Comparison of Intravenous Bolus vs. Infusion of Heparin Diffusion through Cubital Vein

BENG 221
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Table of Contents

INTRODUCTION

What is Heparin?: Heparin is a linear polysaccharide common in all animals and is known for its anticoagulant properties. Heparin is found in white blood cells and is responsible for several biological functions, such as mediating anti-inflammatory responses, developmental processes, angiogenesis, and the coagulation cascade[1]. Although some functions have been characterized, much is still unknown about the role of heparin in the body. Molecularly, it occurs as a proteoglycan (HSPG) in which two or three heparin chains are attached in close proximity to cell surfaces or extracellular matrix proteins[2].

Medical uses and side effects: Medically, Heparin is administered as an anticoagulant to treat pulmonary embolism[3], deep vein thrombosis, or to assist with the treatment of myocardial infarction. Heparin is also used before surgery to decrease the risk of blood clots. After administration, the therapeutic effects of Heparin are expected to take place within minutes[4]. However, the timing and dosage of administration can be dependent on the patient's size and the indicated application. Typically, administration begins with an intravenous (I.V.) bolus injection into the blood vessel of choice, followed by an I.V. infusion.

Due to Heparin's potent ability to bind to other proteins, diffusion of medically administered Heparin to untargeted areas can cause serious adverse effects. For example, Heparin may increase bleeding or induce skin lesions[5]. Other side effects of Heparin include acute systemic reactions, thrombocytopenia, or hyperkalemia[6]. Thrombocytopenia and hyperkalemia are of strong concern due to the high risk of limb loss or death caused by these heparin induced disorders. They are also prime examples of positive feedback reactions caused by the binding of Heparin to proteins that disturb the homeostasis.

Heparin Induced Thrombocytopenia (HIT) begins with the binding of Heparin to the protein Platelet Factor 4, resulting in an abnormal Immunoglobulin G (IgG) antibody[7]. The IgG antibodies create a complex with heparin and PF4, initiating blood clot formations. HIT is a condition characterized by low blood platelet count below 150,000. It is a severe reaction to Heparin that occurs with even the smallest dosage of Heparin. It occurs four to five days after onset of Heparin treatment and leads to limb-threatening thrombotic complications.

Hyperkalemia is another serious side-effect of Heparin treatment. Heparin is a potent inhibitor of aldosterone production in the adrenal gland (zona glomerulosa) resulting in high levels of potassium in the blood stream[8]. Like thrombocytopenia, hyperkalemia's onset can be triggered by even the smallest Heparin dosage in hypersensitive patients. Common symptoms are heart palpitations, muscle pain, muscle weakness, and an abnormal heart rate that can result in cardiac arrest or death.

Importance: Heparin has demonstrated great potential in research for long term treatment of diseases due to its ability to bind to proteins and regulate chemical

pathways. However these same abilities make it dangerous for patients and study subjects when Heparin diffuses to untargeted areas. To reduce this risk, it is necessary to understand the properties of Heparin such as its diffusion of Heparin through the blood vessel walls. This information will assist researchers and physicians alike to better regulate Heparin dosage or design ulterior methods of administration.

PROBLEM STATEMENT

Blood vessels transport substances such as nutrients, hormones, and oxygen throughout the body and allow diffusion into peripheral tissues. Diffusion of a substance is dependent on its structure, size, and polarity which can modeled by Fick's Second Law of Diffusion. Modeling of species diffusion from blood vessels allows higher accuracy for dosage monitoring, leading to enhanced patient-centered care.

Currently, clinical practice relies on the pathophysiology of patient at the time of injection, to determine the dose of Heparin to reduce its side effects. This method is unreliable because the physiological base of the dosage is not well understood. In this report, we create a model that approximates the axial diffusion of Heparin through the **cubital vein with diameter of 1.8×10^{-3} *m***, the most common blood vessel used in intravenous injections. The model consists of a partial differential equation that is iterated over **four different scenarios** and solved analytically and numerically. Concentration profiles of Heparin in the cubital vein are assessed in space axially and in time (Figure 1). The dosage modeled **was 5,000 units BID (1.48×10^{3} *mmol/m*^{3})** since it is the lowest administered dosage. Because side effects of Heparin diffusion into untargeted areas do not appear until 3 to 4 days, a longer **modeling period of 27 hours** was chosen. The results of each condition is then compared. Such quantitative analysis is intended to be used in conjunction with available patient data in the future to determine the correlation between Heparin diffusion and patient outcomes. This will help predict the optimal dose of Heparin for each individual medical case.

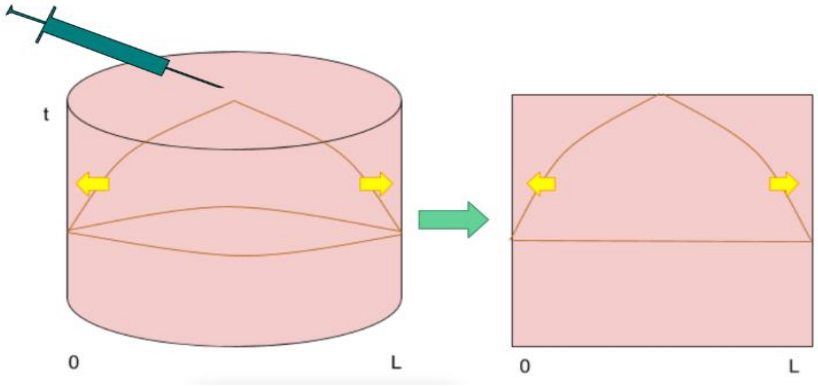

Figure 1. The Cartesian Diagram used for modeling Heparin diffusion through the Cubital Vein. It is assumed the injection occurs at the center of the vein and heparin diffuses symmetrically outwards towards the vein walls.

