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ADVECTION-REACTION-DIFFUSION MODEL OF DRUG CONCENTRATION IN A LYMPH NODE

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ADVECTION-REACTION-DIFFUSION MODEL OF
DRUG CONCENTRATION IN A LYMPH NODE

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ADVECTION-REACTION-DIFFUSION MODEL OF
DRUG CONCENTRATION IN A LYMPH NODE

A Dissertation Presented to the Graduate Faculty of the
Dedman College
Southern Methodist University

in
Partial Fulfillment of the Requirements
for the degree of
Doctor of Philosophy

with a
Major in Computational and Applied Mathematics

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It is recognized that there exist reservoirs of HIV located outside the bloodstream, and that these reservoirs hinder the efficacy of antiretroviral medication regimens in combating the virus. The prevailing theories regarding these reservoirs point to the lymphatic system. In this work, we discuss a novel computational model of viral dynamics in the lymph node, to allow numerical studies of viral “reservoirs” causing reinfection. Our model consists of a system of advection-reaction-diffusion partial differential equations (PDEs), where the diffusion coefficients vary between species (virus, drugs, lymphocytes) and include discontinuous jumps to capture differing properties of internal lymph node structures. We present the mathematical model and discuss our current work on implementing this using the MFEM finite-element infrastructure. Using this model, we analyze the clinical course of HIV infection and the effects of different combinations of anti-retroviral drugs, and then use this model to test the hypothesis whether the lymph node can serve as a reservoir of HIV.
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Chapter 1
Introduction

The first cases of the **acquired immune deficiency syndrome (AIDS)** were found in 1981 in Los Angeles among five young men, but it is believed that cases of the disease had been occurring unrecognized for several years before its identification. As it seemed to be spread by contact with body fluids, it was early suspected to be caused by a new virus, and by 1983 the agent now known to be responsible for AIDS, called the **human immunodeficiency virus (HIV)**, was isolated and identified.

HIV infection does not immediately cause AIDS. It may take more than ten years for HIV infected patients to progress to positive disease. Nowadays, HIV is a worldwide pandemic and, although great progress has been made to understand the pathogenesis and epidemiology of the disease, the number of infected people around the world continues to grow at an alarming rate, presaging the death of many people from AIDS for many years to come. Estimates from the World Health Organization are that 16.3 million people have died from AIDS since the beginning of the epidemic [36].

![Figure 1.1. Adult HIV prevalence](image source: KFF.org)
With the advent of powerful anti-HIV drugs developed in the 1990’s, the inevitability of getting AIDS after being diagnosed with HIV has drastically changed. In fact, antiretroviral therapy (ART) changed HIV from a terminal into a chronic disease. Unfortunately, the medical community was a bit overly optimistic; when the viral load became undetectable, patients would be removed from drug therapy and the virus would rebound [22]. Now it is recognized that there are reservoirs of HIV located outside the bloodstream. With the notable exception of a famous patient in Berlin, Germany, all HIV positive patients taken off drug therapy (when the viral level appears to have dropped to zero in the bloodstream) have had a return of the virus, sometimes within only a few weeks. It is therefore an urgent requirement to locate these reservoirs, understand the mechanisms of how they are formed, and find a new drug therapy to cure HIV completely [28].

There are several prevailing theories about why HIV has remained incurable so far [28]. First, the host cells for the virions are CD4 T helper cells, white blood cells essential to a functioning immune system. Their main role is to signal other T-cells to destroy pathogens. Once a CD4 T-cell becomes actively infected by HIV, the immune cell is usually destroyed; although it can also happen that the HIV enters the cell and produces viral DNA but does not complete the replication process. While drug therapies appear to inhibit the replication of virtually all active susceptible virions in the blood, there seem to be virions hiding outside the path of the drugs [28].

Although viral load and turnover are usually measured by detecting the viral RNA present in viral particles in the blood, the majority of HIV infection happened in lymphoid tissue, in which infected CD4 T-cells, monocytes, macrophages, and dendritic cells are found. More than 95% of the virus that can be detected in the plasma is derived from productively infected cells, which have a very short half-life. Productively infected CD4 lymphocytes are found in the T-cell areas of lymphoid tissue, and these are thought to succumb to infection in the course of being activated in an immune response. Latently infected memory CD4 cells that are activated in response to antigen presentation also produce virus. Such cells have a longer half-life of 2 to 3 weeks from the time that they are infected. Once activated, HIV can
spread from these cells by rounds of replication to other activated CD4 T-cells. In addition to the cells that are infected productively or latently, there is a further large population of cells infected by defective proviruses; although such cells are not a source of infectious virus [36].

Secondly, virus continuously replicates in the lymph nodes, away from the bloodstream, and when it hits the bloodstream it is destroyed by the ongoing drug regimen. However, when drugs are stopped, the virus has no restrictions to its replication and the viral levels soar again. This works since the blood circulates quickly, on a much faster time scale than lymph.

Another theory is that some T-cells in the lymphatic system are harboring resting T-cells that hold the viral DNA but are not producing more virus. Such type of non-productive infected cells, also known as latent cells, carry the infection without triggering replication or destroying the cells [21].

Although there exist numerous mathematical models in biology, there are very few mathematical models of the lymphatic system. While there do exist some basic models for the entire lymphatic system, there are indeed very few highly accurate models for individual elements of the lymphatic system such as the lymph node. Thus to analyze the functionality of drug therapies, and how these enter and interact with HIV in the lymph node, we need to first construct a high-fidelity mathematical model for these organs, which served as an inspiration for this research.

For this work, we wish to derive a three-dimensional geometric model of the lymph node. With this new model in hand, we will implement scalable parallel solver algorithms to generate approximate solutions to these partial differential equations using continuous finite element methods.

We have organized this thesis as follows. Chapter 2 introduces the basic biological concepts, including the human immune response to HIV. We then present the framework of our mathematical model response to the HIV (or Ebola) infection in the lymph node, as well as our model for how relevant products are transported to and from the lymph node.
In Chapter 3 we present the algorithmic details behind our solution process. In Chapter 4 we discuss our investigation of optimal preconditioners for accelerating convergence when using the GMRES methods as an iterative linear solver. In Chapter 5 we present the numerical preparation for solving the model, including the details of mesh generation and the various tests we employed to verify each part of our model and solution process. With these in place, we then proceed to the overall biological model in Chapter 6, where we analyze the model with all known biological parameters included, and test our hypothesis regarding HIV reservoir effects of the lymph node. Finally, in Chapter 7 we summarize the contributions from this thesis and discuss areas of future work.
Chapter 2
Model

As shown in Figure 2.1, the human lymph node is an oval or bean-shaped organ of the lymphatic system. It plays a critical role in the development of an appropriate and efficient immune response. Lymph nodes are a type of peripheral or secondary lymphoid organ. They are found in many locations throughout the body where lymphatic vessels converge, and are sites where adaptive immune responses are initiated [36]. There are a variety of biological and physical process that are involved in the immune reaction such as diffusion, chemotaxis, receptor expression, etc. As soon as an Antigen (Ag) is captured by Ag-processing cells it is transmitted to the nearest lymph node, where it is then presented to specific lymphocytes to trigger an immune response [9].

![Figure 2.1. The lymph node](image)

In order to discuss the immune response, we must first define some basic terminology. The first one is pathogens: a bacterium, virus, or other microorganism that can cause
disease. **Antigens** are any substance foreign to the body that evokes an immune response either alone or through forming a complex with a larger molecule and that is capable of binding with a product of the immune response. Finally an **antibody** is any one of a large number of proteins of high molecular weight that are produced normally by specialized B cells after stimulation by an antigen, and that act specifically against the antigen in an immune response [49].

In the body, the blood and the extracellular spaces are the only areas where pathogens can be accessed by antibodies. However, some bacterial pathogens and all viruses replicate inside cells where they cannot be detected by antibodies. The destruction of these invaders is the function of the T **lymphocytes**, which are responsible for the cell-mediated immune responses of adaptive immunity [36]. The T lymphocyte, or T-cell, is a type of lymphocyte which arises from stem cells in bone marrow and differentiates in the thymus. T lymphocytes migrate from these tissues and are carried in the bloodstream to the peripheral or secondary lymphoid organs (e.g., the lymph nodes). There are two essential classes of T-cells, the T helper cell (T_h cell), also known as CD4 cells or suppressor T-cells, that take fine control of the immune response through the secretion of cytokines, whereas the Cytotoxic T-cells kill the foreign or intracellularly infected cells directly.

Cell-mediated reactions depend on direct interactions between T lymphocytes and cells bearing the antigen that the T-cells recognize. The actions of cytotoxic T-cells are the most direct. These recognize any of the body’s cells that are infected with viruses, which replicate inside cells, using the biosynthetic machinery of the cell itself. The replicating virus eventually kills the cell, releasing new virus particles. Antigens derived from the replicating virus are, however, displayed on the surface of infected cells, where they are recognized by cytotoxic T-cells. These cells can then control the infection by killing the infected cell before viral replication is complete (Figure 2.2). Cytotoxic T-cells typically express the molecule CD8 on their cell surfaces [36].

CD4 T lymphocytes, which carry out different functions in defending the body, in particular from bacterial infections, can be divided into two subsets. The first subset of CD4 T
lymphocytes, known as a T\textsubscript{H}1 cells, is important in the control of intracellular bacterial infections. T\textsubscript{H}1 cells will activate macrophages, inducing the fusion of their lysosomes with the vesicles containing the bacteria and at the same time stimulating other antibacterial mechanisms of the phagocyte. In addition to killing infected cells and activating macrophages, T-cells also have a central role in the destruction of extracellular pathogens by activating B cells. This is the specialized role of the second subset of CD4 T-cells, called T\textsubscript{H}2 cells [36].

The human immunodeficiency virus (HIV) is an enveloped retrovirus, which interacts with the immune system and that ultimately leads to loss of immune control of multiple pathogens and cancers. As shown in Figure 2.3, each virus particle, or virion, contains two copies of an RNA genome, which are transcribed into DNA in the infected cell and integrated into the host cell chromosome.

