c first order reaction term (Datta & Rakesh, 2010)
Rti_r:-kti*c first order reaction term(Datta & Rakesh, 2010)

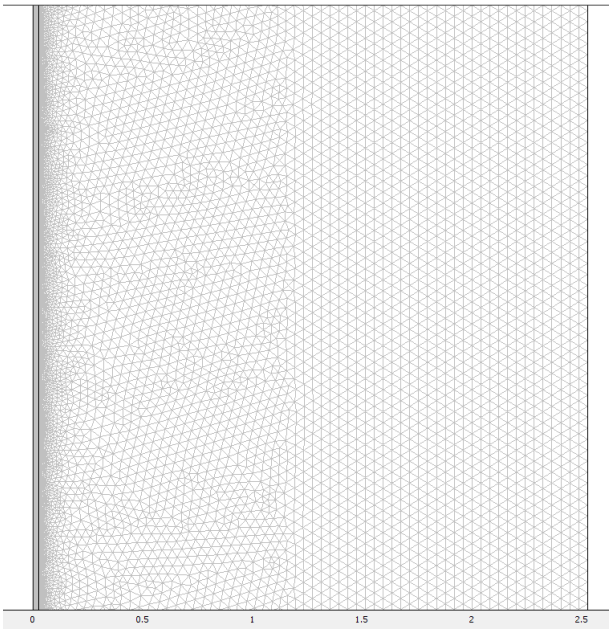
For the diffusion coefficient of caffeine in blood, we use the limiting diffusion coefficient for caffeine in an aqueous solution, 7.78E-10 m^2/s (Price, 1989). To adjust for blood, the diffusivity is lowered by a factor of 100 so that it becomes 7.78E-12 m^2/s. There are no previous reports of a diffusion coefficient of caffeine in muscle, but based on experience we can assume that the diffusion should be faster in the blood than in the muscle. We approximate this by using a value of 6.79E-10 m^2/s that was obtained from a previous study dealing with agar solution (McCabe, 1972). Again we adjust this agar diffusivity to correspond with muscle by lowering it by a factor of 100. No velocity term is needed for the muscle so it is set to 0. The degradation rate in the blood is calculated assuming that the reaction term is first order using equation t=ln(2)/k with an experimentally determined half-life of 5.5 hours (Holstege, Kurz, Weinbeck, & Gerok); the resulting value is 3.5*10^-5 /s. The degradation rate of caffeine in the muscles is assumed to be the same as that of the blood as no existing literature could be found to identify the value. There is initially no caffeine in both the blood stream and muscle. Since the capillary wall is so small, we can assume that it has the same diffusivity as the blood, therefore we do not need to model it as separate domain. The caffeine enters through the inlet of the blood stream at a concentration of 0.045 mols/m^3. The outlet of the blood stream is set as convective flux while all other boundaries are insulated.

APPENDIX B: SOLUTION STRATEGY

Implemented Mesh:



(a) Final meshing of capillary and muscle domains.



(b) Zoomed-in version of meshing of capillary and muscle domains.

Figure 10.*Views of meshing of the capillary and muscle domains before solving problem.*

For our mesh, we used free mesh parameters with a maximum element size of 5×10^{-7} in the blood stream and 5×10^{-6} in the muscle. Below is the calculation for mesh convergence, which led us to choosing the previously stated maximum element sizes.

Mesh Convergence:

Table 2.*Mapped meshparameters and subdomainintegrals*

Number of Edge Elements at Boundaries			Volume Integral (m^3)	Concentration (moles)	Average Concentration in the Muscle (mol/m^3)	Total Mesh Elements
Axisymmetric side	Inlet of Capillary	Muscle at inlet side				
281	1	12	2.00E-10	1.01E-12	5.04E-03	3718
300	2	15	2.00E-10	1.00E-12	4.99E-03	5100
350	5	20	2.00E-10	9.98E-13	4.98E-03	8750
400	10	25	2.00E-10	9.95E-13	4.97E-03	14000
450	15	30	2.00E-10	9.94E-13	4.96E-03	20250
500	20	35	2.00E-10	9.92E-13	4.95E-03	27500
550	25	40	2.00E-10	9.92E-13	4.95E-03	35750
600	30	45	2.00E-10	9.91E-13	4.95E-03	45000