Scenarios:

1) Intravenous Bolus with Constant Flux
2) Intravenous Bolus with Variable Flux
3) Intravenous Infusion with Constant Flux
4) Intravenous Infusion with Variable Flux

Parameters:

$$Initial\ Concentraion\ of Heparin: C_o = 1.48 \times 10^3 \frac{mmol}{m^3}$$

$$Cubital\ Vein\ Diameter: L = 1.8\ \times 10^{-3}\ m$$

$$Generation\ Constant: \gamma = 32 \times 10^{-3} \frac{mmol}{s}$$

$$Diffusion\ Coefficent: D = 1.2 \times 10^{-12} \frac{m^2}{s}$$

$$Flux: \Phi = 0.48\ \times 10^3 \frac{mmol}{m^3 s}$$

$$Scaling\ Factor: \alpha = 5 \times 10^3\ m$$

ASSUMPTIONS

Below are the listed simplifying assumptions of our model:

1. The system is rotationally symmetrical therefore can be modeled as a 2-D problem and diffusion as a 1-D problem (Figure 1)
2. For the first scenario, flux is constant over time
3. Heparin is the only particle in the blood vessel
4. Diffusion is passive
5. Our section of blood vessel is small enough that blood flow is insignificant and therefore not included in the model.
6. Time starts from 0
7. Concentration of Heparin in Blood is Zero

ANALYTICAL AND NUMERICAL SOLUTIONS

Our model is governed by the diffusion equation:

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} + \ Q(x,t)$$

To analytically solve, apply canonical Green's integrals (Cases 1 and 2):

$$\int_0^L C(x,0)G(x,t;x_0,0)dx_0 + \int_0^L \int_0^t Q(x_0,t_0)G(x,t;x_0,t_0)dt_0dx_0 - \int_0^t D\frac{\partial C}{\partial x}(0,t_0)G(x,t;0,t_0)dt_0 + \int_0^t D\frac{\partial C}{\partial x}(L,t_0)G(x,t;L,t_0)dt_0$$

C(x,t) is the concentration of Heparin in the axial direction of the cubital vein (Figure 1) that is dependent on time, *t* and location *x*, L is the distance along the diameter of the cubital vein. D is the constant of diffusivity and Q(x,t) is the generation term which is nonzero in scenarios 2 and 4. G(x,t;x_0,t_0) are the Green's function for flux-flux boundary condition:

$$G(x,t;x_0,t_0) = \frac{1}{L} + \sum_{n=1}^{\infty}\frac{2}{L}\cos\left(\frac{n\pi x}{L}\right)\cos\left(\frac{n\pi x_0}{L}\right)e^{-D\left(\frac{n\pi}{L}\right)^2(t-t_0)}$$

Scenario 1:

In the first scenario, the model takes on the following generation terms, initial conditions, and boundary conditions:

$$Q(x,t) = 0$$
$$C(x,0) = \delta(t)C_0$$
$$-D\frac{\partial C}{\partial x}(0,t) = -\varphi_0$$
$$-D\frac{\partial C}{\partial x}(L,t) = \varphi_L$$

Here, the initial condition is a delta dirac function which models a bolus injection. The amplitude of the delta dirac function is scaled according to the concentration of the Heparin solution to be injected. The constant flux boundary condition models the flow of Heparin through the walls of the cubital vein. By applying the Green's functions, we solved the governing partial differential equation under these conditions:

$$C(x,t) = C_0 - \frac{(\varphi_0+\varphi_L)t}{L} - \sum_{n=1}^{\infty}\frac{2L}{D(n\pi)^2}(\varphi_0+(-1)^n\varphi_L)\cos\left(\frac{n\pi x}{L}\right)\left(1-e^{-D\left(\frac{n\pi}{L}\right)^2 t}\right)$$

The step-by-step analytical solution and its graph are found in the appendix. Below is the numerical solution obtained by using MATLAB's pdepe solver which resembles the analytical solution as expected.