The primary infection with HIV is asymptomatic in 50% of cases but often causes an influenza-like illness with an abundance of virus in the peripheral blood and a marked drop in the numbers of circulating CD4 T-cells. This acute viremia is associated in virtually all patients with the activation of CD8 T-cells, which kill HIV-infected cells, and subsequently with antibody production, or seroconversion. Infection with HIV generates an adaptive immune response that contains the virus but only very rarely. Seroconversion is the clearest evidence for an adaptive immune response to infection with HIV, but the generation of
T lymphocytes responding to infected cells is thought by most experts to be central in controlling the infection. Both CD8 cytotoxic T-cells and T_{H}1 cells specifically responsive to infected cells are associated with the decline in detectable virus after the initial infection. These T-cell responses are unable to clear the infection completely and can cause some pathology. Nevertheless, there is evidence that the virus itself is cytopathic, and T-cell responses that reduce viral spread should therefore, on balance, reduce the pathology of the disease. There are three dominant mechanisms for the loss of CD4 T-cells in HIV infection. First, there is evidence for direct viral killing of infected cells; second, there is increased susceptibility to the induction of apoptosis in infected cells; and third, there is killing of infected CD4 T-cells by CD8 cytotoxic lymphocytes that recognize viral peptides. The typical course of an infection with HIV is shown in Fig 2.4. However, it has become increasingly clear that the course of the disease can vary widely. Thus, although most people infected with HIV go on to develop AIDS and ultimately to die of opportunistic infection or
Typically, “during primary HIV infection, the viral load in plasma increases rapidly, reaches a peak, and then declines until it reaches a set point level” [59, 53]. There are several biological and statistical research studies about the viral growth at the early stage of HIV infection. In Figure 2.5, we show observed viral load data and the corresponding fitted model curves for 10 patients, from [59]. Similarly, Figure 2.6 shows the early viral load profiles for 15 patients from a different study [53]. In both figures, we can observe the rapid increase of the viral load soon after infection, followed by a decrease that may be caused by the immune response or the lack of susceptible cells. Even after this decrease, the viral load remains steady, allowing HIV to eventually develop into AIDS. However, we also point out the wide variability in the data between patients, indicating that at best we can hope to reproduce the overall qualitative behavior of the infection within any mathematical model.
Figure 2.5. Theoretical curves using estimated parameters vs. observed viral load data (♦) for 10 patients [59].
Figure 2.6. Early viral load profiles for 15 patients, showing a viral peak and postpeak decay [53].

HIV, and AIDS specifically, received severe attention because of its wide spread and mortality. This changed in 1995, with the introduction of protease inhibitors and non-nucleoside
reverse transcriptase inhibitors (NNRTI) to antiretroviral treatment regimens, that began the era of highly active antiretroviral therapy (HAART). This treatment promoted the dramatic improvement in the mortality and morbidity of HIV, as determined by a decreased incidence of opportunistic infections, tumors, and deaths. Within only four years, between 1994 and 1998, the incidence of AIDS in Europe was reduced from 30.7 to 2.5 per 100 patient years. With the development of medical science and abundant research on HIV, there are approximately 36 antiretroviral drugs on the market, which are generally prescribed and taken in combinations of 3 or more, with some patients needing to take 30 pills a day to decrease the incidence of AIDS. In general, these antiviral particles diminish the viral infections through different mechanisms [21]. We can summarize these mechanisms in the following ways:

- diminish the virus’s ability to infect susceptible cells by reducing the infection rate,

- diminish virus replication by reducing the number of new virus particles generated by infected cells.

Despite all the therapeutic advantages achieved during the last decades, once an individual has been infected, eradication of the virus still remains impossible [32].

One of the primary reasons for the difficulty in eradication of HIV, the **latently infected cells**, needs to be mentioned. Latently infected cells, which are a group of infected T-cells that are not actively producing HIV, represent long-living cellular reservoirs for HIV. After long-term suppression, HIV still remains detectable in latently infected cells, and nobody knows how long can these latently infected cells survive. Nevertheless, a small number of latently infected cells would be sufficient for the infection to blow up as soon as treatment is interrupted [32]. Cardiac output, which is the amount of blood the heart pumps through the circulatory system in a minute, of an adult is normally 4.7 liters. Meanwhile, the estimation of total post-nodal (efferent) flow-rate for lymphatic circulation is around 4 L/day [50]. Thus we can see that the flow rate of lymphatic circulation is much lower than the blood circulation. Moreover, there is a zone in the lymph node composed of cortex and paracortex that has
even lower diffusivity where the latently infected cells could reside. Hence we hypothesized that this would be a good place to start when studying latent HIV infection.

From the previous discussion, we can see that there are complex reactions between the development of HIV infection, medicine and T lymphocytes corresponding to adaptive immune response. To quantitatively analyze the clinical course of HIV with medicine in the human lymph node, we propose a mathematical model consisting of a system of partial differential equations (PDEs) to model the reactions among HIV, medicine and T lymphocytes, as well as the transport of these to and from the lymph node.

Based on the biological characteristics of the lymph node, our model is divided into two regions:

- the sector $\Omega_1$ that comprises the lymph node itself, and
- the sinus region $\Omega_2$ surrounding the lymph node, where products are transported to and from the lymph node.

Due to the higher density of the lymph node in region $\Omega_1$, particles primarily move through diffusion; whereas since $\Omega_2$ consists of afferent/efferent lymphatic vessels and medullary sinus, transport in that region is modeled as an incompressible fluid.

2.1. $\Omega_1$ within the lymph node

The immune response of HIV infection in the lymph node is very complex, as is clear from the previous discussion. To quantitatively study the phenomena, hereby, we need to integrate the experimental biological data into a mathematical model. From the biological perspective, we must consider data at various levels of the immune system, as well as immune interactions with the virus both with and without medicine. On the mathematical side, we must consider system analysis and computational modeling techniques. Our objective is to combine these to develop a three-dimensional geometric computational model of viral dynamics in the lymph node, to allow numerical studies of viral reservoirs causing reinfection once drugs are stopped.
For the model in region $\Omega_1$, we consider the concentration of the particles at time $t$ on the spatial location $(x,y,z) \in \Omega_1$. We analyze the spatio-temporal dynamics of the concentrations of HIV ($V$), medicine ($M$), chemoattractant ($c$), T-cells ($T$) and infected cells ($I$) using an advection-reaction-diffusion system of PDEs.

Our model builds off of a rich history of previous work in the mathematical modeling of viral infection dynamics. In the next section we briefly summarize the main models on which our work extends.

2.1.1. Previous models

To construct a model of the human lymph node, both the biological structure and the function of the lymph node are required. However, although there exist numerous models of HIV dynamics in the blood, there are only a few that focus specifically on the lymph node itself.

2.1.1.1. Reaction-diffusion model in lymph node

The first model to study the role of the lymph node structure on HIV is “Reaction-Diffusion modelling of Interferon Distribution in Secondary Lymphoid Organs” by G. Bocharov and collaborators in 2011, that proposed a quantitative model of reaction-diffusion type to examine the distribution of interferon-α (IFNα) in a lymph node [12].

Interferon-α is an interferon produced by various white blood cells that inhibits viral replication, suppresses cell proliferation and regulates immune response, and that is used in a form obtained from recombinant DNA to treat hairy cell leukemia, AIDS-related Kaposi’s sarcoma, condylomata acuminata, and certain chronic hepatitides [49].

The efficacy of immune responses relies on a productive interaction between antigen-presenting cells (APCs) and lymphocytes. APCs protection by interferon requires that the in situ IFNα concentration should exceed a certain threshold, which was Bocharov’s motivation for studying the distribution of interferon-α in the lymph node.

In the first part of their paper, the authors apply a quantitative model to measure the ki-
netic parameters of the interferon response using experimental data. The high-resolution data comes from the well-described mouse hepatitis virus infection and a set of delay-differential equations describing the interaction between the virus, plasmacytoid dendritic cells and macrophages.

Afterwards, the authors proposed their reaction-diffusion model of IFN dynamics by considering the concentration of the interferon $I$ at time $t$ on position $x \in \Omega \subset \mathbb{R}^3$. Here $\Omega$ is the spatial region occupied by the lymphoid organ. Their model has the form
\[
\frac{\partial I}{\partial t}(x, t) = \nabla \cdot (D \nabla I(x, t)) - d_I I(x, t) + \sum_{l=1}^{L} F_l(x).
\]

In the model, the authors state that: “$D$ stands for the diffusion mass transfer tensor which is assumed to be a scalar constant coefficient depending on the subdomain ($D = D_i \cdot \mathbb{I}, i = 1, \ldots, N$) since diffusion is considered to be isotropic. The term $-d_I I(x, t)$ is used to describe the degradation of interferon, and IFN$\alpha$ secretion by different types of activated cells located at some position $(x_k)_{k=1}^{K_l}$ is represented by the source term. This source term is the sum over Dirac delta functions, $F_l(x) = \sum_{k=1}^{K_l} \rho_l \delta(x - x_k^{(l)})$, with $\rho_l$ representing the per capita cell type specific secretion rate. Due to the singularity of $F_l(\cdot)$ the equations are to be understood in the weak sense.” For the domain $\Omega$ these authors used the domain of a paradigmatic secondary lymphoid organ as shown in Figure 2.7. Functionally, their lymph node consists of three major subdomains [12]:

- an outer antigen-sampling zone (subcapsular sinus, trabecular sinuses, conduit tubes), referred to as subdomain $\Omega_1$ [this is similar to our sinus region, $\Omega_2$],

- B-cell follicles which make subdomain $\Omega_2$ [this forms the majority of our lymph node region, $\Omega_1$],

- T-cell zone (cortex and paracortex) denoted as subdomain $\Omega_3$ [this forms a small, higher-density portion of our lymph node region, $\Omega_1$].

It is noteworthy that the B-cell zone is considered to have a larger hydraulic conductivity than the T-cell zone. Although direct measurements of the hydraulic conductivity with the
T-cell area are missing, it is likely that both diffusion and convection are extremely low [12]. Hence their diffusion coefficients obey the ranking: $D_1 \gg D_2 \gg D_3$.

![Figure 2.7. schematic representation of a paradigmatic secondary lymphoid organ.][12]

These authors used the Open CASCADE technology (see [http://www.opencascade.org](http://www.opencascade.org)) to construct the 3D geometric model for the paradigmatic lymph node in their paper, as shown in Figure 2.8.