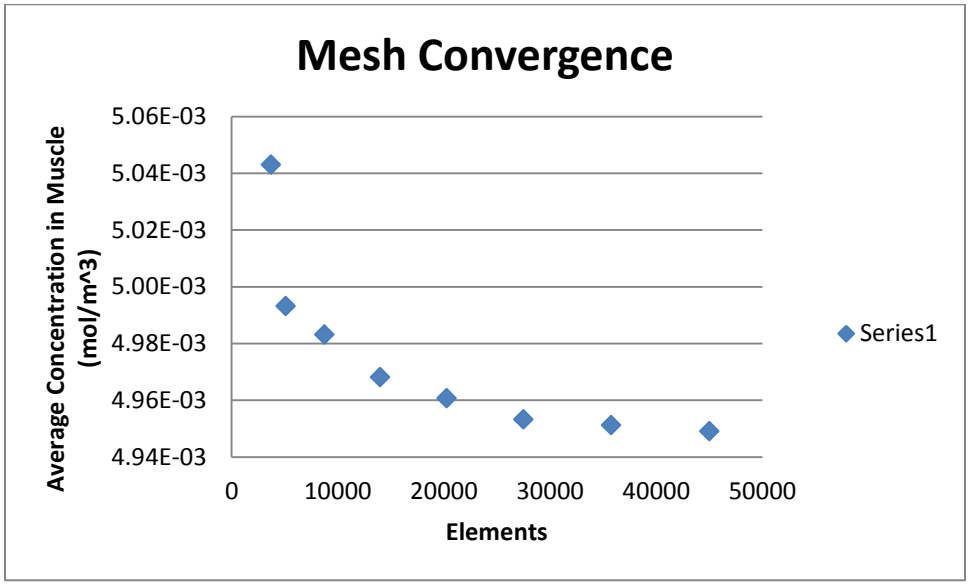


Figure 11.*Mesh convergence for average concentration of caffeine in the muscle.*

For the mesh convergence, we measured the average concentration of caffeine in the muscle over an increasing amount of elements. We performed a mapped mesh because our domains are rectangular and so it would be easier to test for convergence. We chose a constrained edge element distribution for the axisymmetric wall, the inlet of the capillary and the muscle on the inlet side. As we can see from the graph, the average concentration starts to converge at 27500 elements, so we do not need to increase the elements after 27500 due to minimal change in concentration.

APPENDIX C:

Additional figures.

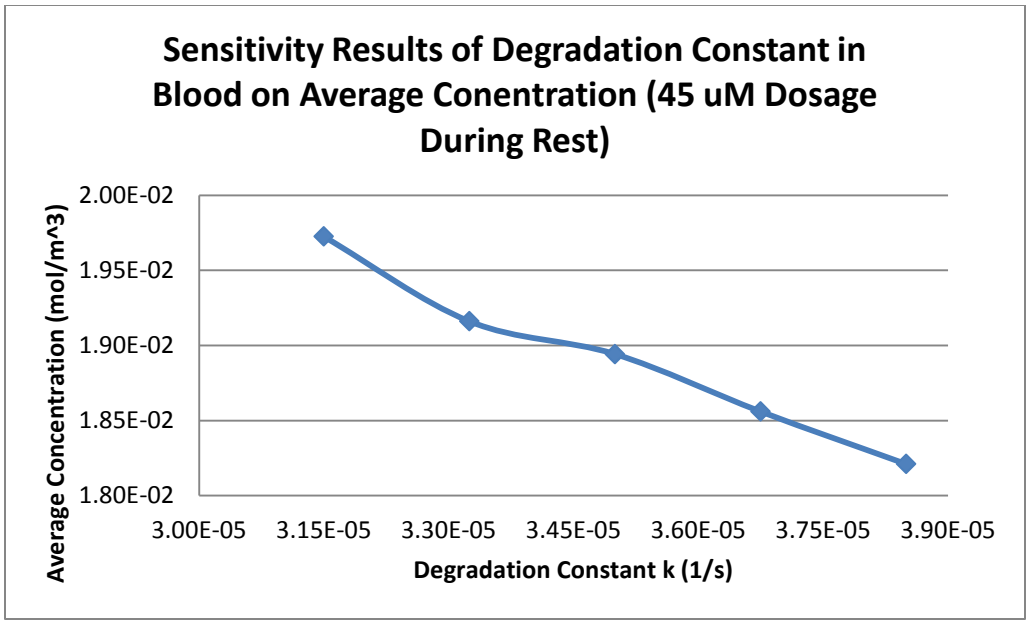


Figure 1: *Results for sensitivity analysis on the degradation constant of caffeine in the blood after a 45 μM injection at rest.*