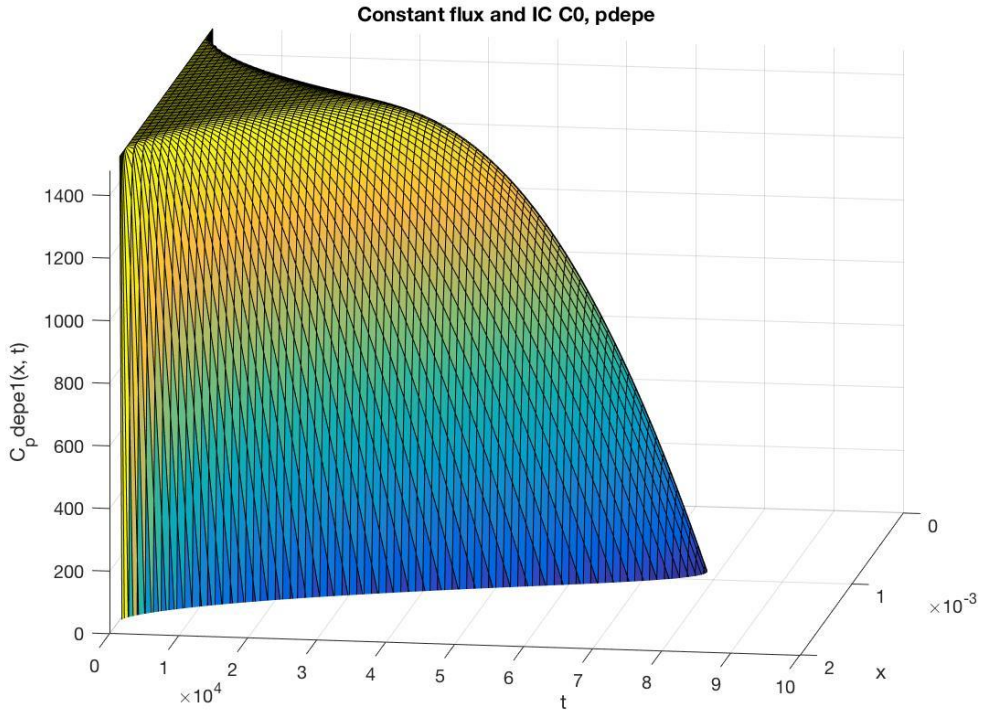

Figure (2): Numerical solution obtained through MATLAB PDEPE for scenario 1

Scenario 2:

For the second scenario, the model takes on the following generation terms, initial conditions, and boundary conditions:

$$Q(x,t) = \gamma$$
$$C(x,0) = 0$$
$$-D\frac{\partial C}{\partial x}(0,t) = -\varphi_0$$
$$-D\frac{\partial C}{\partial x}(L,t) = \varphi_L$$

In this second scenario, the initial condition is set to zero and the generation term is set to a value, gamma. The generation term models the constant amount of Heparin that enters the cubital vein during I.V. infusion. As before, the constant flux boundary condition models the flow of Heparin through the walls of the cubital vein. By applying the Green's functions, we solved the governing partial differential equation under these conditions:

$$\gamma t - \frac{(\varphi_0 + \varphi_L)t}{L} - \sum_{n=1}^{\infty} \frac{2L}{D(n\pi)^2}(\varphi_0 + (-1)^n\varphi_L)\cos\left(\frac{n\pi x}{L}\right)\left(1 - e^{-D\left(\frac{n\pi}{L}\right)^2 t}\right)$$

The step-by-step analytical solution for the second scenario and its graph are found in the appendix. Below is the numerical solution obtained by using MATLAB's pdepe solver which resembles the analytical solution as expected.

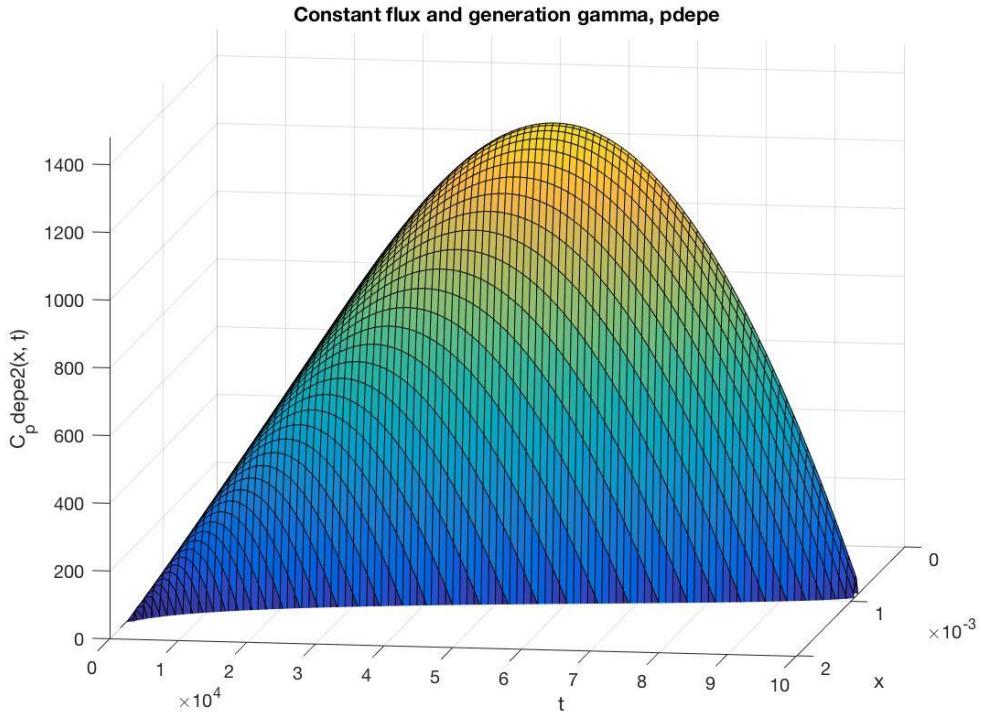

Figure (3): Numerical solution obtained through MATLAB PDEPE for scenario 2

Scenario 3:

For the third scenario, the model takes on the following generation terms, initial conditions, and boundary conditions:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} + Q(x,t)$$
$$Q(x,t) = 0$$
$$C(x,0) = \delta(t)C_0$$
$$-D\frac{\partial C}{\partial x}(0,t) = -\varphi_0 e^{-\alpha t}$$
$$-D\frac{\partial C}{\partial x}(L,t) = \varphi_L e^{-\alpha t}$$

Here, the initial condition is identical to that of the first scenario: a scaled delta dirac function that models a bolus injection at the appropriate concentration. However, unlike the first scenario, which had constant flux boundary conditions, this scenario includes time-varying exponentially decaying flux. This boundary condition attempted to recapitulate a more realistic behavior. In this case, the rational is that the flux of Heparin

is modeled to be at maximum when bolus injection occurs because Heparin concentration is high, and then decreases over time as Heparin concentration also decreases. The solution to the governing partial differential equation was graphed using the numerical solution obtained by MATLAB's pdepe solver:

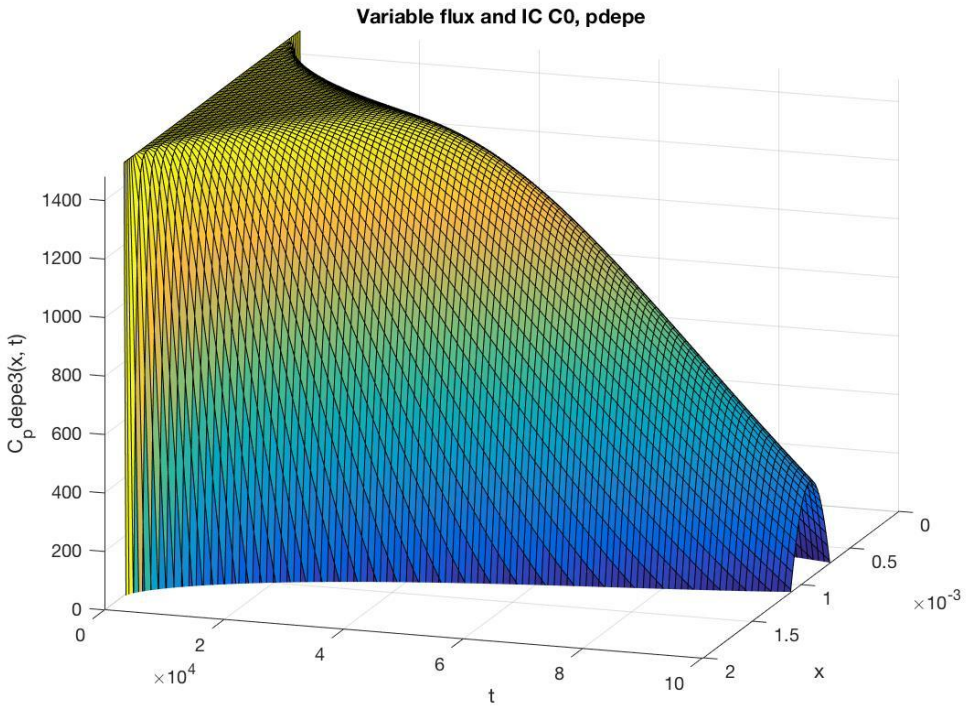

Figure (4): Numerical solution obtained through MATLAB PDEPE for scenario 3

Scenario 4:

For the fourth and last scenario, the model takes on the following generation terms, initial conditions, and boundary conditions:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} + Q(x,t)$$
$$Q(x,t) = \gamma$$
$$C(x,0) = 0$$
$$-D\frac{\partial C}{\partial x}(0,t) = -\varphi_0 e^{-\alpha t}$$
$$-D\frac{\partial C}{\partial x}(L,t) = \varphi_L e^{-\alpha t}$$

Here, the initial condition is identical to that of the second scenario in that the value is zero and like the third scenario, this fourth scenario includes time-varying exponentially decaying flux. The solution to the governing partial differential equation was graphed

using the numerical solution obtained by MATLAB's pdepe solver:

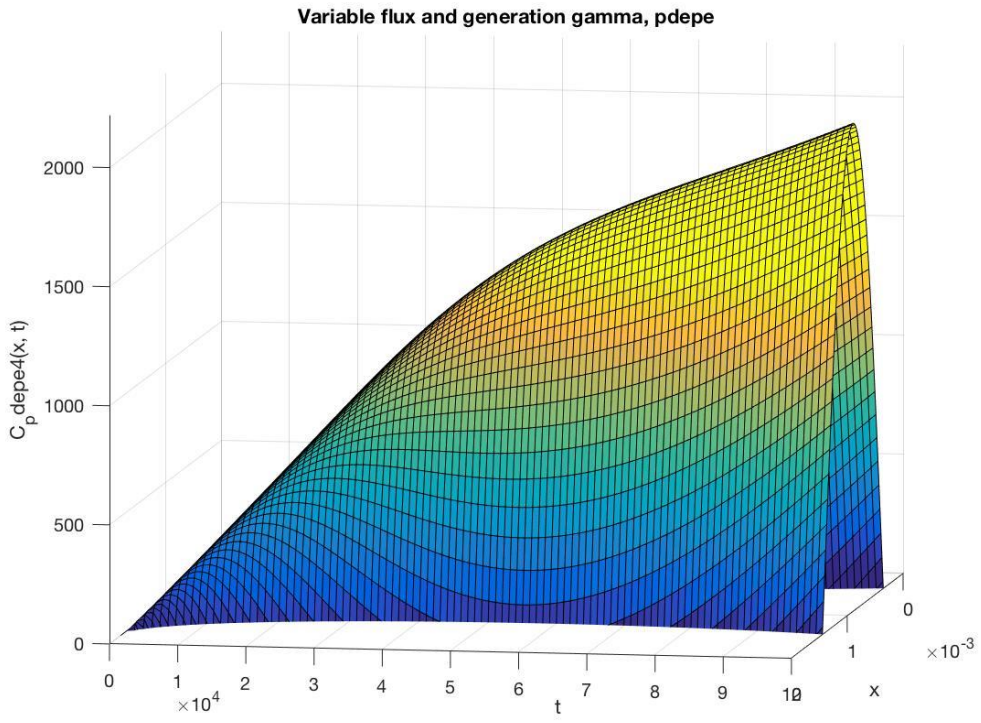

Figure (5): Numerical solution obtained through MATLAB PDEPE for scenario 4

DISCUSSION

In order to visually compare all four scenarios, a plot was created to show the Heparin concentration values over time at the middle of the cubital vein as shown in figure (X). Overall, scenarios 1-3 show a similar characteristic: for large values of time, the concentration of Heparin is low.

In scenario 1 which modeled a bolus injection of Heparin with a constant flux boundary condition, the concentration within the middle of the cubital vein reflected that of the amplitude of the delta dirac function. Since such an impulse occurs only for a short period of time, and the flux condition allows for the Heparin to exit the system, the concentration of Heparin declined over time.

The initial condition of scenario 3 included the same delta dirac function, but its boundary condition was defined as an exponentially-decaying flux. The difference observed between scenario 1 and 3 is that the slope of the concentration over time in scenario 3 declines at a slower rate than that of scenario 1. This is expected. After the impulse of Heparin, the Heparin does exit the system, but as the flux decreases, the rate of which Heparin leaves the system also decreases.

In scenario 4, which modeled an I.V. infusion with a constant generation term and an exponentially-decaying flux, the concentration of Heparin over time seemed to increase without reaching a steady state. This is due to the fact that the Heparin is

constantly being added to the system, but as the flux decays, Heparin does not leave the system and thus, it accumulates indefinitely, which is physiologically unrealistic.

There are several limitations in our model due to assumptions to simplify the scope. Neglecting the flow in the model has the largest impact on the outcomes of the scenarios, as the concentration of the species decreases axially along the vessel as well as radially outward. The use of Cartesian coordinates rather than cylindrical also limits the model's accuracy, and will be implemented in the future. Additionally, the exponentially decaying flux term would be more accurate as a coupled equation rather than the somewhat arbitrary scaling term, α. We also assumed that all heparin will be absorbed by the body, although some will be cleared before it is effectively metabolized.

In order to increase the model's accuracy, we will implement cylindrical coordinates to more effectively model the radial diffusion of heparin. Future development of this model would be well served to address the limitations above as well, such as addressing flow and coupling the flux to the concentration. Figure 9 in the appendix illustrates the model we will be working with to model radial diffusion of heparin.

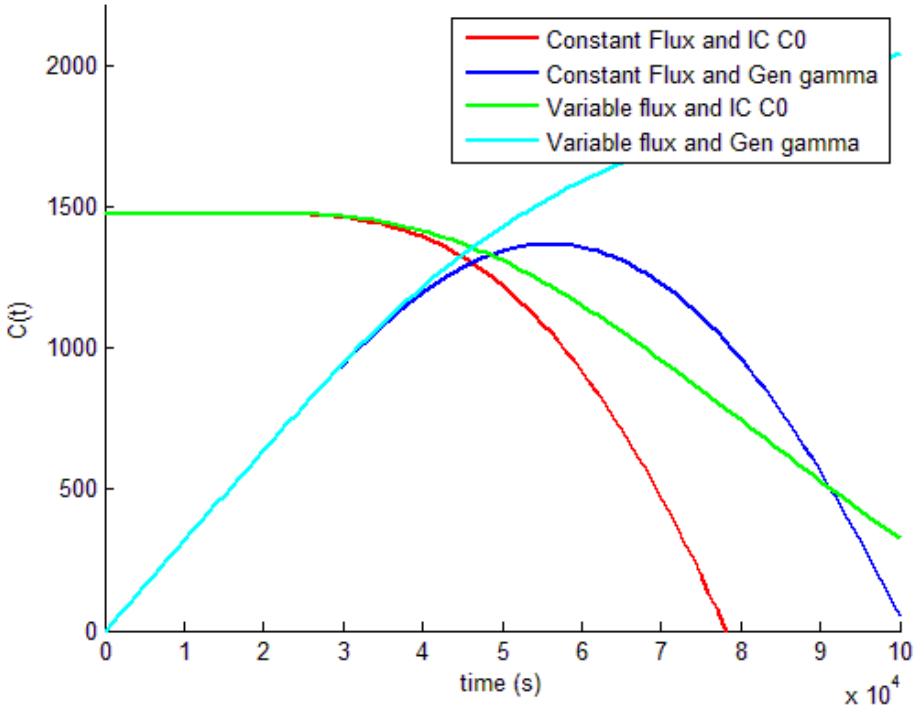

Figure (6): Numerical solutions as functions of concentration and time at the middle of the cubital vein as obtained through MATLAB PDEPE for scenarios 1-4

