Reducing Chemotherapy Induced Alopecia: Scalp Cooling for Reduced Docetaxel Transport

BEE/MAE 4530: Computer-Aided Engineering

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Keywords: Scalp cooling, chemotherapy-induced alopecia, docetaxel, heat transfer, mass transfer, COMSOL.

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1 Executive Summary

Since chemotherapy drugs target rapidly dividing cells, hair follicles are often damaged and many cancer patients develop chemotherapy-induced alopecia (CIA). One strategy used to combat hair loss is scalp cooling, where chemotherapy recipients wear a cold cap before, during, and after infusion. Scalp cooling causes vasoconstriction and decreases drug uptake by follicular cells, thus reducing the cells' overall exposure to the cytotoxic drugs. Our one-dimensional model seeks to understand how the heat transfer of scalp cooling affects the mass transfer of drug diffusion to the hair follicle. We will first model the pre-cooling time, where the cap is placed on the head for thirty minutes before infusion. This will show the temperature drop over time in each layer of the scalp. Then, we will model the transport of the drug during and after the infusion is completed. Drug concentration at the follicle will first increase and then decrease after infusion ends since the drug is metabolized throughout the body and the overall systemic concentration drops. After the model is set up, we will vary the temperature of the cold cap to determine how this affects steady-state temperature and drug concentration at the follicle level. We predicted that by decreasing the upper boundary condition representing the temperature of the cold cap, the scalp would reach lower temperatures and there would be lower drug concentrations at the hair follicle due to a greater degree of vasoconstriction. Our results showed that while the scalp reached lower temperatures, the concentration at the follicle did not change significantly. Decreasing the cold cap temperature only slowed drug transport. This indicates that the physical scenario may not be fully understood and may explain why cold caps have variable efficacy.

2 Introduction

Chemotherapy-induced alopecia (CIA) is an inevitable side effect of many breast cancer treatments. In an attempt to destroy rapidly dividing tumor cells, cytotoxic agents may also damage proliferative cells at the hair follicle. Breast cancer accounts for 30% of all female cancers annually and can lead to defeminizing consequences such as mastectomies and hair loss [2]. Consequently, negative psychological effects may arise such as anxiety, depression, lowered self esteem, and even refusal of treatment. Docetaxel is a widely used antineoplastic drug in the treatment of breast cancer. It induces cell arrest in dividing cells by inhibiting microtubule depolymerization [9]. Significant alopecia was reported in 74.2% of patients treated with docetaxel. To combat these unintended side effects, many cancer patients choose to wear a cold cap, which may contain cryogel or connect to a cooling device that circulates cold fluid [12].

Scalp cooling causes vasoconstriction in the scalp skin, which reduces the total amount of drug that is delivered to the hair follicle. Additionally, colder temperatures decrease follicular drug uptake, further reducing the cytotoxic effects of chemotherapy drugs and increasing the amount of hair that is preserved. Typically, cooling begins 30 minutes before infusion to ensure that the subcutaneous layer of the scalp reaches the target temperature of 22℃ before the drug enters the body [6]. Subcutaneous refers to the layers beneath the skin. The cooling is maintained

throughout the infusion and for some time after its end. Scalp cooling is generally well tolerated, with common adverse effects including headaches, nausea, dizziness, coldness, and claustrophobia. The effectiveness of scalp cooling depends on many factors relating to both the patient and the chemotherapy, and many of the current scalp cooling practices have been the result of trial and error. That being said, several scalp cooling machines have been approved by the Food and Drug Administration and have been incorporated into the National Comprehensive Cancer Network guidelines for breast cancer patients.

The following paper models the effect of scalp cooling on docetaxel delivery to hair follicles. Both heat and mass transfer equations will be used in order to link temperature to drug diffusion as blood perfusion decreases with cooling. Since the effect of head curvature is very small compared to the thickness of the region of interest, a cross section of the scalp is modeled as a rectangular slab with three distinct layers: compressed hair, epidermis, and dermis. A hair follicle is typically embedded 1 mm below the skin surface in the dermis which serves as the depth of interest for drug concentration. It is assumed that only the dermis layer is vasculated and that chemotherapy cannot exit the skin surface. The cooling cap will serve as a constant temperature boundary condition of 3℃ at the hair surface.

3 Problem Statement

Each cold cap comes with its own set of user recommendations, specifically regarding cooling temperatures and times. The discrepancies in these instructions have led to variable successes of the product, with the ultimate issue being hair loss due to toxic levels of chemotherapy drug reaching hair cells. Current studies measure the efficacy of scalp cooling through qualitative patient input without quantifying the physical details of the process as a whole. Other computational models only seek to investigate the heat transfer that occurs during scalp cooling. This paper aims to bridge that gap by determining the effect of changing cold cap temperature on steady-state temperature as well as drug concentration at the follicle.

The cooling cap process will be modeled in COMSOL Multiphysics as 1D heat transfer through the hair and skin layers as the cap is applied, and 1D mass transfer as the chemotherapy drug (docetaxel) is transported in the capillaries through the dermis layer and diffuses through the epidermis. The cooling cap temperature will be varied to model the steady state temperature's effect on blood vessel cooling and corresponding drug concentration delivered to the hair follicles.

4 Design Objectives

The scalp cooling process will be divided into three stages: pre-cooling, cooling during infusion, and post-infusion cooling as seen in Figure 1. Therefore our goals are to:

1) Model heat transfer in the scalp to determine the time it takes for the follicle temperature to reach steady state.

2) Model mass transfer during and after infusion to obtain a curve for concentration over time at the follicle level.
3) Graph concentration over time at follicle depth for various temperatures to better understand the effect of cap temperature on drug delivery.
4) Compare simulation results to commercially available cold caps in order to better understand their effect on hair follicles.
5) Since the efficacy of cold caps depends on both environmental and patient characteristics, determine the effect of variable parameters on steady-state temperature or concentration at the follicle.

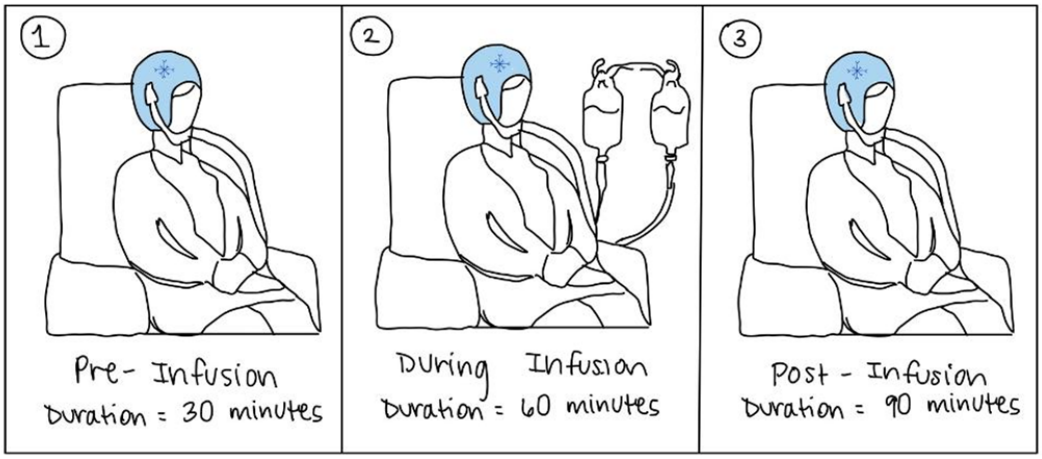

Figure 1: Stages of cold cap process. 1) Cap is placed on the head and scalp cooling begins. 2) After pre-cooling, intravenous infusion starts. Docetaxel circulates throughout the body and is delivered to the scalp via the blood. 3) Infusion stops. Cold cap stays on as the drug is metabolized systemically.

5 Schematic

The same schematic/domains can be used for all stages of the process but some of the boundary conditions will change with time, accounting for the differences in each stage. There are three layers in our schematic: compressed hair, epidermis, and dermis. The root of the follicle is embedded within the dermis, 1 mm below the skin surface, and is denoted as “follicle depth” in Figure 2.

Assumptions/Simplifications:

- Cold cap is applying a constant temperature.
- Since skull curvature is minimal compared to the thin domain of focus, model skin layers as infinite slabs. The only relevant direction of heat and mass transfer is 1D, modeled using no flux boundary conditions on the right and left boundaries.
- Consider follicles as a depth within dermis (not separate circular domains).
- Blood perfusion only occurs in the dermis (velocity u = 0 in epidermis and hair).
- Drug does not exit the epidermis/enter the compressed hair layer (zero flux).

- Blood perfusion of many capillaries is considered as an average across a rectangular section and represented by the temperature-dependent velocity/flow term in the mass transfer governing equation in the dermis.
- Assume blood flow through the dermis is uniform.
- Assume blood velocity (u) has the same form of equation as blood perfusion (ω) from heat transfer.

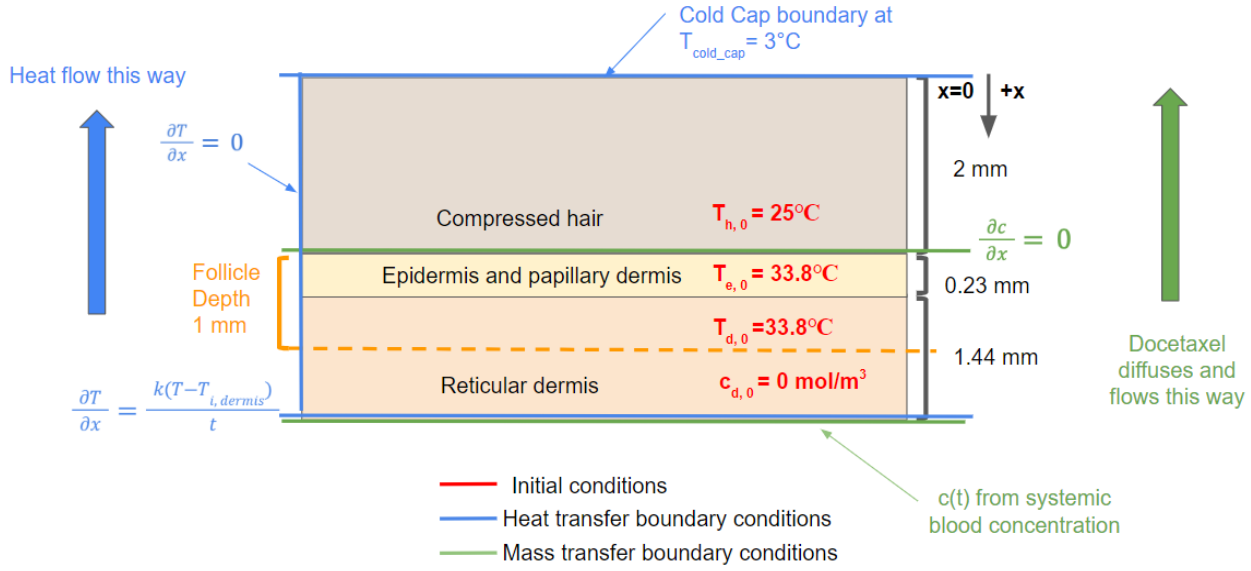

Figure 2: Model geometry for hair and scalp layers, including boundary conditions and initial conditions for heat and mass transfer.