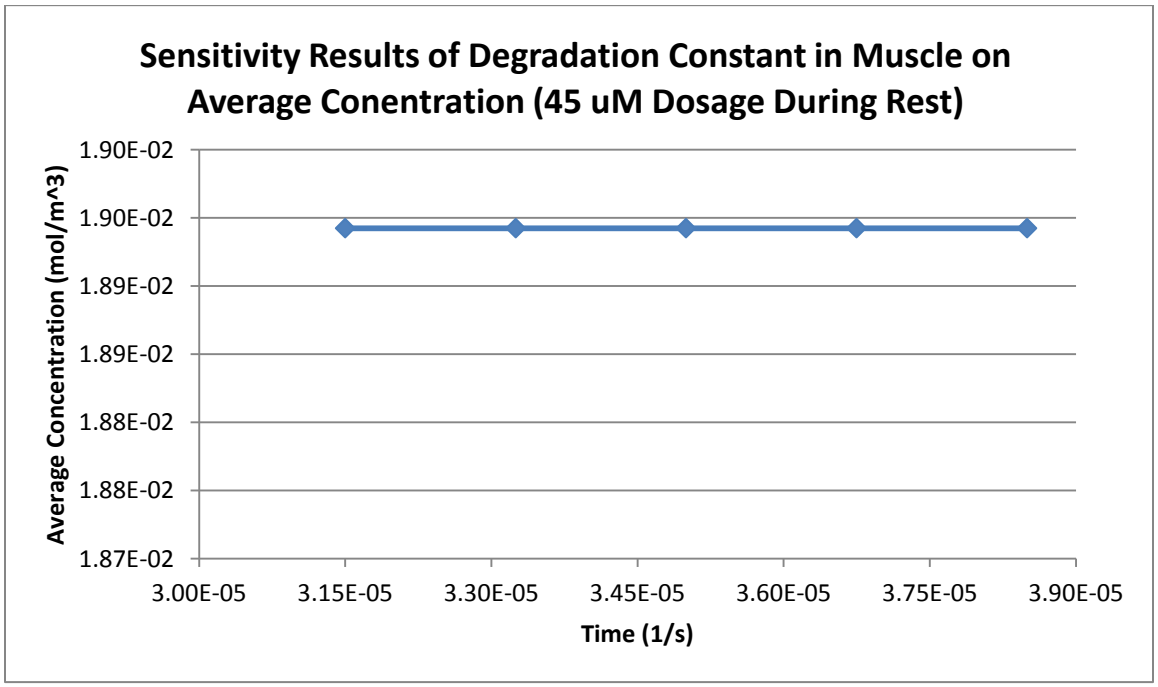


Figure 2: *Results for sensitivity analysis on the degradation constant of caffeine in the muscle after a 45 μM injection during rest.*