For the numerical results, they only analyzed the steady-state distribution of IFNα across the subdomains of their domain $\Omega$. The corresponding reduced model reads:

$$D \left( \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2} \right) I(x, t) + d_t I(x, t) = F(x),$$

where $D = D_i \cdot \mathbb{I}$ in $x \in \Omega_i$, $i = 1, 2, 3$, and $F(x) = \sum_{k=1}^{K} \rho \delta(x - x_k)$. They completed their model using homogeneous Neumann boundary conditions.

Their study results suggest that the spatial stationary distribution of IFNα is essentially heterogeneous across the lymph node. This result implies that for some infections the...
pathogens can escape the IFN$\alpha$ effect if the infected target cell are localized, and/or migrate into poorly protected SLO (Secondary lymphoid Organs) regions [12].

Despite their simplistic domain and study of only the steady-stage concentration of IFN$\alpha$, this paper was the first to propose a reaction-diffusion PDE model that realized the importance of lymphatic structure for understanding particle dynamics in lymph nodes.

2.1.1.2. Mathematical model of viral infection dynamics

The second paper we discuss is “Mathematical modeling of viral infection dynamics in spherical organs” by R. Dunia and R. Bonnecaze in 2013 [21]. In this work the authors present a general mathematical model of viral infections inside a spherical organ. Transferred quantities are used to represent external cells or viral particles that penetrate the organ surface to either promote or combat the infection. A spherically-symmetric diffusion mechanism is considered for the migration of transferred quantities to the inner organ tissue. Although this diffusion model and geometry are simplistic, the paper provides an excellent mathematical model of interacting processes within such organs. Cases that include the effect of penetration, diffusion and proliferation of immune system cells, the generation of latently infected cells and the delivery of antiviral treatment are analyzed. In addition, different antiviral mechanisms are modeled in the context of spatial variation [21].

This work assumes that virus particles are initially circulating through the blood stream, and that there is a small initial concentration of virus at the host organ surface. Their
proposed model reads:

$$\frac{\partial T}{\partial t} = D^2 \cdot \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial T}{\partial r} \right) + G(S, T),$$

where $S = [S_1 \ S_2 \ \cdots \ S_m]^T$ is a vector of stationary variables, and $T = [T_1 \ T_2 \ \cdots \ T_l]^T$ represents a vector of transported variables. The evolution equations for the stationary variables are given by

$$\frac{\partial S}{\partial t} = F(S, T),$$

where $F$ is a vector of nonlinear functions that represent the generation-consumption terms of the stationary variables. Such a function provides the rate of proliferation and mortality of the different organ cells. The term $D^2 \cdot \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial T}{\partial r} \right)$ models the radial diffusion. Finally, the vector function $G$ denotes the generation-consumption terms for the transported variables.

The model is analyzed in several different ways, including:

- the basic virus model in the absence of immune cells,
- the effect of the immune system in the infected organ as an external agent,
- the distinction between productively and latently infected cells, and
- different antiviral mechanisms of action.

In the basic model for virus dynamics analysis, the authors only considered $S = [X \ Y]^T$ where $X$ and $Y$ denote uninfected and infected cells, respectively, and $T = V$ represents free virus particles. The generation-consumption terms are given by

$$F(S, T) = \begin{bmatrix} \lambda - dX - \beta XV \\ \beta XV - aY \end{bmatrix},$$

$$G(S, T) = kY - uV.$$
infected cells, $k$ represents the release rate of virus from infected cells, and $u$ represents the death rate of the virus. The results illustrate the radial distribution and predict the effect of physical parameters on the propagation of a viral infection through a spherical organ in the absence of an immune response.

Then, the model considers immune cells as transported quantities that penetrate the infected organ with a rate proportional to the number of infected cells at the organ surface. Here, $Z$ was used to denote this density of immune cells, and thus the model becomes

$$F(S, T) = \begin{bmatrix} \lambda - dX - \beta X V \\ \beta X V - aY - pY Z \end{bmatrix},$$

$$G(S, T) = \begin{bmatrix} kY - uV \\ cYZ - bZ \end{bmatrix},$$

where $S = [X \ Y]^T$ and $T = [V \ Z]^T$. Here, $p$ represents the infected cell elimination rate by the immune cells, $c$ represents the generation rate of immune cells, and $b$ represents the death rate of immune cells.

The authors then expanded their study to include the latently infected cells as we described in the beginning of this chapter. With these included, their model becomes

$$F(S, T) = \begin{bmatrix} \lambda - dX - \beta X V \\ q\beta X V - aY - pYZ + \alpha Y_L \\ (1 - q)\beta X V - a_L Y_L - \alpha Y_L \end{bmatrix},$$

$$G(S, T) = \begin{bmatrix} kY - uV \\ -bZ \end{bmatrix},$$

for $S = [X \ Y \ Y_L]^T$ and $T = [V \ Z]^T$, and where $Y_L$ denotes the latently-infected cells. In the model, $q$ represents the portion of productively infected cells, $\alpha$ represents the activation rate of latently-infected cells, and $\alpha_L = 0.2\alpha$. 
Finally, the effect of antiviral drug therapy is considered. This effect was applied in two ways: (a) reduce the virus’ ability to infect susceptible cells, and (b) suppress viral replication-production in infected cells. The population of antiviral particles is a transported quantity denoted by $W$ with no generation term inside the solid organ. Including these effects, the model leads to

$$\begin{align*}
F(S,T) &= \begin{bmatrix}
\lambda - dX - \beta W XV \\
q\beta W XV - aY - pYZ + \alpha Y_L \\
(1-q)\beta W XV - a_L Y_L - \alpha Y_L
\end{bmatrix}, \\
G(S,T) &= \begin{bmatrix}
k_W Y - uV - gVW \\
-bZ \\
-eW
\end{bmatrix},
\end{align*}$$

with $S = [X \ Y \ Y_L]^T$ and $T = [V \ Z \ W]^T$. Here, $\beta W$ and $k_W$ denote the infection rate by the virus and the release rate of virus from infected cells under antiviral therapy, respectively. $g$ represents the virus elimination rate by antiviral particles, and $e$ represents the clearance rate of antiviral particles.

A particular contribution of this model is that it gives the flexibility to consider the significant variety of infection cases step by step, including some ideas about the usage of medicine throughout the clinical course of infection. While the previous study by Bocharov and collaborators indicated the need for a PDE model that includes the spatial inhomogeneity of the lymph node, this model clearly illustrated the need to include a larger set of complex interactions between free virus, immune cells, infected (and latently infected) cells, and medicine.

2.1.1.3. Chemotaxis

The last work we need to refer to is not just a single paper, but a framework that has been developed since the 1970s. As we see from the previous two papers, the movement
of particles in the lymph node is typically modeled using diffusion. However, as a part of the adaptive immune system, T-cells also undergo oriented migration, chemotaxis, as an essential feature of the immune response [9]. Chemotaxis is the influence of chemical substances in the environment on the movement of mobile species [33]. As shown in Figure 2.9, the movement towards a higher concentration of the chemoattractant is termed positive chemotaxis and the movement towards regions of lower chemorepellent is called negative chemotactical movement [33].

![Image of oriented migration](image)

**Figure 2.9.** Oriented migration

To study this phenomena mathematically, we consider $c(x, t)$ to be the concentration of chemoattractant at time $t$ in position $x$, and we consider $T(x, t)$ the concentration of the moving cells. The classical chemotaxis model is the Keller-Segel model [38, 39], proposed by E. F. Keller and L. A. Segel in the 1970s, which consists of four coupled reaction-advection-diffusion equations. By reducing their model under quasi-steady-state assumptions, we arrive at the general form [30],

\[ T_t = \nabla \cdot (k_1 \nabla T - k_2 T \nabla c) + k_3 \]

\[ c_t = \nabla \cdot (D_c \nabla c) + k_4 - k_5 c \]

where each of the terms $k_i = k_i(T, c)$; $k_1$ describes the diffusivity of the cells, $k_2$ is the chemotactic sensitivity, $k_3$ describes cell growth and death, and $k_4$ and $k_5$ are kinetic functions.
that denote production and degradation of the chemical signal, respectively.

We note that solutions of the Keller-Segel model do not always globally exist, and numerous researchers have studied solvability conditions for the Keller-Segel model. Here we highlight one conclusion \cite{65}. Consider the minimal Keller-Segel model with homogeneous Neumann boundary conditions and given initial condition,

\begin{align}
  u_t &= \Delta u - \nabla \cdot (u \nabla v), & x \in \Omega, t > 0, \\
  v_t &= \Delta v - v + u, & x \in \Omega, t > 0, \\
  \frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} &= 0, & x \in \partial \Omega, t > 0, \\
  u(x, 0) &= u_0(x), & v(x, 0) = v_0(x), & x \in \Omega,
\end{align}

in a bounded domain $\Omega \subset \mathbb{R}^n$, with initial functions $u_0 \in C^0(\bar{\Omega})$ and $v_0 \in C^1(\bar{\Omega})$ assumed to be nonnegative. The results from \cite{65} state that:

- if $n = 1$, then all solutions of 2.1 are global in time and bounded;
- if $n = 2$, then
  - in the case $\int_{\Omega} u_0 < 4\pi$, the solution will be global and bounded,
  - for any $m > 4\pi$ satisfying $m \notin \{4k\pi \mid k \in \mathbb{N}\}$ there exits initial data $(u_0, v_0)$ with $\int_{\Omega} u_0 = m$ such that the corresponding solution of (2.1) blows up either in finite or infinite time, provided $\Omega$ is simply connected;
- if $n \geq 3$,
  - given any $q > \frac{n}{2}$ and $p > n$ one can find a bound for $u_0$ in $L^q(\Omega)$ and for $\Delta v_0$ in $L^p(\Omega)$ guaranteeing that $(u, v)$ is global in time and bounded,
  - $\Omega$ is a ball then for arbitrarily small mass $m > 0$ there exist $u_0$ and $v_0$ having $\int_{\Omega} u_0 = m$ such that $(u, v)$ blows up either in finite or infinite time.

However, we believe that in the context of our problem, the solution will not blow up since we do not have an infinite supply of T-cells in the domain $\Omega$.  

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2.1.2. Our model

Based on the aforementioned work we now propose our own model, where we consider the concentration of HIV ($V$), medicine ($M$), chemoattractant ($c$), T-cells ($T$) and infected cells ($I$).