6 Governing Equations

6.1 Heat Transfer in the Hair

First, we consider heat transfer between the cold cap and the layers of hair/scalp. Each layer has a different material property as well as degree of perfusion. Both hair and the epidermis, a non-vascular tissue, can be described sufficiently via the general heat equation. Since the temperature of the scalp is changing with time, we are dealing with a transient problem. In both cases, the lack of blood supply results in no heat generation term. Similarly, we make the assumption that hair is compressed and are able to neglect the convective term of air between the strands. The resulting general heat equation without the generation and convection terms reduces to Eq. 1:

$$\rho_{eff} C_{p,eff} \frac{\partial T}{\partial t} = k_{eff} \frac{\partial^2 T}{\partial x^2} \qquad (1)$$

We can consider the hair layer as a porous medium using ρ_{eff}, $c_{p,eff}$, and k_{eff} taking into account the combination of hair and air and a porosity value (ε_p) of 0.5. The calculation of these effective values are detailed below in Eq. 2 and Eq. 3. The numerical values for these quantities for the hair and epidermis layers are listed in Table 2.

$$(\rho C_p)_{eff} = \theta_h \rho_h C_{p,h} + \varepsilon_p \rho_a C_{p,a} \quad (2)$$

$$k_{eff} = \theta_h k_h + \varepsilon_p k_a \quad (3)$$

6.2 Heat Transfer in the Epidermis

Similarly to the hair layer, heat transfer in the epidermis can be described using the general heat equation as seen in Eq. 4. We neglect any heat generation terms due to the assumption that there is no blood flow in the epidermis.

$$\rho c_p \frac{\partial T}{\partial t} = k \frac{\partial^2 T}{\partial x^2} \quad (4)$$

Here, ρ, C_p, and k are the density, specific heat, and thermal conductivity, respectively.

6.3 Heat Transfer in the Dermis

Next, we consider heat transfer in the vasculated dermis. We include two heat generation terms in order to reflect the impact of blood perfusion and metabolic heat generation on temperature. The source term for blood perfusion incorporates density of blood into the omega term. The resulting equation is referred to as the Pennes Bioheat Equation (Eq. 5):

$$\rho C_p \frac{\partial T}{\partial t} = k \frac{\partial^2 T}{\partial t^2} + \underbrace{(C_p \omega)_{blood} (T_{artery} - T)}_{\text{Due to blood flow}} + \underbrace{Q_{metabolic}}_{\text{Due to metabolic heat}} \quad (5)$$

$Q_{metabolic}$ and ω correspond to metabolic heat generation and blood perfusion respectively and are both functions of temperature as denoted in Eqs. 6 and 7. Blood perfusion is represented using the Fiala Model [8] which includes the Q_{10} effect, stating that a temperature drop of 10°C results in a 50% decrease in metabolic heat production. This is described in Eq. 6:

$$Q_{metabolic} = Q_{M,0} \cdot 2^{(T - T_{d,0})/10} \quad (6)$$

The impact of temperature on blood perfusion is quantified via the Fiala model Eq. 7:

$$\omega = \frac{\omega_0}{1 + Cs} \cdot 2^{(T - T_{d,0})/10} \quad (7)$$

Here, ω represents the blood perfusion due to the vasculature within the dermis and ω_0 corresponds to the initial blood perfusion. The Cs term describes the reaction of local skin blood flow to variations in mean skin temperature of the whole body and can be described by Eq. 8:

$$Cs = 2.92[\tanh(0.0284\,\Delta T_{dermis} + 1.07) - 1]\Delta T_{dermis} + 0.326(\Delta T_{dermis}) * \frac{dT}{dt} \quad (8)$$

With ΔT_{dermis} defined as: $\Delta T_{dermis} = T_{dermis} - T_{d,0}$ (9)

The relationship between blood perfusion and temperature (Eqn. 7) can be visualized in Figure 3.

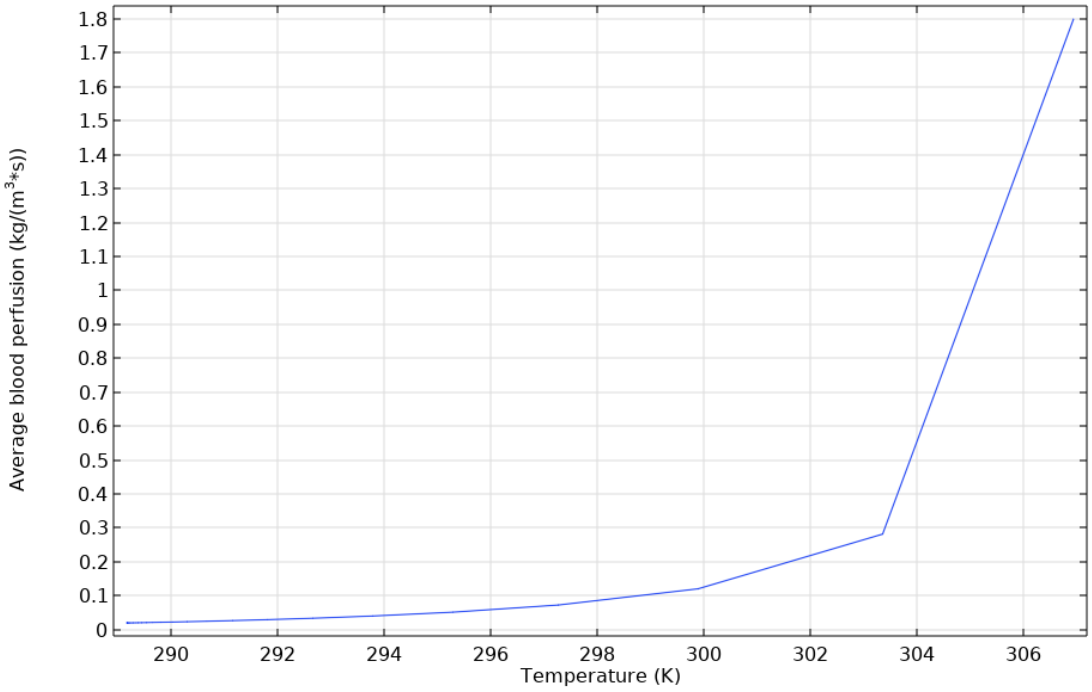

Figure 3. Visualization of the blood perfusion term from the Fiala model

6.4 Drug Transport in the Epidermis

The second aspect of the scalp cooling process that is being modeled is transport of the drug, docetaxel, from the blood to the hair follicle. Mass transfer occurs in all of the layers except the hair. Since there is no vasculature in the epidermis, the convective term is neglected in the general mass transfer equation.The diffusivity of the chemotherapy drug in the dermis is represented by D. The mass transfer equation in the epidermis reduces to Eq. 10:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \quad (10)$$

6.5 Drug Transport in the Dermis

In the vasculated dermis, the convection term is included and is a function of temperature (Eq. 7). Similar to the epidermis, the reaction term is omitted since there is no drug metabolism in this layer. It is important to note that the diffusive term was neglected in the dermis because the assumption was made that the drug is contained primarily within the capillaries and is transported through convection. Therefore, the general mass transfer equation for the dermis becomes:

$$\frac{\partial c}{\partial t} + u\frac{\partial c}{\partial x} = 0 \qquad (11)$$

The blood velocity (u) is altered by temperature dependent vasoconstriction. We made the assumption that the blood velocity's dependence on temperature is described by the same relationship as blood perfusion described in Eq. 7 because blood velocity and perfusion are proportional. The resulting equation is shown below with resting velocity of blood flowing through capillaries in the skin taken to be u_0 = 0.47 mm/s [13].

$$u = \frac{u_0}{1+Cs} \cdot 2^{(T-T_{d,0})/10} \qquad (12)$$

The given relationship between blood velocity and temperature (Eq. 12) can be visualized in Figure 4.