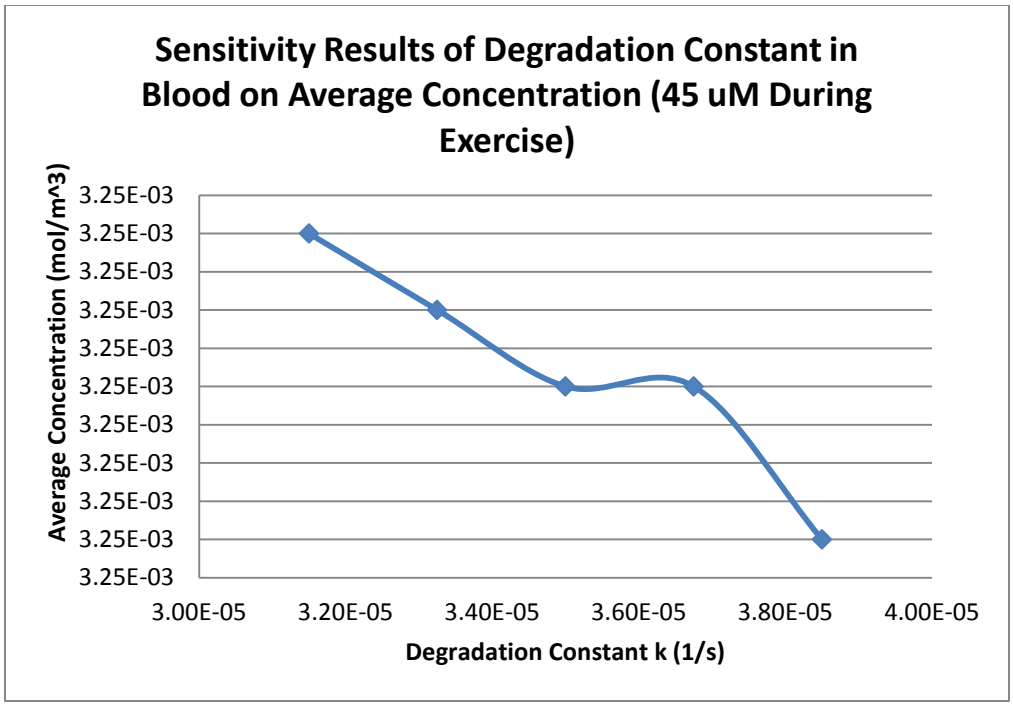


Figure 3: *Results for sensitivity analysis on the degradation constant of caffeine in the blood after a 45 μM injection during exercise.*

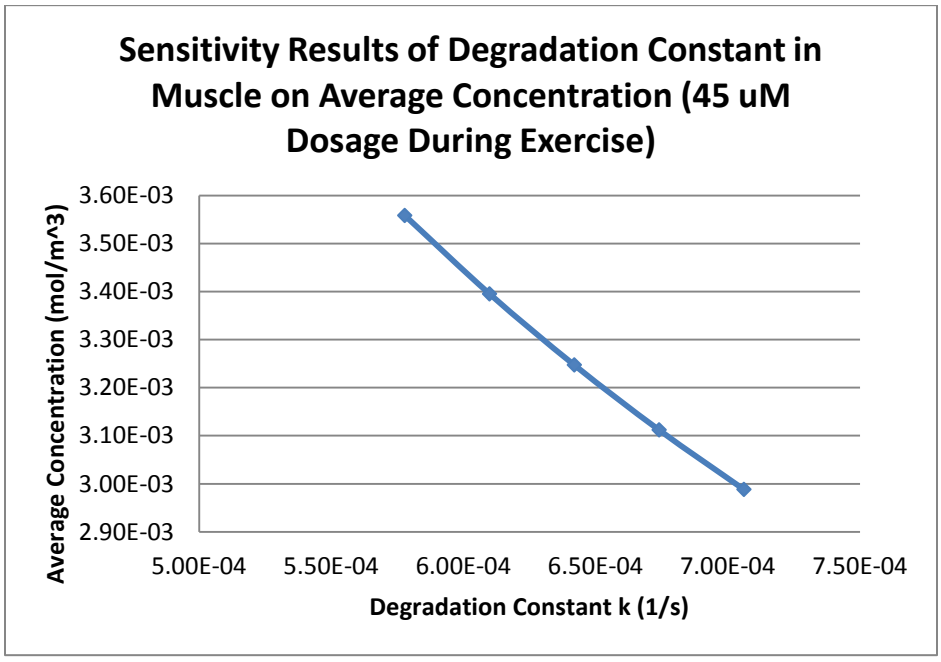


Figure 4: *Results for sensitivity analysis on the degradation constant of caffeine in the muscle after a 45 μM injection during exercise.*