![Figure 2.10. sector $\Omega_1$](image)

We begin with the lymph node region $\Omega_1$, corresponding to both the “B-cell” and “T-cell” regions of the Bocharov model described in Section 2.1.1.1. Our schematic of this region is shown in Figure 2.10, where the lower-density “B-cell” region is shown in blue, and the higher-density “T-cell” region is shown in orange. All of the modeled particle concentrations are transported through diffusion in the region $\Omega_1$, except the T-cells that undergo advection-diffusion due to chemotaxis, as described above. Thus $D_V$, $D_M$, $D_c$, $D_T$, and $D_I$ are the diffusion coefficients for the particles $V$, $M$, $c$, $T$, and $I$, respectively. As we have learned from [12], the hydraulic conductivity varies significantly between the different zones of the lymph node, and hence these diffusion coefficients are not constant throughout space. Since diffusion is much slower in the T-cell zone than in the B-cell zone, we should have $D_{kB,zone} \gg D_{kT,zone}$, for $k \in \{V, M, c, T, I\}$. Moreover, since T-cells undergo chemotaxis, we can apply the Keller-Segel model directly with the term $\nabla \cdot (D_T \nabla T - \chi \nabla c)$ where $\chi$ is a constant named the chemotactic sensitivity. In addition to the time and transportation terms in each equation, we also need to include the reaction terms.
Following the biological mechanisms described above, the interaction of virus with lymphocytes and medicine should be taken into consideration. In simple terms, T-cells and medicine can kill the virus while T-cells are susceptible to infection by HIV. The replication of virus depends on the amount of infected T-cells, \( I \). Therefore, the coefficient multiplying the reaction term between virus and lymphocytes in the virus evolution equation is composed of both the elimination rate of virus by lymphocytes, and the infection rate of T-cells. Mathematically, this may be modeled by a reaction term \( f_T VT \), where \( f_T \) is a combination of the virus elimination rate \( e_T \) by the T-cells and the infection rate \( i_T \) of T-cells, i.e., \( f_T = e_T - i_T \). The coefficient multiplying the reaction term between virus and medicine, \( e_M \), is determined by the clearance rate of the virus by the medicine. Finally, \( r_I \) denotes the virus replication rate that multiplies the concentration of infected cells, and \( d_V \) is the virion clearance rate constant. Combining these terms, along with our model for spatial diffusion, our model for the dynamics of the virus population is

\[
\frac{\partial}{\partial t} V - \nabla \cdot \left( D_V \nabla V \right) = -f_T VT - e_M VM + r_I I - d_V V.
\]

Similarly, our model for the interaction of medication with the virus must be taken into account. Thus, we include a \( e_M VM \) term to represent the elimination of virus by medicine. Likewise, we model the medicine clearance as having rate constant \( d_M \). Combining these reaction terms with their spatial diffusion, our model for the dynamics of medication particles in the lymph node is

\[
\frac{\partial}{\partial t} M - \nabla \cdot \left( D_M \nabla M \right) = -e_M VM - d_M M.
\]

Based on working mechanisms of the antiretroviral drugs as discussed previously, the therapy takes effect in our model in the following ways:

- To diminish the virus’s ability to infect susceptible cells, we reduce the infection rate \( f_T \). For these reverse transcription inhibitors, we can simply express this effect of \( M \) in \( f_T \) by

\[
f_{Tm} = \frac{f_T}{1 + \Phi M}
\]
where Φ is a constant that determines the effectiveness of the medication in preventing cell infection. We note that \( M = 1/\Phi \) represents the 50\% inhibitory concentration, denoted by \( IC_{50} \).

- To diminish virus replication by reducing the number of new virus particles generated by infected cells, we reduce \( r \). This works through protease inhibitors, and can be modeled by reducing \( r \) following an equivalent expression to the one above,

\[
ri_M = \frac{r}{1 + \Psi M},
\]

where the larger \( \Psi \) (or the smaller the \( IC_{50} = 1/\Psi \)) the more effective \( M \) is in reducing replication in productively infected cells.

We may therefore test different drug combinations by changing the constants \( \Phi \) and \( \Psi \). We will examine the effects of these parameters in detail in Chapter 6.

Our model for the concentration of infected T-cells, \( I \), similarly includes a growth term corresponding to the infection rate of healthy T-cells by the virus, \( i_T VT \), as well as a standard clearance term \( \delta I \). Combining these with the spatial diffusion of these cells, we have the model

\[
\frac{\partial}{\partial t}I - \nabla \cdot (D_I \nabla I) = i_T VT - \delta I.
\]

For the chemoattractant \( c \) equation, we follow the classical chemotaxis model, with clearance term \( \lambda c \) and chemical signal production term \( p_c VT \). Combined with the diffusion of the chemoattractant, this equation becomes

\[
\frac{\partial}{\partial t}c - \nabla \cdot (D_c \nabla c) = -\lambda c + p_c VT.
\]

We lastly consider the reaction network for the healthy T-cell concentration. As we mentioned before, T-cells mature in the lymph node, corresponding to a source term \( g_T \) in the equation due to this maturation rate. Additionally, we include a reaction term \(-k_T VT\) between virus and T-cells to model the rate at which healthy T-cells are infected. As always, there exists a clearance term \( d_T T \) with death rate \( d_T \). Combining these with our advection-diffusion terms for the T-cell chemotaxis motion, we have the equation

\[
\frac{\partial}{\partial t}T - \nabla \cdot (D_T \nabla T - \chi T \nabla c) = -k_T VT - d_T T + g_T.
\]
In summary, our model describes the movement and reaction of virus, immune cells, medicine and chemoattractant in the human lymph node region $\Omega_1$. This corresponds to an advection-diffusion-reaction model for the variables $(V, M, c, I, T)$ given by:

\[
\frac{\partial}{\partial t} V - \nabla \cdot (D_V \nabla V) = -f_T VT - e_M VM + r_I I - d_V V, \quad (2.2a)
\]

\[
\frac{\partial}{\partial t} M - \nabla \cdot (D_M \nabla M) = -e_M VM - d_M M, \quad (2.2b)
\]

\[
\frac{\partial}{\partial t} c - \nabla \cdot (D_c \nabla c) = -\lambda c + p_c VT, \quad (2.2c)
\]

\[
\frac{\partial}{\partial t} I - \nabla \cdot (D_I \nabla I) = i_T VT - \delta I, \quad (2.2d)
\]

\[
\frac{\partial}{\partial t} T - \nabla \cdot (D_T \nabla T - \chi T \nabla c) = -k_T VT - d_T T + g_T. \quad (2.2e)
\]

Each of these variables are functions of $(x, t) \in \Omega_1 \times [0, t_f]$ and the equations are defined on the space

\[
S = \mathcal{U} \times \mathcal{U} \times \mathcal{U} \times \mathcal{U} \times \mathcal{U} \quad (2.3)
\]

where $\mathcal{U} = \mathcal{H}^1(\Omega_1) \times \mathcal{I}$. Here, $\mathcal{H}^1$ represents the Sobolev space given by

\[
\mathcal{H}^1 = \{ u(x) \in L_2(\Omega_1) \mid \nabla u \in L_2(\Omega_1) \}, \quad (2.4)
\]

and $\mathcal{I}$ represents the time space

\[
\mathcal{I} = [0, t_f]. \quad (2.5)
\]

The corresponding initial and boundary conditions are specific to each test, and are discussed as each test is presented in Chapter 5. In Table 2.1.2 we present the full set of modeling parameters, along with their physical values (and the sources where these were found). We note that not all of these parameters have been determined experimentally; for these we show our best guess at the values. We note that from this data we can easily see the difference of diffusion coefficients in the B- and T-cell regions.
Table 2.1. Model parameters and variables. Those that vary between the “B-cell” and “T-cell” regions show two values, denoted by “B” and “T” for the two regions, respectively (values are based on the lymph node cell density).

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_V$ virus diffusion coefficient</td>
<td>$1 \text{ cm}^2/\text{day (B)}, 0.1 \text{ cm}^2/\text{day (T)}$</td>
<td>[21, 12]</td>
</tr>
<tr>
<td>$D_M$ medicine diffusion coefficient</td>
<td>$2 \text{ cm}^2/\text{day (B)}, 0.2 \text{ cm}^2/\text{day (T)}$</td>
<td>[21, 12]</td>
</tr>
<tr>
<td>$D_c$ chemoattractant diffusion coefficient</td>
<td>$0.8 \text{ cm}^2/\text{day}$</td>
<td></td>
</tr>
<tr>
<td>$D_I$ infected T-cell diffusion coefficient</td>
<td>$0.1 \text{ cm}^2/\text{day (B)}, 0.01 \text{ cm}^2/\text{day (T)}$</td>
<td>[21, 12]</td>
</tr>
<tr>
<td>$D_T$ healthy T-cell diffusion coefficient</td>
<td>$0.1 \text{ cm}^2/\text{day (B)}, 0.01 \text{ cm}^2/\text{day (T)}$</td>
<td>[21, 12]</td>
</tr>
<tr>
<td>$\chi$ the chemotactic sensitivity</td>
<td>$1.0$</td>
<td></td>
</tr>
<tr>
<td>$e_T$ virus elimination rate by T-cells</td>
<td>$1.65 (\mu l \text{ virion-day}^{-1}) \times 10^{-3}$</td>
<td></td>
</tr>
<tr>
<td>$i_T$ infected rate of T-cells</td>
<td>$0.65 (\mu l \text{ virion-day}^{-1}) \times 10^{-3}$</td>
<td>[59]</td>
</tr>
<tr>
<td>$f_T$ reaction rate between T-cells and virus</td>
<td>$1.0 (\mu l \text{ virion-day}^{-1}) \times 10^{-3}$</td>
<td></td>
</tr>
<tr>
<td>$e_M$ virus elimination rate by medicine</td>
<td>$0.5 1/\text{mol.day}$</td>
<td>[21]</td>
</tr>
<tr>
<td>$r_I$ virus replication rate from one infected cell</td>
<td>$18, 1000 \text{ vir}/(\text{cell.day}), 850 \text{ (virion day}^{-1})$</td>
<td>[21, 53, 59]</td>
</tr>
<tr>
<td>$d_V$ clearance rate for free virus</td>
<td>$23 \text{ day}^{-1}$</td>
<td>[53]</td>
</tr>
<tr>
<td>$d_M$ medicine clearance rate</td>
<td>$0.3 \text{ day}^{-1}$</td>
<td>[21]</td>
</tr>
<tr>
<td>$\lambda$ degradation rate of the chemical signal</td>
<td>$0.5 \text{ day}^{-1}$</td>
<td></td>
</tr>
<tr>
<td>$p_c$ production rate of chemical attractant</td>
<td>$0.1 \text{ mm}^3/(\text{imm cell.day})$</td>
<td></td>
</tr>
<tr>
<td>$\delta$ clearance rate of infected T-cells</td>
<td>$0.39 \text{ day}^{-1}, 0.6 \text{ day}^{-1}$</td>
<td>[53, 59]</td>
</tr>
<tr>
<td>$d_T$ death rate of T-cells</td>
<td>$0.01 \text{ day}^{-1}$</td>
<td>[59]</td>
</tr>
<tr>
<td>$g_T$ proliferation rate of T-cells in the lymph node</td>
<td>$2 \text{ mm}^3/(\text{imm cell.day})$</td>
<td>[26]</td>
</tr>
</tbody>
</table>
2.2. **The sinus region** $\Omega_2$