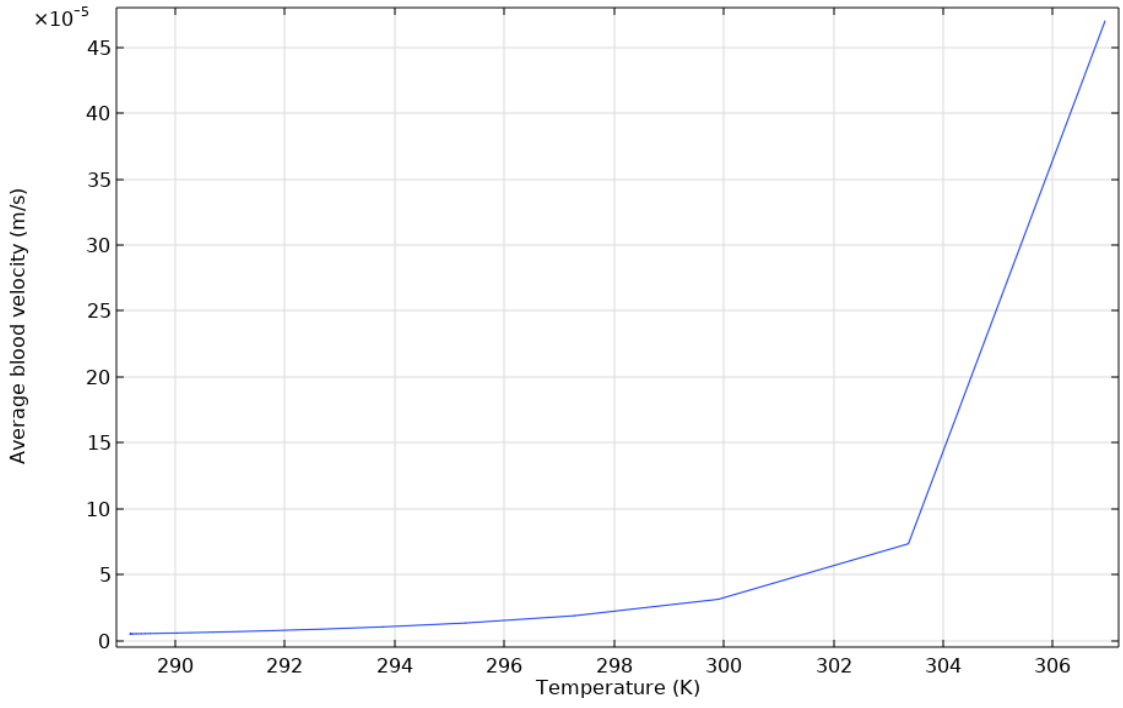

Figure 4. Temperature vs. average blood velocity

7 Boundary and Initial Conditions

7.1 Boundary Conditions

For the heat transfer problem, we consider two boundary conditions: one at the hair surface and one deep within the dermis. The cold cap we chose to consider was "DigniCap," the first FDA approved cold cap, which applies a constant temperature of 3℃ at the surface of the hair.

$$T(x = 0\,mm) = 3℃$$

Next, the temperature deep within the scalp remains at body temperature (37 ℃) throughout the process. This can be denoted as: $T(x = \infty) = 37℃$. However, COMSOL does not allow for the definition of infinite boundary conditions and thus a heat flux boundary condition is imposed. We assume a steady state temperature profile at depths >3.67 mm (or below the dermis layer). Using this linear profile, the flux at the boundary can be computed based on the temperature difference between the actual temperature at the boundary and that of body temperature in the subcutaneous fat layer beneath the dermis.

$$\frac{\partial T}{\partial x}(x = 3.67\,mm) = \frac{k(T-310.15)}{\delta}$$

In this equation, k represents the thermal conductivity of the fat layer, T represents the temperature of the dermis at x = 3.67 mm, body temperature is 310.15 K, and δ represents the thickness of the subcutaneous fat layer.

For the mass transfer problem, we make the assumption that no drug leaves the epidermis by imposing a no flux boundary condition.

$$\frac{\partial c}{\partial x}(x = 2\,mm) = 0$$

Next, we consider a time dependent concentration at the base of the dermis. As the drug is metabolized in the body, the systematic concentration changes with time leading to the boundary condition:

$c\,(x = 3.67\,mm)$ = From interpolated systemic concentration data in Figure 5

The docetaxel concentration c(t) that is delivered to the dermis over time is zero during pre-cooling, increases linearly during infusion, and exponentially decays post-infusion as the drug is metabolized by the body. This boundary condition can be visualized in Figure 5.

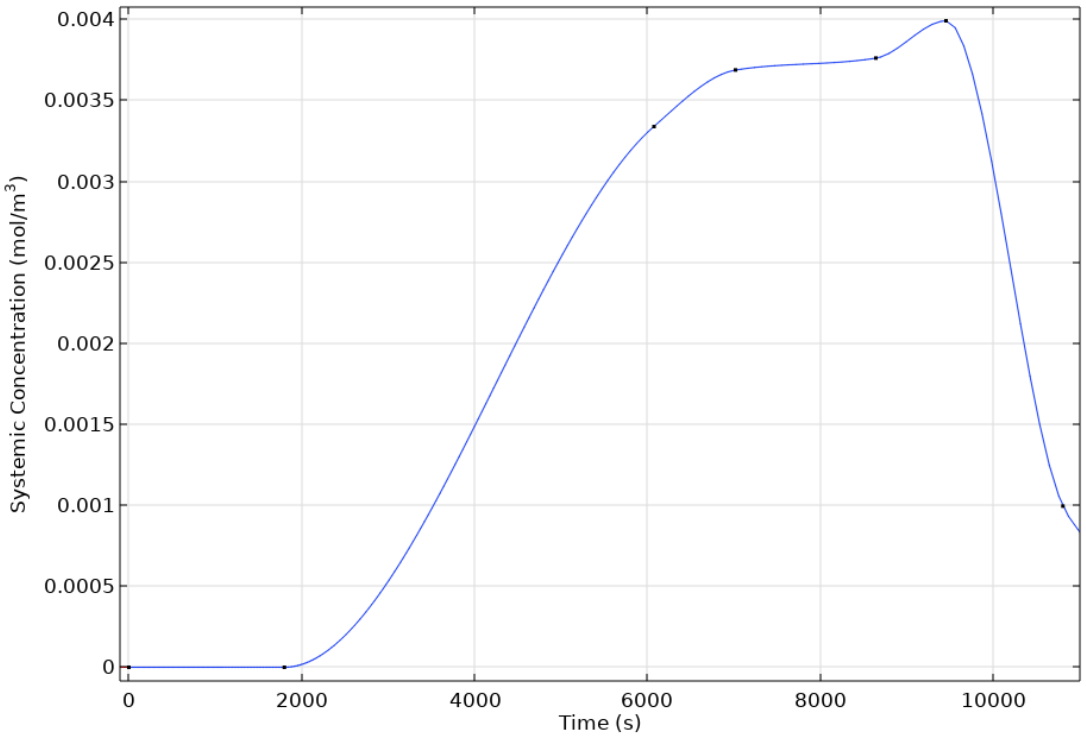

Figure 5. Systemic docetaxel concentration used as boundary condition at the bottom of the dermis

7.2 Initial Conditions

When modeling heat transfer, each layer of the skin starts at its thermoneutral temperature before the cold cap is applied. The compressed hair layer was taken to initially be at room temperature. When modeling mass transfer, the initial drug concentration is zero across all layers before infusion starts. There is no drug diffusion across the hair layer, so initial concentration can be ignored (although it is still zero). These values are shown below in Table 1.

Table 1: Initial temperature and concentration values for scalp layers

Domain	Initial condition (at t = 0)	Symbol	Value	Unit	Source
Hair	Initial temperature	$T_{h,0}$	298. 15	K	[3]
Epidermis	Initial temperature	$T_{e,0}$	306. 95	K	[3]
	Initial docetaxel concentration	$C_{e,0}$	0	mol/m^3	-
Dermis	Initial temperature	$T_{d,0}$	306. 95	K	[3]
	Initial docetaxel concentration	$C_{d,0}$	0	mol/m^3	-

8 Important Parameters

The properties of each tissue layer and relevant parameters for the bioheat equation and diffusion equations are displayed in Table 2.

Table 2: Input parameter definitions and values for scalp layers

Domain	Parameter	Symbol	Value	Unit	Source
Hair	Density of hair	ρ_h	1	kg/m^3	[8]
	Specific heat of hair	$C_{p,h}$	1000	J/kg K	[8]
	Thermal conductivity of hair	k_h	0.25	W/m K	[9]
	Density of air	ρ_a	1.225	kg/m^3	[1]
	Specific heat of air	$C_{p,a}$	700	J/kg K	[1]
	Thermal conductivity of air	k_a	0.025	W/m K	[1]
	Porosity	ε_p	0.5	-	
Epidermis	Density	ρ_e	1085	kg/m^3	[3]
	Specific heat	$C_{p,e}$	3680	J/kg K	[3]
	Thermal conductivity	k_e	0.45	W/m K	[3]
Dermis	Density	ρ_d	1085	kg/m^3	[3]
	Specific heat	$C_{p,d}$	3680	J/kg K	[3]
	Thermal conductivity	k_d	0.45	W/m K	[3]
	Initial volumetric metabolic heat generation	M_0	1800	W/m^3	[8]
	Initial blood perfusion rate	ω_0	1.8	kg/m^{3}s	[8]
	Resting blood velocity through skin capillaries	u_0	0.00047	m/s	[13]
	Diffusivity of docetaxel through skin cells	D	4.25×10^{-9}	m^2/s	[9]

	Temperature of blood within the body	T_{artery}	310. 15	K	[8]

The arterial temperature (T_{artery}) was estimated as the core body temperature to be used in the blood perfusion term in the bioheat equation. The units of blood perfusion are kg/m^{3}s because it incorporates density, which is also why there is not an additional density multiplication in the blood perfusion source term in Eq. 3 The initial blood velocity in the dermis (u_0) was taken as the resting velocity of blood through capillaries in the skin which is a best approximation based on blood flow near the skin surface [13]. There was minimal data within literature regarding the diffusivity of docetaxel (D), so this value was estimated based on paclitaxel, another breast cancer chemotherapy drug of similar size and molecular weight to docetaxel [9].

9 Mesh and Time Step Convergence

Mesh convergence was performed on the model to determine the number of elements required to eliminate error due to mesh size. The variable chosen to model was concentration rather than temperature because the behavior is more variable over a very small change in value. Three mesh sizes were tested: extra coarse (180 elements), coarser (260 elements), and normal (500 elements). The concentration vs. time at a cut point at the follicle level was plotted for each mesh size as seen in Figure 6. The overlapping of the three lines indicates mesh convergence even with the concentration being highly variable over time as shown by the complex shape of the curve. A coarser mesh (260 elements) was selected since it was in the middle of the three sizes, allowing for reduced computation time but still stable results. The final chosen mesh with quadratic elements can be seen in Figure 7.