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APPENDIX

Step-by-step analytical solution for scenario 1:

Governing equation:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} + Q(x,t)$$

Boundary conditions, initial conditions, and generation term:

$$Q(x,t) = 0$$
$$C(x,0) = \delta(t)C_0$$
$$-D\frac{\partial C}{\partial x}(0,t) = -\varphi_0$$
$$-D\frac{\partial C}{\partial x}(L,t) = \varphi_L$$

Applying conditions to Green's integrals:

A

$$\int_0^L \delta(t_0)C_0\left[\frac{1}{L} + \sum_{n=1}^{\infty}\frac{2}{L}\cos\left(\frac{n\pi x}{L}\right)\cos\left(\frac{n\pi x_0}{L}\right)e^{-D\left(\frac{n\pi}{L}\right)^2(t-t_0)}\right]dx_0$$

B

$$-\int_0^t \varphi_0\left[\frac{1}{L} + \sum_{n=1}^{\infty}\frac{2}{L}\cos\left(\frac{n\pi x}{L}\right)\cos\left(\frac{n\pi x_0}{L}\right)e^{-D\left(\frac{n\pi}{L}\right)^2(t-t_0)}\right]dt_0$$

C

$$+\int_0^t -\varphi_L\left[\frac{1}{L} + \sum_{n=1}^{\infty}\frac{2}{L}\cos\left(\frac{n\pi x}{L}\right)\cos\left(\frac{n\pi x_0}{L}\right)e^{-D\left(\frac{n\pi}{L}\right)^2(t-t_0)}\right]dt_0$$

Solving for each integral:

A

$$\int_0^L \delta(0)C_0\left[\frac{1}{L} + \sum_{n=1}^{\infty}\frac{2}{L}\cos\left(\frac{n\pi x}{L}\right)\cos\left(\frac{n\pi x_0}{L}\right)e^{-D\left(\frac{n\pi}{L}\right)^2 t}\right]dx_0$$

$$= \int_0^L \frac{\delta(0)C_0}{L}dx_0 + \int_0^L \delta(t_0)C_0\frac{2}{L}\sum_{n=1}^{\infty}\cos\left(\frac{n\pi x}{L}\right)\cos\left(\frac{n\pi x_0}{L}\right)e^{-D\left(\frac{n\pi}{L}\right)^2 t}dx_0\Bigg\} = 0$$

$$= C_0$$

B

$$-\int_0^t \varphi_0\left[\frac{1}{L} + \sum_{n=1}^{\infty}\frac{2}{L}\cos\left(\frac{n\pi x}{L}\right)\cos\left(\frac{n\pi(0)}{L}\right)e^{-D\left(\frac{n\pi}{L}\right)^2(t-t_0)}\right]dt_0$$

$$= -\frac{\varphi_0}{L}t - \frac{2\varphi_0}{L}\sum_{n=1}^{\infty}\cos\left(\frac{n\pi x}{L}\right)e^{-D\left(\frac{n\pi}{L}\right)^2 t}\int_0^t e^{D\left(\frac{n\pi}{L}\right)^2 t_0}dt_0$$

$$= -\frac{\varphi_0}{L}t - \sum_{n=1}^{\infty}\frac{2\varphi_0 L}{D(n\pi)^2}\cos\left(\frac{n\pi x}{L}\right)\left(1 - e^{-D\left(\frac{n\pi}{L}\right)^2 t}\right)$$

C

$$\int_0^t -\varphi_L\left[\frac{1}{L} + \sum_{n=1}^{\infty}\frac{2}{L}\cos\left(\frac{n\pi x}{L}\right)\cos\left(\frac{n\pi L}{L}\right)e^{-D\left(\frac{n\pi}{L}\right)^2 t - t_0}\right]dt_0$$

$$= -\frac{\varphi_L t}{L} - \frac{2\varphi_L}{L}\sum_{n=1}^{\infty}\frac{2}{L}(-1)^{\mathrm{n}}\cos\left(\frac{n\pi x}{L}\right)e^{-D\left(\frac{n\pi}{L}\right)^2 t}\int_0^t e^{-D\left(\frac{n\pi}{L}\right)^2 t_0}\,dt_0$$

$$= -\frac{\varphi_L t}{L} - \sum_{n=1}^{\infty}\frac{2\varphi_L(-1)^{\mathrm{n}}}{D(n\pi)^2}\cos\left(\frac{n\pi x}{L}\right)\left(1 - e^{-D\left(\frac{n\pi}{L}\right)^2 t}\right)$$

Combining each integral solution: A+B+C=

$$C(x,t) = C_0 - \frac{(\varphi_0 + \varphi_L)t}{L} - \sum_{n=1}^{\infty}\frac{2L}{D(n\pi)^2}(\varphi_0 + (-1)^n\varphi_L)\cos\left(\frac{n\pi x}{L}\right)\left(1 - e^{-D\left(\frac{n\pi}{L}\right)^2 t}\right)$$