The region $\Omega_2$ surrounding the lymph node is the area which is composed of the subcapsular sinus and afferent/efferent lymphatic vessels, a schematic of which is shown in Figure 2.11. Similar with the model in region $\Omega_1$, we consider the concentrations of virus, medicine and infected/uninfected T-cells, again using the variables $V$, $M$, $I$ and $T$. The subcapsular sinus receives lymph from the afferent lymphatic vessels and passes it to the cortical sinus. In this region, particles are delivered to and from the lymph node with the free movement of lymphatic fluid, whose flow may be best modeled as an incompressible fluid. Therefore, we combine the Navier-Stokes equations for incompressible flow and conservation of mass with our reaction modeling terms used in $\Omega_1$. However, we remove the modeling terms from (2.2) that correspond to T-cell generation, since that only occurs inside the lymph node itself, and we remove the chemoattractant since the T-cells do not undergo chemotaxis in this region.

![Figure 2.11. sinus region $\Omega_2$](image)

A fluid is said to be incompressible when its density is not changed by external forces acting on the fluid. In other words, the rate of change of fluid density $\rho$ following the motion is zero, which is

\[
\frac{D\rho}{Dt} = 0.
\]

Thus, the fluid density is given by a constant $\rho$, and when a shear stress is applied to any fluid, it will deform continuously so long as the shear stress is applied. The viscosity is a measure
of the resistance of the fluid to flow. The kinematic viscosity measures the resistance to flow of a fluid under the influence of gravity. Here we denote the constant kinematic viscosity by \( \nu \). Since the virus, lymphocytes and medicine particles all have different sizes, these should experience different viscosities as they move through the flow. Thus, in the flow model we introduce the flow velocity field \( \mathbf{u} = \mathbf{u}(x, y, z, t) \) at the spatial location \( (x, y, z) \in \Omega_2 \) at the time \( t \in [t_0, t_f] \) and the fluid pressure \( p = p(x, y, z, t) \). By the conservation of mass, we have the equation

\[
\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{u}) = 0.
\]

Including the incompressibility condition, this equation reduces to \( \nabla \cdot \mathbf{u} = 0 \).

We thus have the following model for the sinus region \( \Omega_2 \):

\[
\frac{\partial}{\partial t} \mathbf{u} + (\mathbf{u} \cdot \nabla) \mathbf{u} - \nu \nabla^2 \mathbf{u} = \frac{1}{\rho} \nabla p, \tag{2.6a}
\]

\[
\nabla \cdot \mathbf{u} = 0, \tag{2.6b}
\]

\[
\frac{\partial}{\partial t} V + (\mathbf{u} \cdot \nabla) V - \nu_v \nabla^2 V = -f_T VT - e_M VM + r_I I - d_V V, \tag{2.6c}
\]

\[
\frac{\partial}{\partial t} M + (\mathbf{u} \cdot \nabla) M - \nu_M \nabla^2 M = -e_M VM - d_M M, \tag{2.6d}
\]

\[
\frac{\partial}{\partial t} I + (\mathbf{u} \cdot \nabla) I - \nu_T \nabla^2 I = i_T VT - \delta I, \tag{2.6e}
\]

\[
\frac{\partial}{\partial t} T + (\mathbf{u} \cdot \nabla) T - \nu_T \nabla^2 T = -k_T VT - d_T T. \tag{2.6f}
\]

The model in region \( \Omega_1 \) is an advection-diffusion-reaction PDEs to analyze the dynamics and interactions of the virus, medicine and T-cell concentrations in the dense lymph node, while the model in region \( \Omega_2 \) is an incompressible flow model to analyze the transport of these quantities into and out of the lymph node. By coupling the models together, we can quantitatively study these biological phenomena in the human lymph node to better understand the effects of various drug treatments for HIV. In the next two chapters we discuss the numerical methods that we apply to approximate solutions to this model. We then demonstrate the qualitative and quantitative performance of this model on studying HIV dynamics in the human lymph node in Chapter 5.
Chapter 3
Algorithm

In this chapter, we present the numerical methods we used to approximate solutions to the model equations (2.2) in region $\Omega_1$. We use the finite element method to discretize the spatial domain, which leads to a time-dependent nonlinear system of ordinary differential equations (ODEs). We then apply a variety of ODE solvers to convert the problem to a corresponding system of nonlinear algebraic equations for each time step. We then solve these nonlinear systems using a standard Newton’s method supplied with residual and Jacobian. Since calculation and solution of the corresponding linear systems is computationally costly, we investigate four different types of preconditioners applied to a standard GMRES iterative linear solver. Due to the size of the three-dimensional problem and the desire for high-resolution simulations, all of these algorithms are performed in parallel. The computational domain is approximated by an unstructured tetrahedral mesh, which will be discussed in Chapter 5. We separately discuss the details of each aspect of our numerical method in the following sections.

3.1. Finite element discretization

Consider a triangulation $\mathcal{T}$ of the spatial domain $\Omega_1$. Then the solution $(V, M, c, I, T)$ of the model problem is defined in the space:

$$\mathcal{S} = \mathcal{U} \times \mathcal{U} \times \mathcal{U} \times \mathcal{U} \times \mathcal{U}$$  \hspace{1cm} (3.1)

where $\mathcal{U} = \mathcal{H}^1(\Omega_1) \times \mathcal{I}$. Here, $\mathcal{H}^1$ represents the Sobolev space given by

$$\mathcal{H}^1 = \{ u(x) \in L_2(\Omega_1) \mid \nabla u \in L_2(\Omega_1) \}.$$  \hspace{1cm} (3.2)
and \( I \) represents the time space

\[
I = [0, t_f].
\]

We point out that we do not include the boundary conditions in the finite element space above since we utilize a variety of different boundary conditions in the test problems that follow, where we consider homogeneous Neumann, nonhomogeneous Neumann, homogeneous Dirichlet and nonhomogeneous Dirichlet boundary conditions. We will discuss these in detail when introducing each test. Here we just consider the simple homogeneous Neumann boundary conditions for convenience when describing the algorithm.

We can then derive the weak formulation of our model problem using a Galerkin formulation. Let \((v, \mu, \kappa, \iota, \tau) \in S\) be the test functions corresponding to our solutions \((V, M, c, I, T)\). Then the variational form of our model is:

\[
\langle \frac{\partial V}{\partial t}, v \rangle + \langle D_V \nabla V, \nabla v \rangle + \langle f_T V T, v \rangle + \langle e_M V M, v \rangle - \langle r_I I, v \rangle + \langle d_V V, v \rangle = \langle \text{rhs}_V, v \rangle, \tag{3.4a}
\]

\[
\langle \frac{\partial M}{\partial t}, \mu \rangle + \langle D_M \nabla M, \nabla \mu \rangle + \langle e_M V M, \mu \rangle + \langle d_M M, \mu \rangle = \langle \text{rhs}_M, \mu \rangle, \tag{3.4b}
\]

\[
\langle \frac{\partial c}{\partial t}, \kappa \rangle + \langle D_c \nabla c, \nabla \kappa \rangle + \langle \lambda c, \kappa \rangle - \langle p_c V T, \kappa \rangle = \langle \text{rhs}_c, \kappa \rangle, \tag{3.4c}
\]

\[
\langle \frac{\partial I}{\partial t}, \iota \rangle + \langle D_I \nabla I, \nabla \iota \rangle - \langle i_T V T, \iota \rangle + \langle \delta I, \iota \rangle = \langle \text{rhs}_I, \iota \rangle, \tag{3.4d}
\]

\[
\langle \frac{\partial T}{\partial t}, \tau \rangle + \langle D_T \nabla T, \nabla \tau \rangle - \langle \chi T V c, \nabla \tau \rangle + \langle k_T V T, \tau \rangle + \langle d_T T, \tau \rangle = \langle g_T, \tau \rangle, \tag{3.4e}
\]

for all \((v, \mu, \kappa, \tau) \in S\). Here we use the notation \(\langle \cdot, \cdot \rangle\) to represent the standard \(L^2\) inner product. From finite element view, we take all of these \(\text{rhs}\) as forcing terms. In our biology model, there is no \(\text{rhs}\) term except for the last equation, and thus for our biology tests we set these to be 0 in practice. However, for some of our other tests, we will manipulate these \(\text{rhs}\) terms as needed. For the last \(T\) equation, we just simply contain the \(\text{rhs}\) inside the \(g_T\) term.
We spatially discretize our model by restricting the variational problem (3.4) to a pair of discrete trial and test spaces. We utilize a Galerkin formulation: find \((V_h, M_h, c_h, I_h, I_h, T_h) \in S_h \subset S\) such that