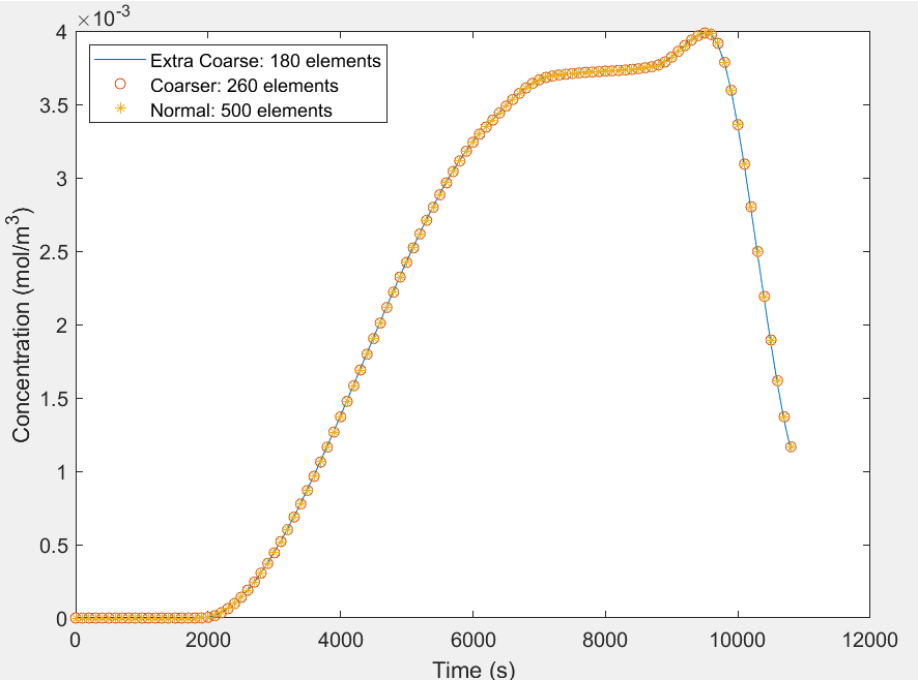

Figure 6: Graph showing concentration vs. time at follicle level for three different mesh sizes. Convergence is obtained as demonstrated by the overlapping of the three lines.

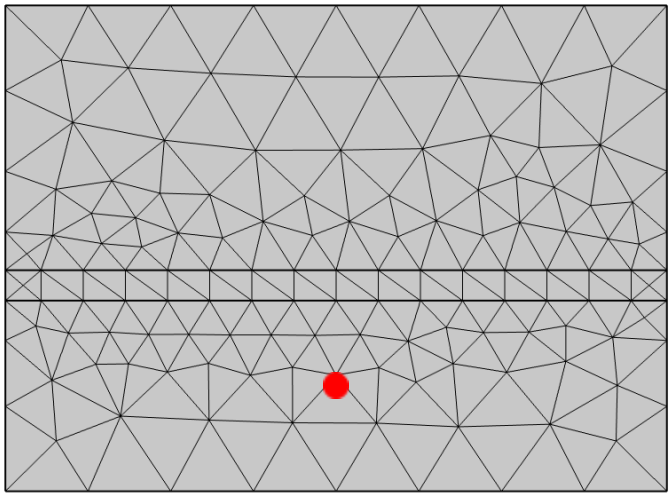

Figure 7. Final mesh including 260 elements and a quadratic element type showing location of cut point at follicle level

Time step convergence was also performed to determine the best time step that would yield stable results. The model was run with three different time steps: 0.5 s, 1 s, and 10 s. All of the tested time steps yielded equivalent results as shown by the overlapping plots in Figure 8. The final selected time step was the default 1 second to balance computation time and stability.

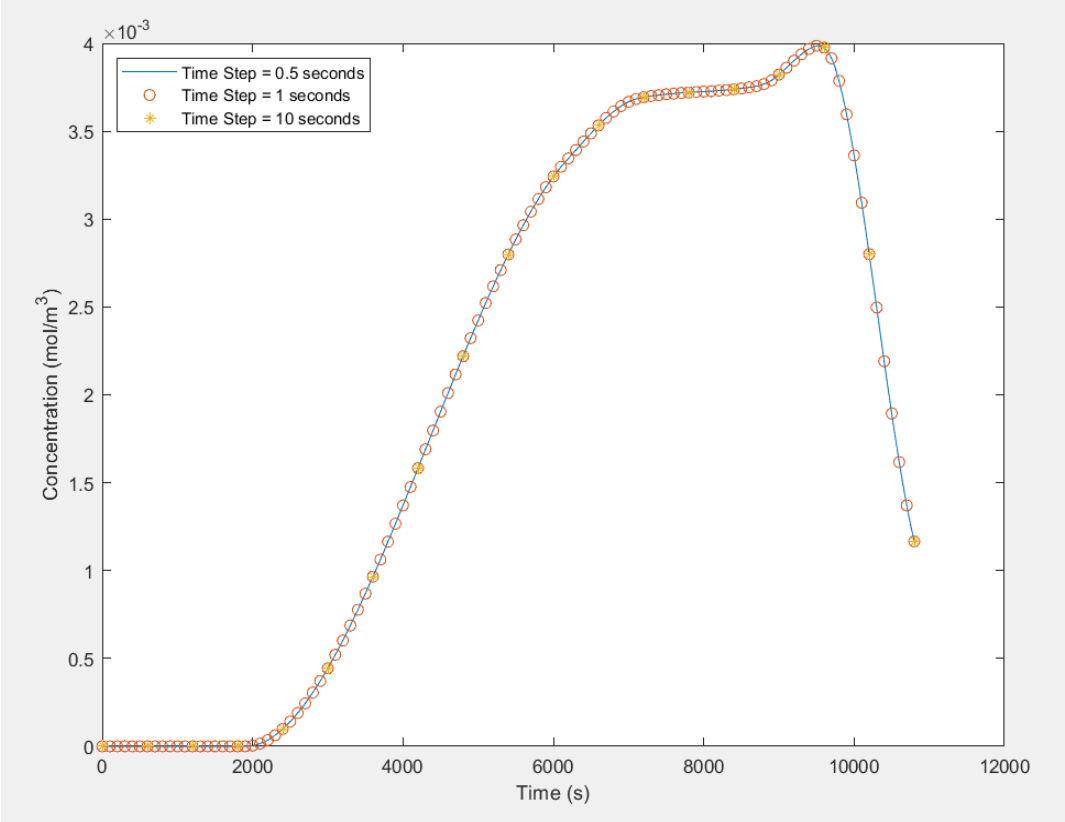

Figure 8: Graph showing concentration vs. time at follicle level for three different time steps. Convergence is obtained as demonstrated by the overlapping of the three lines.

10 Results and Discussion

We ran our model in COMSOL to collect temperature and concentration data over a three-hour (10800 seconds) time period, taking data points in 10-second intervals. The model included a pre-cooling time of a half hour with no concentration at the boundary, an hour-long infusion, and a 1.5 hour post-infusion cooling time. We exported the concentration and temperature data over time throughout the domain. In particular, we examined the resulting temperature and concentration curves at follicle level since damage to cells resulting in hair loss occurs at this point of interest.

Figure 9 depicts the steady-state temperature profile within all layers of the domain. We see that the temperature at the top boundary is 276.15 K, which is equivalent to the applied cold cap temperature of 3℃. Temperature increases as depth within the scalp increases.

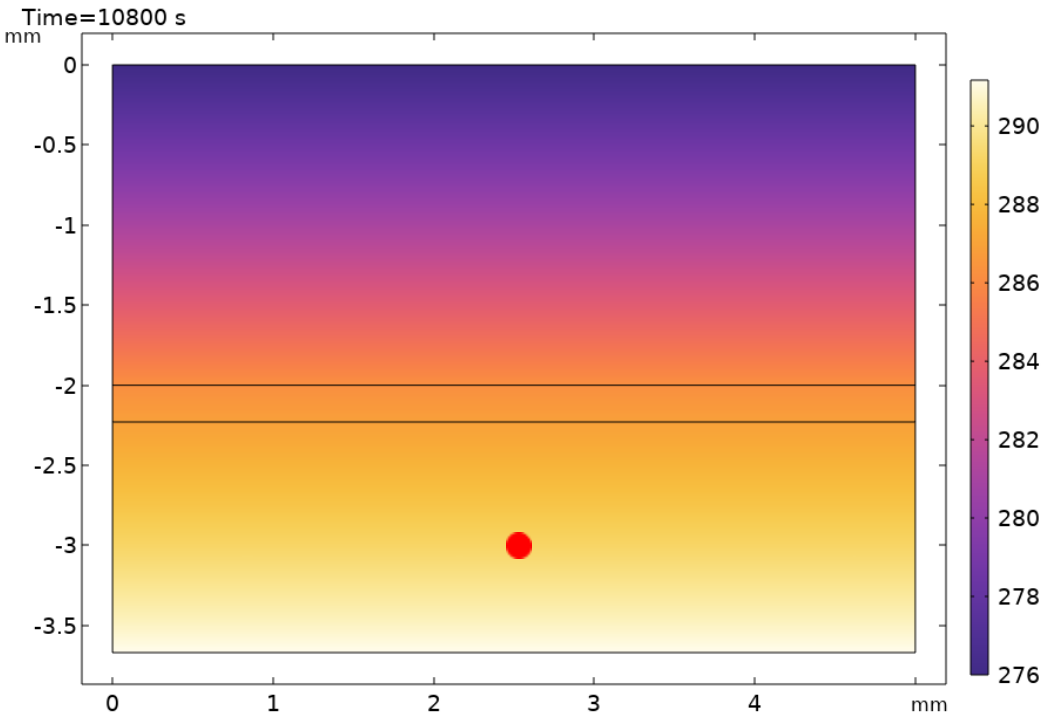

Figure 9. Steady state temperature profile at the end of the cold cap process with red dot indicating follicle level for following analyses

Figure 10 shows temperature over time at the follicle depth. Initially, the temperature decreases rapidly until it reaches a steady state temperature of 289 K which persists through the end of the post-infusion cooling stage. This steady state temperature occurs at ~200 seconds which is significantly lower than clinical recommendations of a 1800s (30 min) pre-cooling time.

Since we were looking at such a small section of the scalp, it is possible that our model over-simplified the process resulting in more rapid cooling.