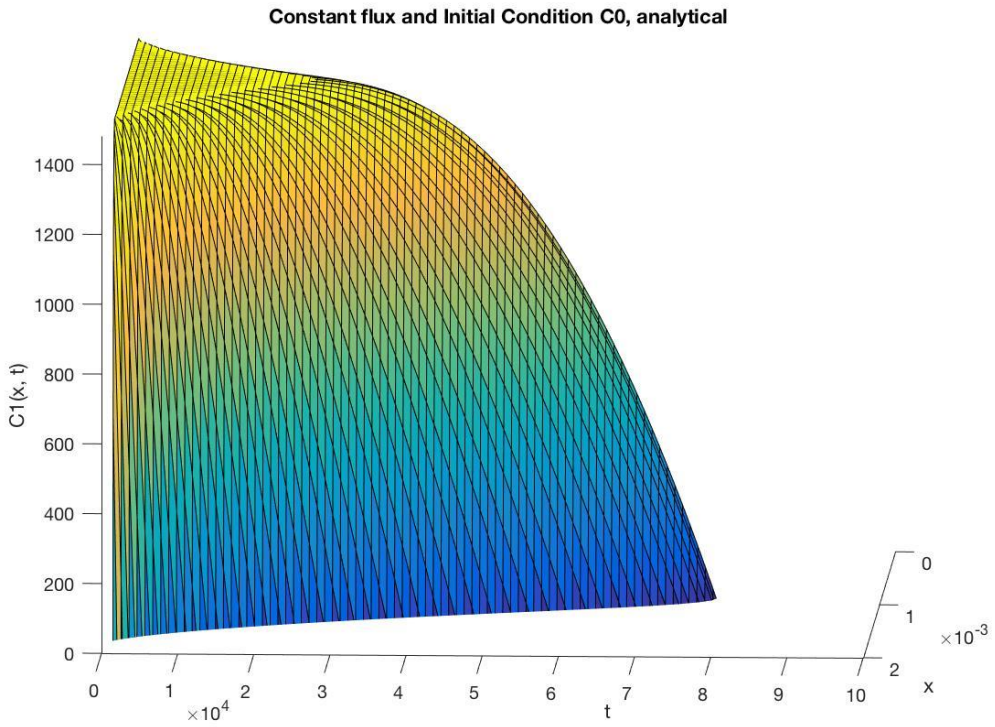

Figure (7): Graph of the analytical solution for scenario 1.

Step-by-step analytical solution for scenario 2:

Governing equation:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} + Q(x,t)$$

Boundary conditions, initial conditions, and generation term:

$$Q(x,t) = \gamma$$
$$C(x,0) = 0$$
$$-D\frac{\partial C}{\partial x}(0,t) = -\varphi_0$$
$$-D\frac{\partial C}{\partial x}(L,t) = \varphi_L$$

Applying conditions to Green's integrals:

A

$$\int_0^L \int_0^t \gamma \left[\frac{1}{L} + \sum_{n=1}^{\infty} \frac{2}{L}\cos\left(\frac{n\pi x}{L}\right)\cos\left(\frac{n\pi x_0}{L}\right) e^{-D\left(\frac{n\pi}{L}\right)^2 (t-t_0)}\right] dt_0 dx_0$$

B

$$-\int_0^t \varphi_0 \left[\frac{1}{L} + \sum_{n=1}^{\infty} \frac{2}{L}\cos\left(\frac{n\pi x}{L}\right)\cos\left(\frac{n\pi x_0}{L}\right) e^{-D\left(\frac{n\pi}{L}\right)^2 (t-t_0)}\right] dt_0$$

C

$$+\int_0^t -\varphi_L \left[\frac{1}{L} + \sum_{n=1}^{\infty} \frac{2}{L}\cos\left(\frac{n\pi x}{L}\right)\cos\left(\frac{n\pi x_0}{L}\right) e^{-D\left(\frac{n\pi}{L}\right)^2 (t-t_0)}\right] dt_0$$

Solving for each integral:

A

$$\int_0^L \int_0^t \frac{\gamma}{L} dt_0 dx_0 + \int_0^L \int_0^t \sum_{n=1}^{\infty} \frac{2\gamma}{L}\cos\left(\frac{n\pi x}{L}\right)\cos\left(\frac{n\pi x_0}{L}\right) e^{-D\left(\frac{n\pi}{L}\right)^2 (t-t_0)} dt_0 dx_0$$

$$= \gamma t + \int_0^L \int_0^t \sum_{n=1}^{\infty} \frac{2\gamma}{L}\cos\left(\frac{n\pi x}{L}\right)\cos\left(\frac{n\pi x_0}{L}\right) e^{-D\left(\frac{n\pi}{L}\right)^2 (t-t_0)} dt_0 dx_0 \Bigg\} = 0$$

$= \gamma t$

B and C are same as Scenario 1

Combining each integral solution: A+B+C=

$$\gamma t - \frac{(\varphi_0 + \varphi_L)t}{L} - \sum_{n=1}^{\infty} \frac{2L}{D(n\pi)^2}(\varphi_0 + (-1)^n \varphi_L)\cos\left(\frac{n\pi x}{L}\right)\left(1 - e^{-D\left(\frac{n\pi}{L}\right)^2 t}\right)$$