\[
\begin{aligned}
\left\langle \frac{\partial V_h}{\partial t}, v_h \right\rangle + \left\langle D_V \nabla V_h, \nabla v_h \right\rangle + \left\langle f_T V_h T_h, v_h \right\rangle + \left\langle e_M V_h M_h, v_h \right\rangle + \left\langle d_V V_h, v_h \right\rangle - \left\langle r_I I_h, v_h \right\rangle &= \left\langle \text{rhs}_V, v_h \right\rangle, \\
\left\langle \frac{\partial M_h}{\partial t}, \mu_h \right\rangle + \left\langle D_M \nabla M_h, \nabla \mu_h \right\rangle + \left\langle e_M V_h M_h, \mu_h \right\rangle + \left\langle d_M M_h, \mu_h \right\rangle &= \left\langle \text{rhs}_M, \mu_h \right\rangle, \\
\left\langle \frac{\partial c_h}{\partial t}, \kappa_h \right\rangle + \left\langle D_c \nabla c_h, \nabla \kappa_h \right\rangle + \left\langle \lambda c_h, \kappa_h \right\rangle - \left\langle p_c V_h T_h, \kappa_h \right\rangle &= \left\langle \text{rhs}_c, \kappa_h \right\rangle, \\
\left\langle \frac{\partial I_h}{\partial t}, \iota_h \right\rangle + \left\langle D_I I_h, \nabla \iota_h \right\rangle - \left\langle i_T V_h T_h, \iota_h \right\rangle + \left\langle \delta I_h, \iota_h \right\rangle &= \left\langle \text{rhs}_I, \iota_h \right\rangle, \\
\left\langle \frac{\partial T_h}{\partial t}, \tau_h \right\rangle + \left\langle D_T \nabla T_h, \nabla \tau_h \right\rangle + \left\langle \chi T_h \nabla c_h, \nabla \tau_h \right\rangle + \left\langle k_T V_h T_h, \tau_h \right\rangle + \left\langle d_T T_h, \tau_h \right\rangle &= \left\langle g_T, \tau_h \right\rangle,
\end{aligned}
\]

for all \((v_h, \mu_h, \kappa_h, \iota_h, \tau_h) \in S_h\). Representing the discretized solution \((V_h, M_h, c_h, I_h, T_h)\) as \(u\), then the variational problem leads to a nonlinear time dependent system of ordinary differential equations

\[
N \dot{u} + A(u) = f(t)
\]

where \(\dot{u}\) denotes partial differentiation of \(u\) with respect to \(t\), \(N\) is a block-diagonal mass matrix,

\[
\begin{aligned}
A_V(u) &= \left\langle D_V \nabla V_h, \nabla v_h \right\rangle + \left\langle f_T V_h T_h, v_h \right\rangle + \left\langle e_M V_h M_h, v_h \right\rangle - \left\langle r_I I_h, v_h \right\rangle + \left\langle d_V V, v_h \right\rangle, \\
A_M(u) &= \left\langle D_M \nabla M_h, \nabla \mu_h \right\rangle + \left\langle e_M V_h M_h, \mu_h \right\rangle + \left\langle d_M M_h, \mu_h \right\rangle, \\
A_c(u) &= \left\langle D_c \nabla c_h, \nabla \kappa_h \right\rangle + \left\langle \lambda c_h, \kappa_h \right\rangle - \left\langle p_c V_h T_h, \kappa_h \right\rangle, \\
A_I(u) &= \left\langle D_I I_h, \nabla \iota_h \right\rangle - \left\langle i_T V_h T_h, \iota_h \right\rangle + \left\langle \delta I_h, \iota_h \right\rangle, \\
A_T(u) &= \left\langle D_T \nabla T_h, \nabla \tau_h \right\rangle - \left\langle \chi T_h \nabla c_h, \nabla \tau_h \right\rangle + \left\langle k_T V_h T_h, \tau_h \right\rangle + \left\langle d_T T_h, \tau_h \right\rangle,
\end{aligned}
\]
We note that the system (3.6) may be equivalently written in explicit first-order form as

\[ \dot{u} + N^{-1}A(u) = N^{-1}f(t) \]  

(3.7)

### 3.2. Time semi-discretization

After spatial discretization, we must solve a large nonlinear time dependent system (3.6) or (3.7). Due to the parabolic nature of the model (2.2), we wish to use a stable, efficient implicit method for the time semi-discretization. In this work, we explore Backward Euler, singly diagonal implicit Runge-Kutta (SDIRK) and Backward Differentiation formula (BDF) time integrators.

We perform our numerical implementation of the discretized model (3.7) using the MFEM library (see [http://mfem.org](http://mfem.org)). MFEM is a free, lightweight, scalable C++ library for finite element methods [2]. MFEM has built-in operators for both diffusion and convection which we use for the diffusion and chemotaxis components of the bilinear forms in our model. However, MFEM does not supply built-in operators for reaction terms, so we needed to implement those components of our model manually within MFEM. Additionally, MFEM includes native implementations of fixed time-step Backward Euler and SDIRK methods, as well as interfaces to the SUNDIALS library ([31], see [https://computation.llnl.gov/projects/sundials](https://computation.llnl.gov/projects/sundials)), that includes the CVODE and ARKODE solvers for temporally-adaptive BDF and SDIRK methods, respectively. We discuss our use of these software packages later on, in Section 3.2.3.
3.2.1. General comments on implicit methods

Time integration methods for problems of the form (3.6) or (3.7) construct approximate solutions $u_n \approx u(t_n)$ at the discrete set of times $t_0 < t_1 < \ldots < t_M$, where $t_{n+1} - t_n = k_n$. When using an implicit method to traverse the time step $t_n \rightarrow t_{n+1}$, we first convert the fully discretized system to an equivalent root-finding problem, $F(u) = 0$ (the solution of which is the time-evolved solution, $u_{n+1}$). We then apply Newton’s method to solve this problem: given an initial guess $u^{(0)}$ to $u$, this constructs iterates

$$u^{(q+1)} = u^{(q)} - J_F(u^{(q)})^{-1} F(u^{(q)}), \quad q = 0, 1, \ldots$$

These iterations are stopped when the estimated solution error $\|u^{(q+1)} - u^{(q)}\|$ is small. Thus in order to apply Newton’s method, we must provide the following items:

(a) the nonlinear root-finding function $F : \mathbb{R}^m \rightarrow \mathbb{R}^m$,

(b) the Jacobian of $F$, $J_F : \mathbb{R}^m \rightarrow \mathbb{R}^{m \times m}$, defined as either

$$J_F(u) = \frac{\partial F}{\partial u}(u) = N + \gamma k_n \left( \frac{\partial A}{\partial u}(u) \right)$$

for the original time-dependent problem (3.6), or

$$J_F(u) = \frac{\partial F}{\partial u}(u) = I + \gamma k_n N^{-1} \left( \frac{\partial A}{\partial u}(u) \right)$$

for the explicit form of the problem (3.7), where the value of $\gamma$ depends on the time integration method under consideration, and

(c) a scalable linear solver to find the updates $\delta u^{(q)}$ within each Newton iteration,

$$\delta u^{(q)} = J_F(u^{(q)})^{-1} F(u^{(q)}) \quad \Leftrightarrow \quad J_F(u^{(q)}) \delta u^{(q)} = F(u^{(q)}).$$

In this work, we utilize a preconditioned Generalized Minimum Residual (GMRES) method [56] for item (c) above, and discuss our preconditioning strategies in Chapter 4. Each specific time integration method will have slightly different formulations of $F$ and values for $\gamma$, which we discuss one by one in the following sections.
3.2.2. Backward Euler and SDIRK

The Backward Euler method approximates the ODE \( u'(t) = g(t, u) \) over a time step \( t_n \rightarrow t_{n+1} \) as \( u_{n+1} - u_n = k_n g(t_{n+1}, u_{n+1}) \). Applying this to our original time-dependent problem (3.6), we have the nonlinear residual function

\[
F(u) = Nu + \gamma k_n A(u) - \gamma k_n f(t_{n+1}) - Nu_n,
\]

and the corresponding Jacobian matrix

\[
J_F = \frac{dF}{du} = N + \gamma k_n \begin{bmatrix}
\frac{\partial A_V(u)}{\partial V} & \frac{\partial A_M(u)}{\partial M} & \frac{\partial A_c(u)}{\partial c} & \frac{\partial A_I(u)}{\partial I} & \frac{\partial A_T(u)}{\partial T}
\end{bmatrix}.
\]

Similarly, for the explicit form of the time-dependent problem (3.7), we have the nonlinear residual function

\[
F(u) = u + \gamma k_n N^{-1} A(u) - \gamma k_n N^{-1} f(t_{n+1}) - u_n
\]

and the corresponding Jacobian matrix

\[
J_F = \frac{dF}{du} = I + \gamma k_n N^{-1} \begin{bmatrix}
\frac{\partial A_V(u)}{\partial V} & \frac{\partial A_M(u)}{\partial M} & \frac{\partial A_c(u)}{\partial c} & \frac{\partial A_I(u)}{\partial I} & \frac{\partial A_T(u)}{\partial T}
\end{bmatrix}.
\]

Mathematically, the Backward Euler method is stable and consistent. The method has accuracy \( O(k_n) \), which is convergent but not efficient. We, therefore, use Backward Euler to verify correctness of the code and compare against the other methods for order of accuracy.
Similar to the Backward Euler method, an SDIRK method is a one-step method with the coefficients in Butcher table form,

\[
\begin{array}{c|cccc}
  c_1 & \gamma \\
  c_2 & a_{21} & \gamma \\
  \vdots & \vdots & \ddots & \ddots \\
  c_s & a_{s1} & a_{s2} & \cdots & \gamma \\
\hline
  b_1 & b_2 & \cdots & b_s
\end{array}
\]

for \( s \) stages. To apply the SDIRK method to an ODE of the form \( \dot{u}(t) = g(t, u) \), one must compute

\[
N\z_i = N\u_n + k_n \sum_{j=1}^{i} a_{ij} g(t_{n,j}, \z_j) \quad i = 1, \ldots, s
\]

\[
N\u_{n+1} = N\u_n + k_n \sum_{j=1}^{s} b_j g(t_{n,j}, \z_j),
\]

where the stage times are given by \( t_{n,j} = t_n + c_j k_n \). Thus, for each stage \( i \), we define the nonlinear residual function

\[
F(\z) = N\z + \gamma k_n (A(\z) - f(t_{n,i})) + k_n \sum_{j=1}^{i-1} a_{ij} (A(\z_j) - f(t_{n,j})) - N\u_n,
\]

(3.8)

and the Jacobian

\[
J_F = \frac{dF}{d\z} = N + \gamma k_n \begin{bmatrix}
\frac{\partial A_v(z)}{\partial v} & \frac{\partial A_v(z)}{\partial M} & \frac{\partial A_v(z)}{\partial c} & \frac{\partial A_v(z)}{\partial t} \\
\frac{\partial A_M(z)}{\partial v} & \frac{\partial A_M(z)}{\partial M} & \frac{\partial A_M(z)}{\partial c} & \frac{\partial A_M(z)}{\partial t} \\
\frac{\partial A_c(z)}{\partial v} & \frac{\partial A_c(z)}{\partial M} & \frac{\partial A_c(z)}{\partial c} & \frac{\partial A_c(z)}{\partial t} \\
\frac{\partial A_I(z)}{\partial v} & \frac{\partial A_I(z)}{\partial M} & \frac{\partial A_I(z)}{\partial c} & \frac{\partial A_I(z)}{\partial t} \\
\end{bmatrix} \quad .
\]