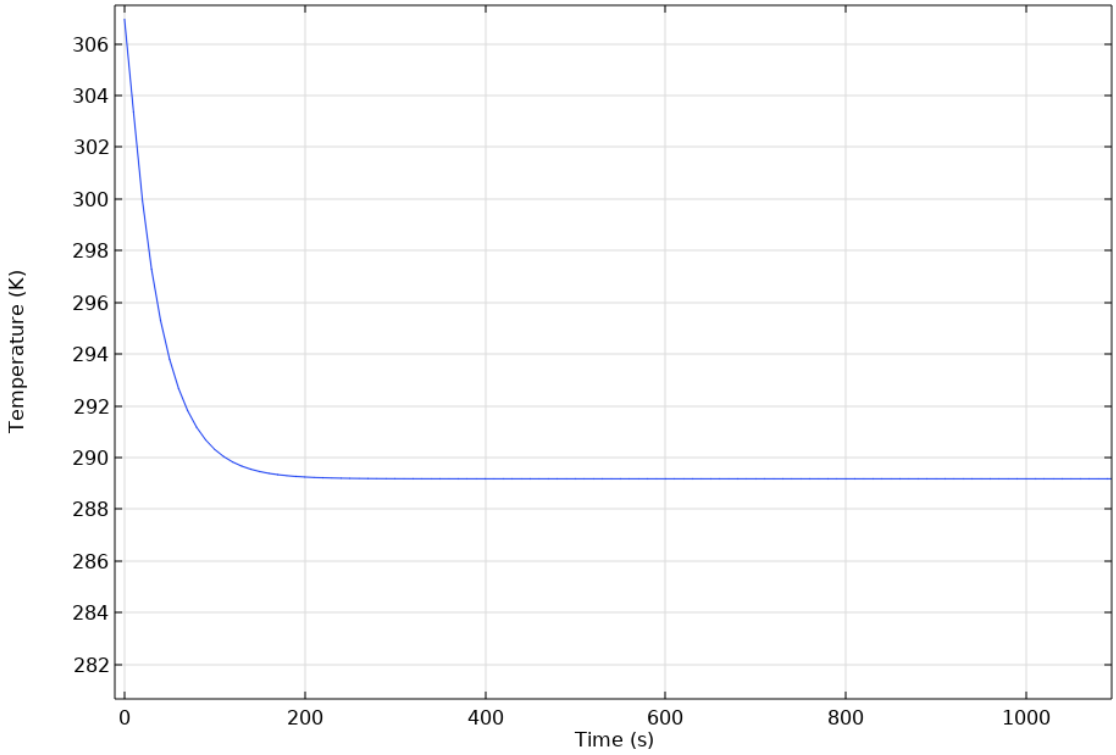

Figure 10. Temperature over time at the follicular level. Steady-state is reached at around 200 seconds and persists through the end of the post-cooling stage.

Next, we sought to understand how the concentration at follicle level differed from systemic concentration applied at the bottom boundary. The graphs of the two concentrations vs. time can be observed in Figure 11. The concentration at the follicle level mirrors the general trend of the changing concentration at the bottom boundary. During the pre-cooling time, there is no docetaxel present in the tissue. During infusion, there is a linear increase in drug concentration. When the infusion ceases at 5400 seconds and the drug concentration at the bottom boundary decreases due to systemic metabolism, the drug continues to diffuse away from the blood towards the follicle. Eventually, the drug passes the follicle depth and travels towards the epidermis. Since there is no additional concentration being supplied post-infusion, the drug concentration at the follicle steadily decreases. There is a slight delay in the change in concentration at the follicle level as compared to systemic concentration. This makes sense since it takes time for the drug to travel from the main artery to the follicle. It is also important to note that there was no source term due to metabolism included in the mass transfer within the epidermis and dermis. Although metabolism occurs which eventually lowers the concentration of the drug throughout the skin tissue, the effects of this process would be seen much later and are not significant compared to the changes in concentration resulting from the drug delivery during and after infusion within the 3-hour cold cap process.

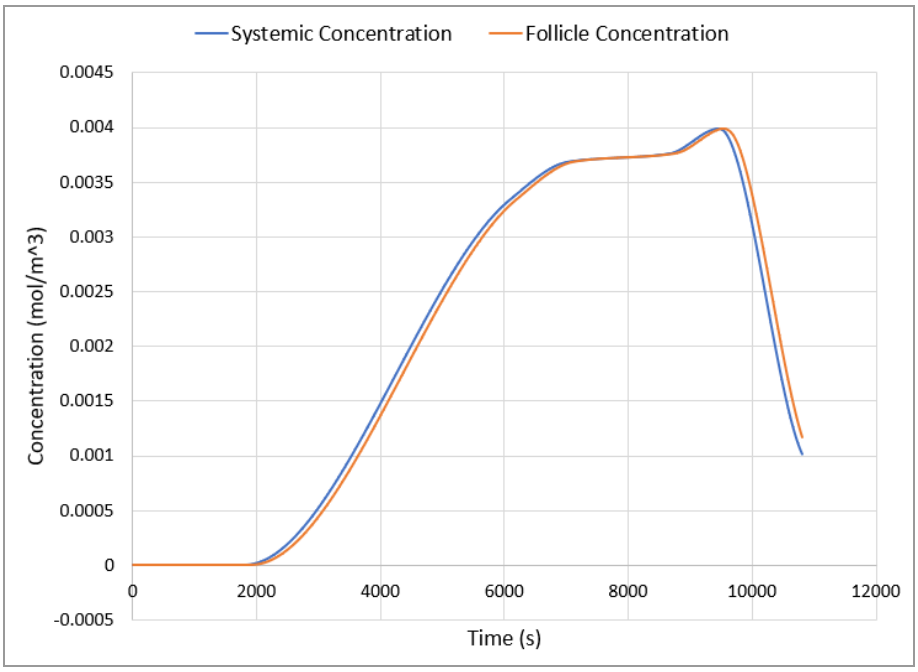

Figure 11: Docetaxel concentration over time at the follicular level plotted next to the input concentration profile applied at the lower boundary of the dermis.

Figures 12-14 track the concentration profile at the end of each stage of cooling. Initially, there is no drug in the tissue as shown in Figure 12. Figure 13 represents the concentration profile immediately after infusion ends. At this point, the concentration of docetaxel is at its peak and has reached the follicle level. Finally, Figure 14 shows the concentration profile after post-cooling has ended. Most of the docetaxel has passed the follicle level and accumulated in the epidermis.

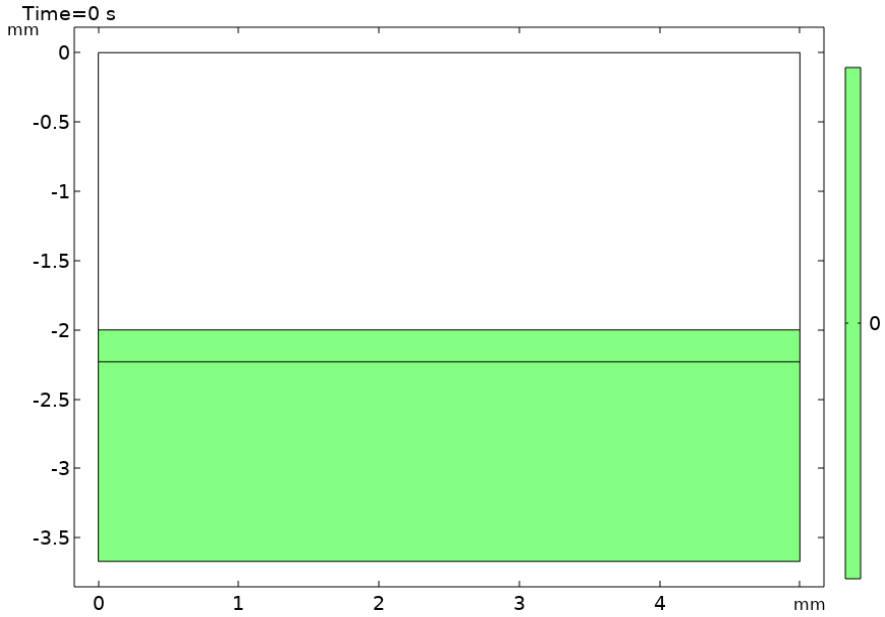

Figure 12. Initial concentration profile of docetaxel in the dermis before infusion is started. There is no drug in the domain at this point.

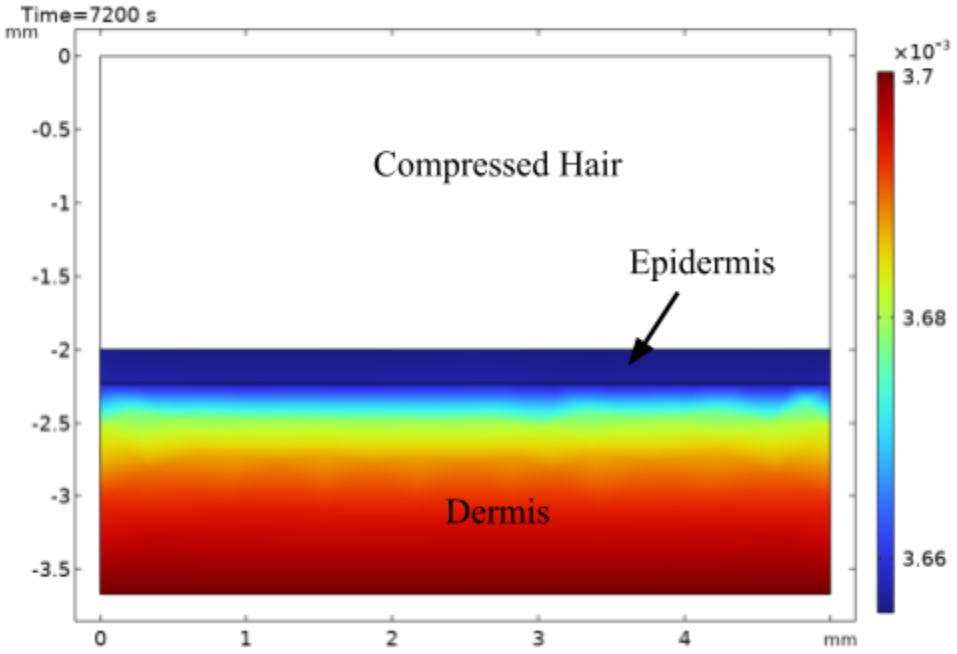

Figure 13. Concentration profile of docetaxel immediately after the 1 hour infusion ends. Drug has been carried through the dermis via blood vessels and diffused through the epidermis.