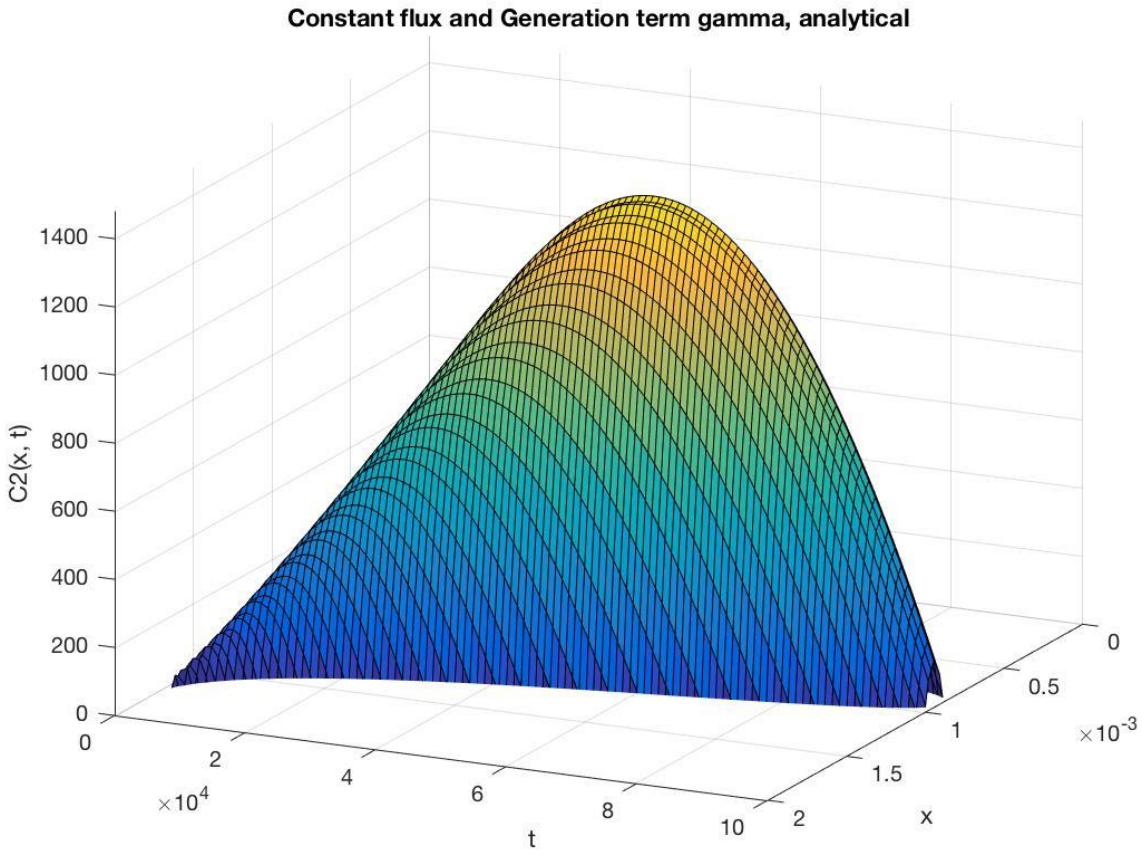

Figure (8): Graph of the analytical solution for scenario 2.

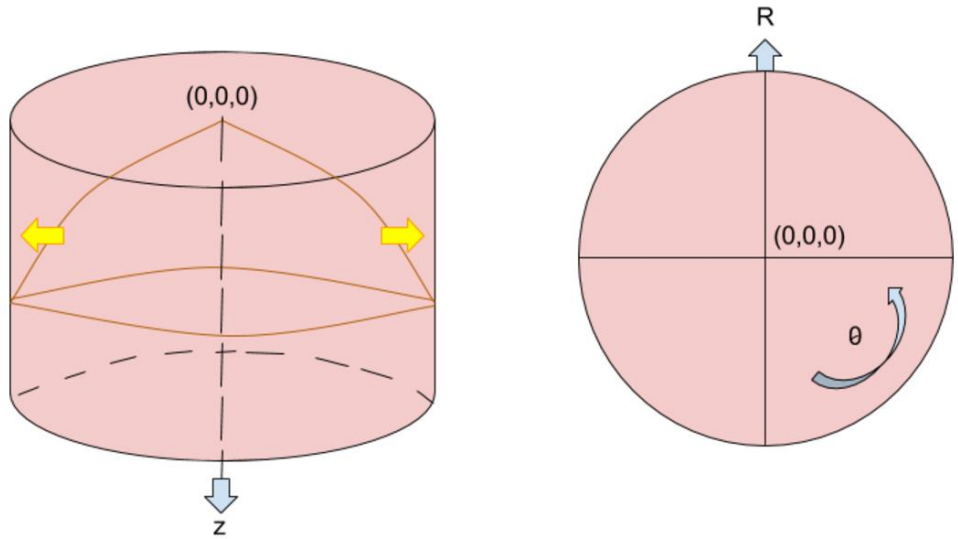

Figure (9): Diagram of Heparin radial diffusion utilizing Radial coordinates