(3.9)

MFEM has the built-in solvers SDIRK34 and SDIRK33. The SDIRK34 solver is a three stage, order 4 method with Butcher table
\[
a = \frac{1}{\sqrt{3}} \cos \left( \frac{\pi}{18} \right) + 0.5 \quad \text{and} \quad b = \frac{1}{6(2a - 1)^2}.
\]
This SDIRK34 method is A-stable but not L-stable, whereas SDIRK33 is an L-stable, order 3 method with three stages with Butcher table

<table>
<thead>
<tr>
<th>a</th>
<th>a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2</td>
<td>1/2-a</td>
</tr>
<tr>
<td>1-a</td>
<td>2a</td>
</tr>
<tr>
<td>b</td>
<td>1-2b</td>
</tr>
</tbody>
</table>

where \( a = \frac{1}{\sqrt{3}} \cos \left( \frac{\pi}{18} \right) + 0.5 \) and \( b = \frac{1}{6(2a - 1)^2} \). This SDIRK34 method is A-stable but not L-stable, whereas SDIRK33 is an L-stable, order 3 method with three stages with Butcher table

<table>
<thead>
<tr>
<th>a</th>
<th>a</th>
</tr>
</thead>
<tbody>
<tr>
<td>c</td>
<td>c-a</td>
</tr>
<tr>
<td>1</td>
<td>b</td>
</tr>
<tr>
<td>b</td>
<td>1-a-b</td>
</tr>
</tbody>
</table>

for \( a = 0.435866521508458999416019 \), \( b = 1.20849664917601007033648 \), and \( c = 0.717933260754229499708010 \).

### 3.2.3. SUNDIALS solvers

As we mentioned above, MFEM has an interface to the SUNDIALS package. SUNDIALS consists of six solvers: CVODE, CVODES, ARKODE, IDA, IDAS and KINSOL. Here we used CVODE, a solver for initial value problems for ordinary differential equation (ODE) systems, and ARKODE, a solver for initial value problems with additive Runge-Kutta methods, that includes support for IMEX methods.

CVODE solves ODE initial value problems (IVPs) of the form \( \mathbf{u}'(t) = g(t, \mathbf{u}) \) using variable-order, variable-step multistep methods based on formulas of the form

\[
\sum_{i=0}^{K_1} \alpha_{n,i} \mathbf{u}_{n-i} + k_n \sum_{i=0}^{K_2} \beta_{n,i} g(t_{n-i}, \mathbf{u}_{n-i}) = 0. \tag{3.10}
\]

For stiff problems, CVODE includes the Backward Differentiation Formulas (BDF) in so-called fixed-leading coefficient (FLC) form, given by \( K_1 = q \) and \( K_2 = 0 \), with order \( q \) varying...
between 1 and 5. Then the nonlinear system (3.10) can be formulated as the root-finding problem

\[ F(u) = u - k_n \beta_n,0 g(t_n, u_n) - a_n = 0, \]

where \( a_n = \sum_{i>0} (a_{n,i} u_{n-i} + k_n \beta_{n,i} g(t_{n-i}, u_{n-i})) \).

Similarly, ARKODE solves ODE initial value problems \( Nu'(t) = g(t, u) \) using additive Runge-Kutta methods by separating the right-hand side function into nonstiff components \( g_E(t, u) \) and stiff components \( g_I(t, u) \). Writing the IVP system in the form \( Nu'(t) = g_E(t, u) + g_I(t, u) \), then applying variable-step, embedded, additive Runge-Kutta methods results in the equations

\[
\begin{align*}
Nz_i &= Nu_{n-1} + k_n \sum_{j=1}^{i-1} A_{i,j}^E g_E(t_{n,j}, z_j) + k_n \sum_{j=1}^{l} A_{i,j}^I g_I(t_{n,j}, z_j), \quad i = 1, \ldots, s, \\
Nu_n &= Nu_{n-1} + k_n \sum_{i=1}^{s} \left( b_i^E g_E(t_{n,i}, z_i) + b_i^I g_I(t_{n,i}, z_i) \right), \\
N\tilde{u}_n &= Nu_{n-1} + k_n \sum_{i=1}^{s} \left( \tilde{b}_i^E g_E(t_{n,i}, \tilde{z}_i) + \tilde{b}_i^I g_I(t_{n,i}, \tilde{z}_i) \right).
\end{align*}
\]

Here \( \tilde{u}_n \) are embedded solutions that approximate \( u(t_n) \), and that are used for error estimation in order to adapt the time step size \( k_n \). While ARKODE supports IMEX methods, MFEM only provides an ARKODE interface for purely explicit or implicit solvers. Considering our model in this thesis, we use the implicit solvers from ARKODE, corresponding to the choice \( g_E = 0 \), and resulting in SDIRK methods. As a result, our nonlinear residual and Jacobian functions match those in equations (3.8) and (3.9).

### 3.3. Implementation in MFEM

We used a variety of software packages when implementing our model. First, to create the mesh we employed the Gmsh package (see http://gmsh.info), a three-dimensional finite element mesh generator with built-in pre- and post-processing facilities [27]. As previously stated, we implemented our finite-element approximation, including time integrators, nonlinear solver, linear solver, and preconditioners using the MFEM finite element infrastructure...
It enables research and development of scalable finite element discretizations and solver algorithms through general finite element abstractions, accurate and flexible visualization, and tight integration with the hypre library (see http://www.llnl.gov/casc/hypre), that provides scalable multigrid methods for large-scale linear systems of equations. Conveniently, MFEM can directly read the Gmsh-generated .msh finite element mesh files.

Given the Gmsh-generated .msh file defining our computational domain \( \Omega_1 \), our MFEM-based implementation of the model (2.2) proceeded by the following steps:

1. Construct the finite element discretization:
   
   (a) Import the Gmsh mesh file.

   (b) Define a finite element space on the mesh with an \( \mathcal{H}^1 \) finite element collection of order \( p \). Our default value is \( p = 1 \), but this may be modified with a command-line option.

2. Define the type of time discretization method to use. MFEM provides different types of time integration methods to choose from. Both MFEM’s built-in implicit time integration methods and SUNDIALS solvers (ARKODE and CVODE) are tested. It is easy to switch the ODE solver as long as we set the Jacobian correctly.

3. Construct the boundary conditions:

   (a) Mark degrees of freedom corresponding to boundary locations with values indicating the type of boundary condition to apply (0=Neumann, 1=Dirichlet).

   (b) For non-homogeneous Dirichlet/Neumann conditions, supply a function to provide the corresponding boundary condition value based on the location of the degree of freedom.

4. Define the block structure of the problem by setting the array of offsets for each variable. Get the number of vector degrees of freedom from the finite element space, and allocate our array \( \mathbf{u} \) of this length.

5. Allocate the relevant grid functions, coefficients, and vectors with their associated finite element space. We relate the grid function with the block vector \( \mathbf{u} \) by making a
reference to the corresponding data. We allocate several coefficients. Initial conditions of the system are used to initialize the function coefficients and the grid function. Also, the parameters in our model are defined using constant coefficients. In the code, we refer to \(-e_M\) by \(a_{12}\) and \(a_{21}\), \(r_I\) by \(a_{14}\), \(-f_T\) by \(a_{15}\), \(p_c\) by \(a_{31}\), \(i_T\) by \(a_{41}\), \(-k_T\) by \(a_{51}\), \(-d_V\) by \(b_1\), \(-d_M\) by \(b_2\), \(-\lambda\) by \(b_3\), \(-\delta\) by \(b_4\) and \(-d_T\) by \(b_5\).

6. Create the time-dependent operator C++ class (derived from the MFEM abstract base class, \texttt{TimeDependentOperator}):

   (a) Define the nonlinear system (3.6). We are using finite element method to do the spatial discretization and write our system to the ODE (3.6). In our time-dependent operator C++ class, we define the bilinear form, the nonlinear form and the corresponding linear form to construct the ODE system.

   (b) Define the nonlinear residual function \(F(u)\).

   (c) Define the corresponding Jacobian function, \(J_F(u)\).

   (d) Define the type of nonlinear solver. We used the MFEM built-in Newton solver, and provided our residual Jacobian functions, \(F(u)\) and \(J_F(u)\).

   (e) Define the type of linear solver. When solving the nonlinear system with Newton method, each iteration requires the solution of a linear system. Since our system is nonsymmetric, we chose to apply GMRES.

7. Create the preconditioner. Since our system of advection-reaction-diffusion PDEs is challenging for GMRES to solve on its own, we tested different types of preconditioners. To this end, we leveraged MFEM’s support for specialized block preconditioners as a user-defined solver. We discuss these further in Chapter 4.

8. The last step is evolving the model over the time interval \([0,t_f]\). We used both fixed-step methods and the adaptive-step solvers from SUNDIALS.

   (a) For the fixed-step method, we tested with Backward Euler. It is easy to set the fixed time step to be used for each simulation before integration in MFEM.
(b) For the CVODE/ARKODE solvers, we needed to develop SUNDIALS-specific functions to set up and perform the implicit solve in the `TimeDependentOperator`. Then in the main code, we needed to define the accuracy tolerances and the types of integration, such as `CV_BDF` or the implicit `ARKStepSolver`. 
Chapter 4
Preconditioning

As discussed in Chapter 3, after discretization in space, our model reduces to a large nonlinear time dependent ODE system (3.6). Applying any of the implicit time integration methods discussed in Section 3.2, we must in turn solve at least one large nonlinear system of algebraic equations per step $t_n \rightarrow t_{n+1}$. For these, we use Newton’s method, which at each iteration must solve a large nonsymmetric linear system of equations

$$J_F \delta u = -F,$$

where $J_F = [j_{lk}]$ is an $n \times n$ coefficient matrix and $-F$ a given right-hand side vector.

Solving this system is the central, and often the most computationally time-consuming part in the numerical simulation. For this purpose, there are a variety of methods, which, generally speaking, are divided into two main classes, direct methods and iterative methods.