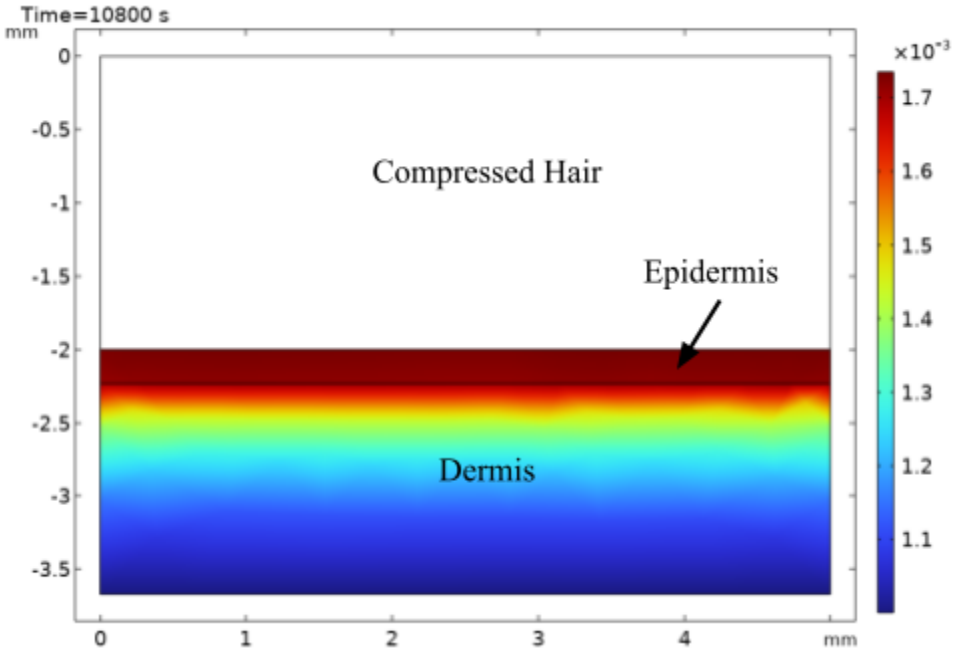

Figure 14. Final concentration profile at 3 hours, after post-infusion-cooling has concluded. Concentration has decreased in the dermis and epidermis because systemic concentration has decreased.

After observing the results for temperature and concentration with an applied cold cap of 3℃, we varied the temperature boundary condition at the surface of the compressed hair layer to simulate different cold cap temperatures. Again, steady state temperatures were reached well before the end of the pre-cooling phase. The steady state temperatures at follicle depth were lower for lower cold cap temperatures as shown in Figure 15. We used a temperature of 25℃, or room temperature, to simulate no cold cap. There is a slight decrease in temperature before approaching steady state although a constant line is expected. This discrepancy is likely the result of using a heat flux boundary instead of a constant temperature boundary condition at the base of the dermis. Initially, we chose to use a flux boundary condition because at very cold temperatures, it is not realistic for the scalp to be maintained at thermoneutral temperature. However, when looking at the results, we got a steady state temperature much lower than expected. Therefore, in future models it might be worthwhile to explore a constant temperature boundary condition deeper within the subcutaneous layers. Also shown in Figure 15, applying a -25℃ surface temperature results in a follicle temperature below freezing (0℃). Therefore, although the amount of drug delivered is reduced, the hair follicle cells would likely die from freezing temperatures instead. The clinical cold caps that use these low temperatures implement a frozen gel application rather than constant temperature liquid coolant which would be modeled differently, including the incorporation of a convective boundary. Our model more closely resembles cold caps which maintain a constant surface temperature with liquid coolant. Using this boundary condition, our model results in lower temperatures.

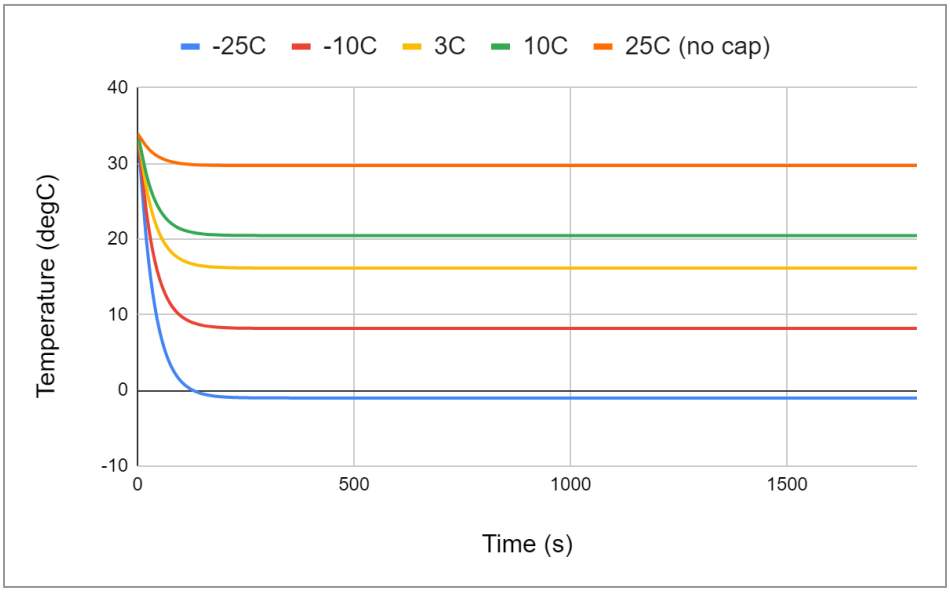

Figure 15. Temperature over time at follicle depth with varying applied cold cap temperatures; different steady state temperatures are reached after the pre-cooling phase.

After identifying the cap temperature's effect on steady state temperatures, we observed the effect of varying temperature on the concentration over time at the follicle level as shown in

Figure 16. We found that the peak concentration was reached later with decreasing cold cap temperatures. However, the peak concentration itself did not seem to decrease until the cap temperature was reduced significantly to -25℃.

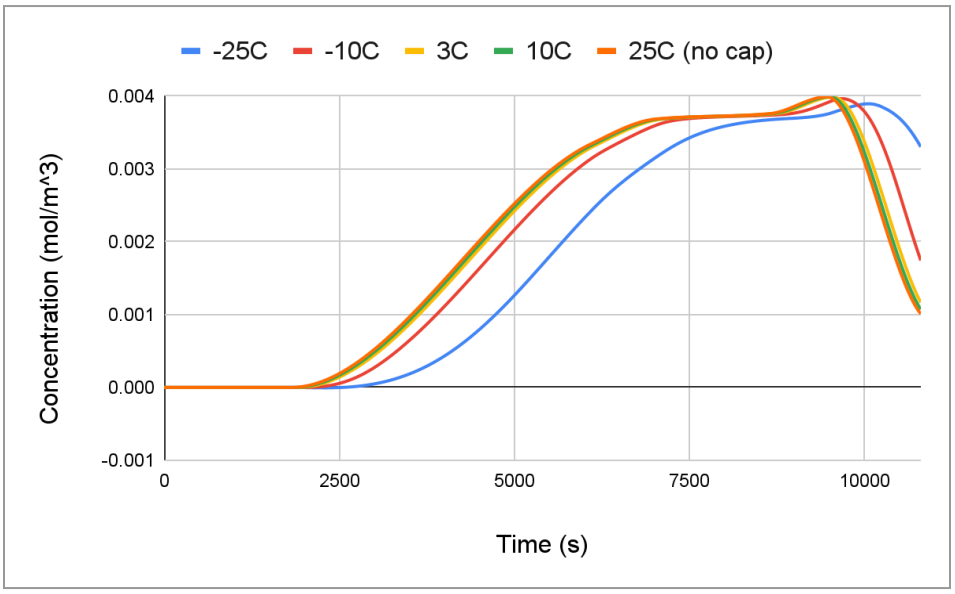

Figure 16. Concentration vs. time at follicle depth with varying applied cold cap temperatures; drug delivery of docetaxel is slowed with decreasing temperatures.

11 Validation

In previous studies, the head geometries vary significantly in terms of size, shape, and layer thickness. Furthermore, each uses different parameters and boundary conditions. Such variation makes it difficult to directly compare our results with those of the other models. That being said, we used several methods of comparison to validate our model with available literature. We were only able to validate our heat transfer results; we could not find comparable data regarding mass transfer due to scalp cooling.

11.1 Subcutaneous steady-state temperature profile comparison

One way in which we validated our model was by using a computational model from another study that measured temperature variation with increasing tissue depth. We compared the overall trend of the steady-state profile of our model to the one found in Baldry et al. 2018. For ease of comparison, we matched the format of Baldry et al. 2018, where a subcutaneous depth of 0 mm corresponds to the top surface of the epidermis. Using similar properties, dimensions, and cooling times, we obtained Figure 17. Our results (orange) are comparable to those in Baldry et al (blue). However, Baldry et. al included a convective and radiative heat flux in addition to the conductive heat flux that we included. This can explain why their data had lower resulting temperatures as the extra heat flux values indicate greater heat exchange.

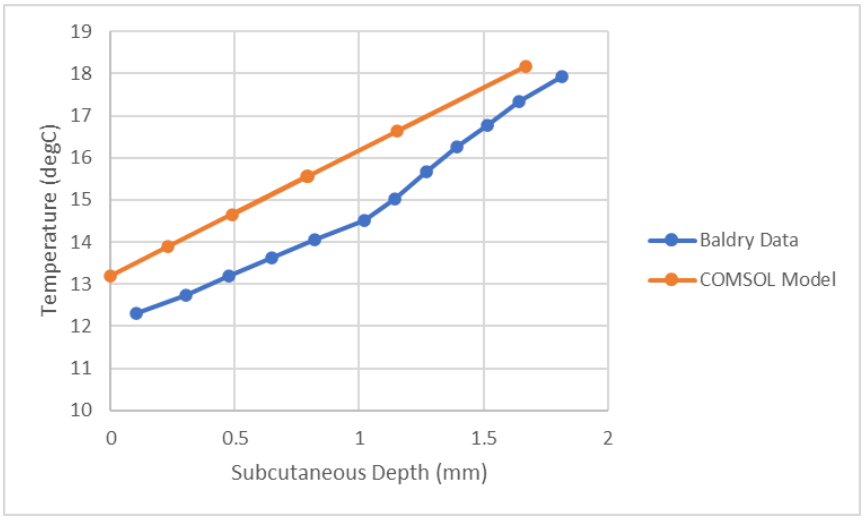

Figure 17. Subcutaneous steady-state profile for our model (blue) and Baldry et al.2018 (orange) using 1000 W/m^2 forced boundary flux cooling and average female head dimensions and subsurface layer thicknesses.