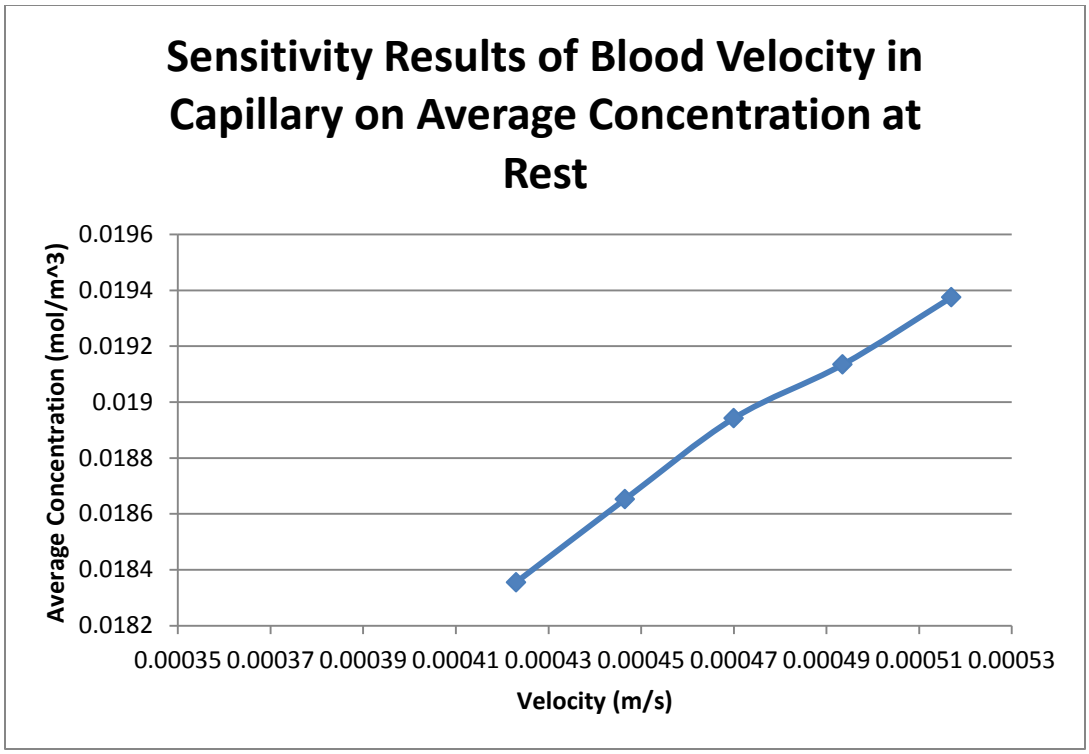


Figure 5: *Results for sensitivity analysis on the blood velocity in the capillary after a 45 μM injection at rest.*

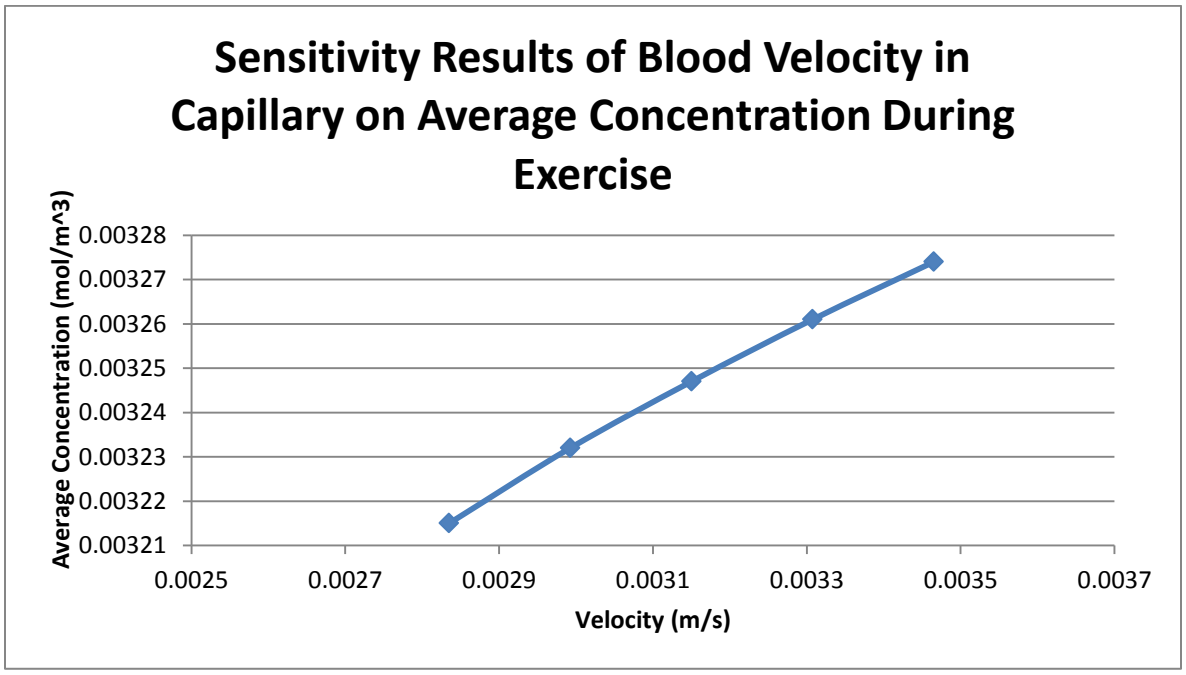


Figure 6: *Results for sensitivity analysis on the blood velocity in the capillary after a 45 μM injection during exercise.*

APPENDIX D: REFERENCES

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