11.2 Follicle level final temperature from model compared to clinical cold cap data

Another way we verified our model was by comparing it to data from the first FDA approved cold cap: DigniCap. This cap maintains a temperature of 3℃ with a recommended pre cooling and post infusion cooling time equivalent to our model (30 minutes for pre-cooling and 90-180 minutes for post-cooling) [4]. A 3℃ cooling cap is most effective when it maintains the scalp temperature at temperatures less than 22℃. Temperatures below this level are known to reduce drug cytotoxicity [6]. Figure 18 shows that our model maintains a follicle temperature below the recommended 22°C.

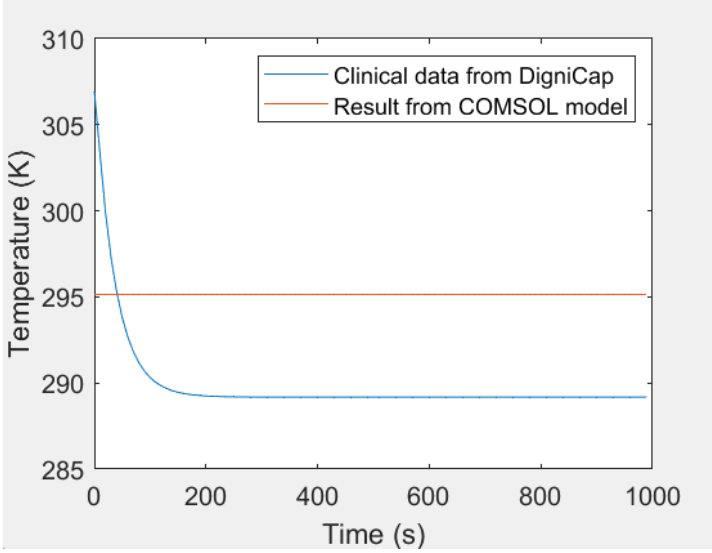

Figure 18. Temperature vs. time at the follicular level an applied cold cap temperature of 3℃ showing that the scalp temperature reaches 289 K (16℃) at steady state which is in the range of acceptable values (less than 295 K or 22℃) based on clinical data of the DigniCap

12 Sensitivity Analysis

12.1 Sensitivity to hair thickness

We chose to explore the sensitivity of our model to different hair types by changing the thickness of the compressed hair layer. Understanding the impact of hair thickness is important because this greatly varies from patient to patient and is also dependent on how far along the individual is in their treatment. We varied the hair thickness by ±10% and ±50% while keeping the other parameters the same. We measured temperature at the follicle level as an indicator of sensitivity. The results are displayed in Figure 19. Thicker layers result in higher temperatures, which is due to hair acting as an insulating layer. A 50% increase in hair thickness led to a 0.9% increase in steady state temperature. However, a 50% decrease in hair thickness did not result in an equivalent decrease in temperature, rather it led to a 1.25% decrease in temperature at the follicle level. Since the impact of temperature on blood perfusion is not linear, we would not expect changing hair thickness to be symmetric. From these results, it is evident that temperature is significantly influenced by the thickness of the hair layer.

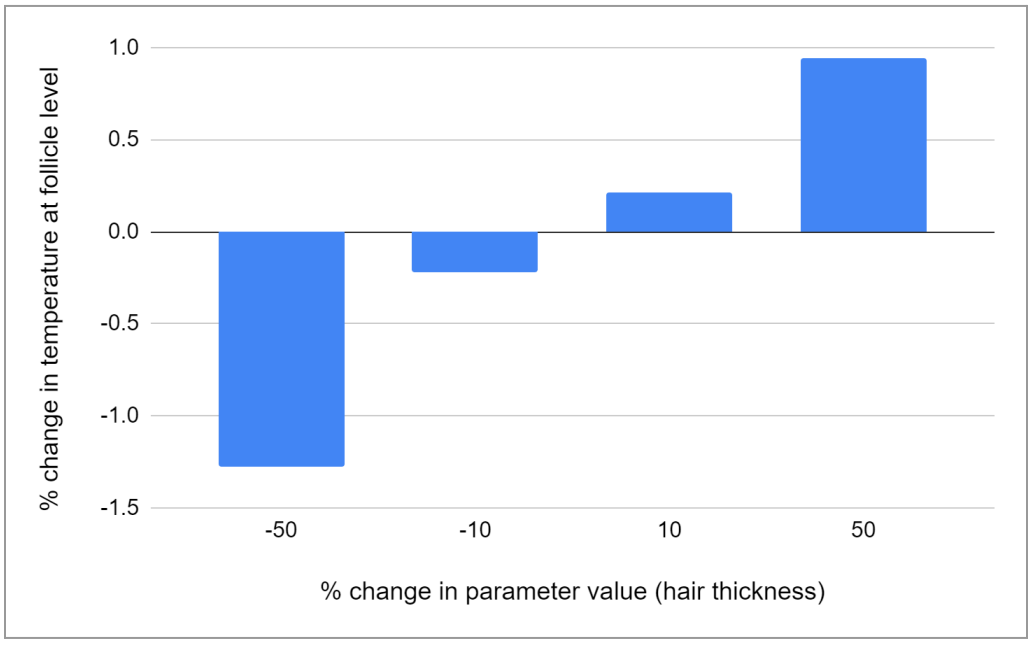

Figure 19. Sensitivity of Temperature at Follicle Level to Hair Thickness.

Our original model used a hair thickness of 2 mm. Knowing that the temperature is highly sensitive to changing hair thickness, we decided to plot the temperature vs. time at follicle level for different hair thicknesses which is displayed in Figure 20. Our model therefore is adaptive to the cooling process for individuals with varying hair types and supports the idea that cold cap success in reducing hair loss is dependent on patient characteristics.

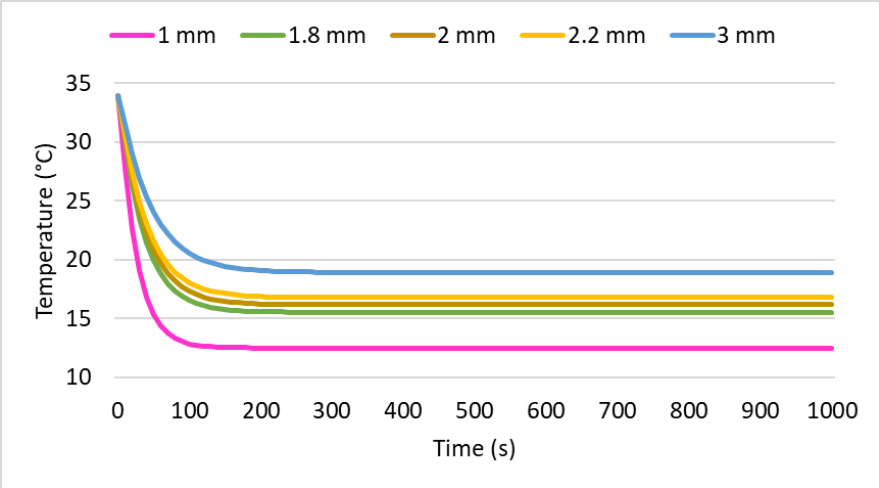

Figure 20. Temperature vs. time at follicle for varying hair thicknesses

12.2 Sensitivity to blood perfusion rate (ω_0)

We varied the initial blood perfusion rate to identify our model's sensitivity to this parameter. Systemically, there can be a large variation in the rate of blood perfusion based on the location in the body and due to variation between individuals. We found little variation in temperature with ±10% change in perfusion, so we drastically increased it to +700% to identify if there was any effect. We could not decrease it by the same amount because the value cannot be negative. Figure 21 shows that a 700% increase in the initial blood perfusion rate resulted in a 0.03% change in temperature and 0.005% increase in peak concentration. This indicates that both temperature and concentration at follicle level are not sensitive to changes in the blood perfusion rate.

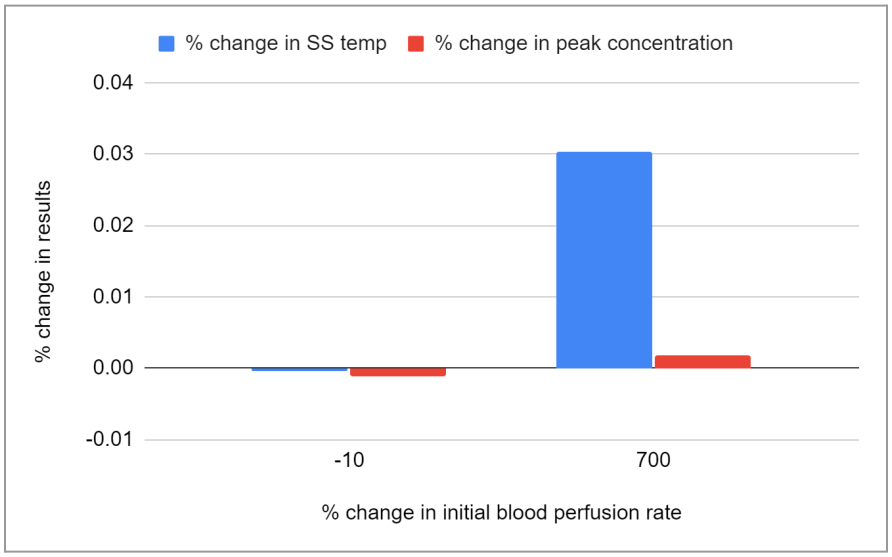

Figure 21. Sensitivity of temperature and peak concentration at follicle level to initial blood perfusion rate.

12.3 Sensitivity to initial blood velocity (u_0)

We wanted to identify if the results for drug concentration were sensitive to blood velocity. The nominal value we used in our model for initial blood velocity was 0.47 mm/s based on resting blood velocity within capillaries in the skin [14]. This value was taken from Stücker et. al. which also found a standard deviation of ± 0.37 mm/s. Therefore we increased the initial blood velocity value by ± 78.72%. Figure 22 demonstrates that increasing initial blood velocity by +0.37 mm/s, or +78.72% had little effect on peak concentration at follicle level, with less than a 0.25% increase, compared to a decrease of the same amount, which resulted in a 1% decrease in concentration.Our drug transport model relies on blood flow to carry the drug because we neglect diffusion through the skin. Therefore, the blood velocity is a dominant factor which is why decreasing its value to near zero impacts the peak concentration value.

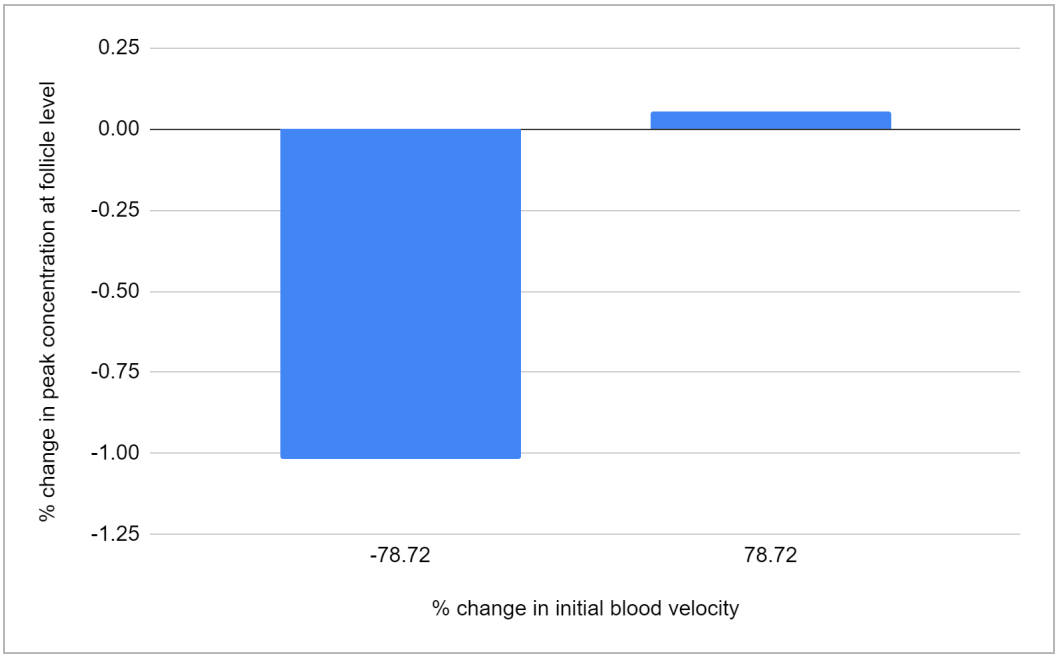

Figure 22. Sensitivity of peak concentration at follicle level to initial blood velocity.

To better visualize the overall concentration profile at the follicle level, a plot of concentration over time for different velocities is shown in Figure 23. Slowing the velocity slows the transport of docetaxel as shown by the blue line. However, both an increase and decrease in velocity do not result in significant changes to peak concentration.

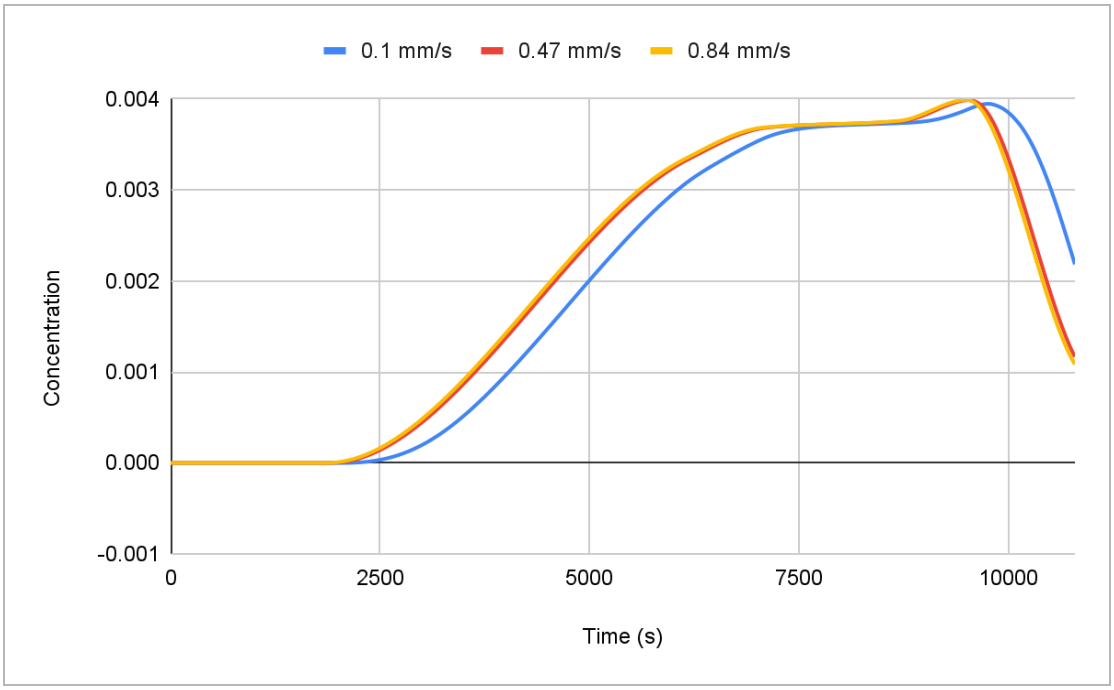

Figure 23. Profile of docetaxel concentration at follicle depth over time

12.4 Blood velocity dependence on temperature

In our problem definition, the drug transport varies with temperature encompassed by the blood velocity term, which is dependent on temperature in the same way as perfusion in the heat transfer equation ($u = \frac{u_0}{1+Cs} \cdot 2^{(T-T_0)/10}$). We ran the model with constant blood velocity ($u = u_0$) to determine if the concentration was in fact decreasing due to the cooling process. The concentration of docetaxel at follicle level over time for these two different blood velocity profiles is depicted in Figure 24. We can see that the drug transport is slowed when blood velocity has temperature dependence and decreases during cooling.

Although there is some variation, there is less variation than expected when blood velocity is altered. This indicates that cooling has minimal effect on blood flow and thus drug transport. Further, these results do not support the central claim that cooling the scalp causes vasoconstriction and consequently decreases the total amount of drug that reaches the hair follicle. The consequence of this finding could lead to one of two conclusions. First, our relationship between perfusion and blood velocity is oversimplified. The second possible explanation is that the accepted claim that temperature dependent perfusion influences drug diffusion is flawed. Our follicle level was located very close to the boundary where the drug infusion occurred, so the concentration at the follicle is very similar to that of the boundary condition and there is a chance that the distance is not great enough to see the full effects of velocity and temperature.

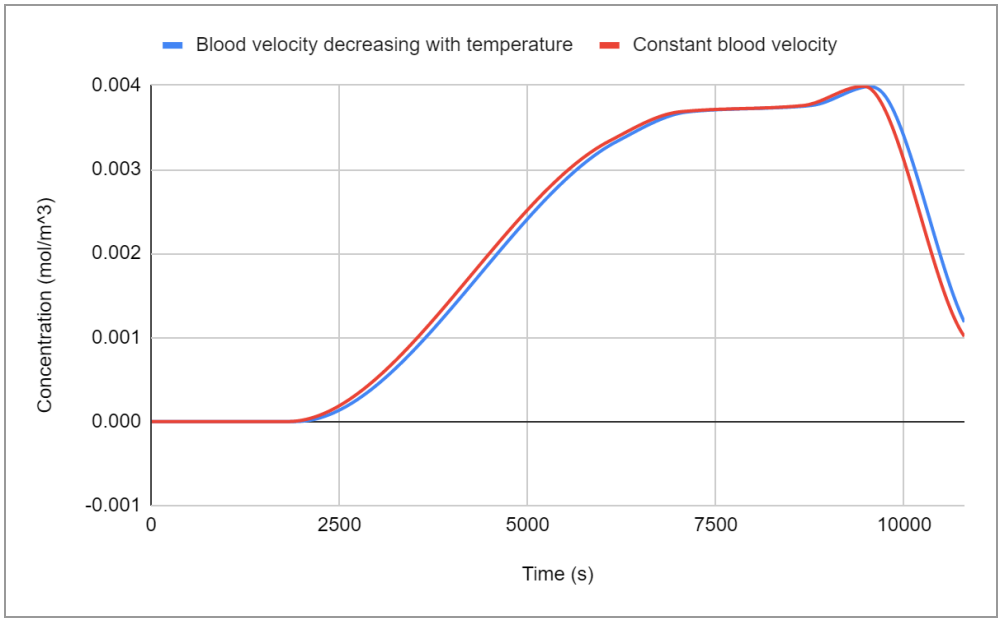

Figure 24. Sensitivity of concentration at follicle level to blood velocity dependence on temperature compared to constant blood velocity $u = u_0$

13 Conclusions and Future Outlook

Our model aimed to combine both heat and mass transfer during scalp cooling which was different from previous computational models and clinical cold cap data which only incorporated scalp temperatures without investigating the corresponding concentration of chemotherapy drugs. However, this made it difficult to validate our mass transfer results and evaluate the efficacy of our model. Our model data does not support the theory that scalp cooling decreases blood perfusion thus reducing the amount of drug that reaches the hair follicle. Instead, we found that decreasing cold cap temperatures reduce blood velocity and slow drug delivery; although slowed, the maximum docetaxel concentration was not notably reduced. Using this information, our model may be used to predict why clinical cold caps are not reliable, as patient testimonies reveal they are only 50% effective in reducing hair loss by 50% [2]. Our model's sensitivity to the thickness of the hair layer can also be useful in predicting why results may vary between patients, as each person's hair thickness and texture is different.

We made simplifications and assumptions to build our model. This does not mean our model is not useful as a whole. However, more research can be done to better understand the physical scenario and improve the model of the process. For example, we assumed that the blood velocity term in the mass transfer equation followed the same trend and dependence on temperature as the blood perfusion term in the heat transfer equation. In future models, the velocity function could be varied to identify its effect on drug concentration. Additionally, it may be worthwhile to construct a model that includes layers below the dermis, such as subcutaneous fat and skull. By increasing the thickness of the domain, a constant temperature boundary condition set to body temperature can be reasonably included, rather than the heat flux boundary

condition that we implemented. Furthermore, there are two main types of cold caps: one that uses a frozen gel and needs to be replaced frequently and the other that continuously circulates coolant into the cap [4]. Our model more closely modeled the second cold cap type, but future models could model the first cold cap type with different assumptions and boundary conditions. Overall, we can conclude that our model provides a new perspective of the cold cap process to further their development and potential of success against hair loss during chemotherapy treatment.

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