Direct methods, based on a factorization of the coefficient matrix $J_F$ into easily invertible matrices, are very robust. These typically include Gaussian elimination, LU decomposition, and QR factorization. But direct methods demand a large amount of time and storage when $J_F$ is large. Therefore, we focus on iterative methods, such as Gauss-Seidel, SOR and Krylov subspace methods. Here, preconditioning techniques must be used to improve the performance and reliability of Krylov subspace methods.

There are several different types of preconditioners that have been developed for multiphysics systems of equations, and the essential requirements of a good preconditioner are:

- the preconditioned system should be easy to solve using the Krylov method, and
- the preconditioner should be cheap to construct and apply [10].
4.1. Preconditioners in our model

As we discussed in Chapter 3, in all of the considered time integration methods we must solve linear systems with the Jacobian $J_F(u)$ arising in Newton’s method, $u^{(q+1)} = u^{(q)} - J_F(u^{(q)})^{-1}F(u^{(q)})$. For the steady-state problem where $u'(t) = 0$, the Jacobian has the form

$$J_{ss}(u) = \frac{\partial A}{\partial u}(u) = \begin{bmatrix}
\frac{\partial A_v(u)}{\partial V} & \frac{\partial A_v(u)}{\partial M} & \frac{\partial A_v(u)}{\partial c} & \frac{\partial A_v(u)}{\partial I} & \frac{\partial A_v(u)}{\partial T} \\
\frac{\partial A_M(u)}{\partial V} & \frac{\partial A_M(u)}{\partial M} & \frac{\partial A_M(u)}{\partial c} & \frac{\partial A_M(u)}{\partial I} & \frac{\partial A_M(u)}{\partial T} \\
\frac{\partial A_c(u)}{\partial V} & \frac{\partial A_c(u)}{\partial M} & \frac{\partial A_c(u)}{\partial c} & \frac{\partial A_c(u)}{\partial I} & \frac{\partial A_c(u)}{\partial T} \\
\frac{\partial A_T(u)}{\partial V} & \frac{\partial A_T(u)}{\partial M} & \frac{\partial A_T(u)}{\partial c} & \frac{\partial A_T(u)}{\partial I} & \frac{\partial A_T(u)}{\partial T} \\
\end{bmatrix},$$

and the time-dependent Jacobian is either

$$J_{time}(u) = N + \gamma k_n \frac{\partial A}{\partial u}(u) = N + \gamma k_n \begin{bmatrix}
\frac{\partial A_v(u)}{\partial V} & \frac{\partial A_v(u)}{\partial M} & \frac{\partial A_v(u)}{\partial c} & \frac{\partial A_v(u)}{\partial I} & \frac{\partial A_v(u)}{\partial T} \\
\frac{\partial A_M(u)}{\partial V} & \frac{\partial A_M(u)}{\partial M} & \frac{\partial A_M(u)}{\partial c} & \frac{\partial A_M(u)}{\partial I} & \frac{\partial A_M(u)}{\partial T} \\
\frac{\partial A_c(u)}{\partial V} & \frac{\partial A_c(u)}{\partial M} & \frac{\partial A_c(u)}{\partial c} & \frac{\partial A_c(u)}{\partial I} & \frac{\partial A_c(u)}{\partial T} \\
\frac{\partial A_T(u)}{\partial V} & \frac{\partial A_T(u)}{\partial M} & \frac{\partial A_T(u)}{\partial c} & \frac{\partial A_T(u)}{\partial I} & \frac{\partial A_T(u)}{\partial T} \\
\end{bmatrix},$$

for our standard form of the time-dependent problem (3.6), or for the problem in explicit form (3.7) the Jacobian is

$$J_{time}(u) = I + \gamma k_n N^{-1} \frac{\partial A}{\partial u}(u) = I + \gamma k_n N^{-1} \begin{bmatrix}
\frac{\partial A_v(u)}{\partial V} & \frac{\partial A_v(u)}{\partial M} & \frac{\partial A_v(u)}{\partial c} & \frac{\partial A_v(u)}{\partial I} & \frac{\partial A_v(u)}{\partial T} \\
\frac{\partial A_M(u)}{\partial V} & \frac{\partial A_M(u)}{\partial M} & \frac{\partial A_M(u)}{\partial c} & \frac{\partial A_M(u)}{\partial I} & \frac{\partial A_M(u)}{\partial T} \\
\frac{\partial A_c(u)}{\partial V} & \frac{\partial A_c(u)}{\partial M} & \frac{\partial A_c(u)}{\partial c} & \frac{\partial A_c(u)}{\partial I} & \frac{\partial A_c(u)}{\partial T} \\
\frac{\partial A_T(u)}{\partial V} & \frac{\partial A_T(u)}{\partial M} & \frac{\partial A_T(u)}{\partial c} & \frac{\partial A_T(u)}{\partial I} & \frac{\partial A_T(u)}{\partial T} \\
\end{bmatrix}.$
It is noticeable that all of these Jacobian matrices only differ by a mass matrix $N$ and a scalar $\gamma_k$. Hence, similar preconditioners can be applied.

With regards of the structure of our model, we consider preconditioners based on block matrix decompositions of the Jacobian. Based upon our model, all $(V, M, c, I, T)$ equations have diffusion and reaction components, but only the equation for $T$ includes chemotaxis. Hence, there are diffusion terms, reaction terms and a chemotaxis term in the matrix $A(u)$. Therefore, we consider a decomposition of our Jacobian into the block form:

$$J = \begin{bmatrix}
  \dot{j}_{VV} & \dot{j}_{VM} & \dot{j}_{Vc} & \dot{j}_{VI} & \dot{j}_{VT} \\
  \dot{j}_{MV} & \dot{j}_{MM} & \dot{j}_{Mc} & \dot{j}_{MI} & \dot{j}_{MT} \\
  \dot{j}_{cV} & \dot{j}_{cM} & \dot{j}_{cc} & \dot{j}_{cI} & \dot{j}_{cT} \\
  \dot{j}_{IV} & \dot{j}_{IM} & \dot{j}_{Ic} & \dot{j}_{II} & \dot{j}_{IT} \\
  \dot{j}_{TV} & \dot{j}_{TM} & \dot{j}_{Te} & \dot{j}_{TI} & \dot{j}_{TT}
\end{bmatrix} = \begin{bmatrix}
  M & U \\
  L & D
\end{bmatrix}$$

(4.1)

with

$$M = \begin{bmatrix}
  \dot{j}_{VV} & \dot{j}_{VM} & \dot{j}_{Vc} & \dot{j}_{VI} \\
  \dot{j}_{MV} & \dot{j}_{MM} & \dot{j}_{Mc} & \dot{j}_{MI} \\
  \dot{j}_{cV} & \dot{j}_{cM} & \dot{j}_{cc} & \dot{j}_{cI} \\
  \dot{j}_{IV} & \dot{j}_{IM} & \dot{j}_{Ic} & \dot{j}_{II}
\end{bmatrix}, \quad U = \begin{bmatrix}
  \dot{j}_{VT} \\
  \dot{j}_{MT} \\
  \dot{j}_{IT} \\
  \dot{j}_{IT}
\end{bmatrix},$$

$$L = \begin{bmatrix}
  \dot{j}_{TV} & \dot{j}_{TM} & \dot{j}_{Te} & \dot{j}_{TI}
\end{bmatrix}, \quad D = \begin{bmatrix}
  \dot{j}_{TT}
\end{bmatrix},$$

Here, $M$ contains diffusion terms along the diagonal, and the off-diagonal block matrices only involve inter-variable couplings due to the reaction terms. Similarly, $U$ contains only reaction terms, $L$ contains both reaction terms and the advection of $T$ based on chemotaxis (inside $j_{Te}$). Finally, $D$ contains reaction, diffusion and advection terms encoding the dependence of $A_T(u)$ on $T$. Based on this block structure, we consider three types of preconditioners: block diagonal, lower triangular, and Schur complement. Each of these preconditioners are discussed in the following subsections.
For ease of notation, in the remainder of this chapter we will denote the block structure of our Jacobian as

\[
J = \begin{bmatrix}
\dot{j}_{11} & \dot{j}_{12} & \dot{j}_{13} & \dot{j}_{14} & \dot{j}_{15} \\
\dot{j}_{21} & \dot{j}_{22} & \dot{j}_{23} & \dot{j}_{24} & \dot{j}_{25} \\
\dot{j}_{31} & \dot{j}_{32} & \dot{j}_{33} & \dot{j}_{34} & \dot{j}_{35} \\
\dot{j}_{41} & \dot{j}_{42} & \dot{j}_{43} & \dot{j}_{44} & \dot{j}_{45} \\
\dot{j}_{51} & \dot{j}_{52} & \dot{j}_{53} & \dot{j}_{54} & \dot{j}_{55}
\end{bmatrix}.
\] (4.2)

4.1.1. Block diagonal preconditioner

The simplest preconditioner is the block diagonal preconditioner

\[
P^{-1}\text{diag} = \begin{bmatrix} M^{-1} \\ D^{-1} \end{bmatrix}.
\]

This gives rise to the left-preconditioned matrix

\[
P^{-1}\text{diag}J = \begin{bmatrix} M^{-1} \\ D^{-1} \end{bmatrix} \begin{bmatrix} M & U \\ L & D \end{bmatrix} = \begin{bmatrix} I & M^{-1}U \\ D^{-1}L & I \end{bmatrix}.
\]

As we can see from the structure of this preconditioner, it would be costly to compute the inverse of the block \(M\) in practice. Hence we approximate the blocks \(M\) and \(D\) by

\[
\tilde{M} = \begin{bmatrix}
\tilde{j}_{11} \\
\tilde{j}_{22} \\
\tilde{j}_{33} \\
\tilde{j}_{44} \\
\tilde{j}_{55}
\end{bmatrix},
\]

\[
\tilde{D} = \begin{bmatrix}
\tilde{j}_{55}
\end{bmatrix},
\]

where \(\tilde{j}_{11}, \tilde{j}_{22}, \tilde{j}_{33}, \tilde{j}_{44}\) and \(\tilde{j}_{55}\) contain only the diffusion and mass matrix contributions from
Here we have

\[
M - \tilde{M} = \begin{bmatrix}
\dot{j}_{11} - \tilde{j}_{11} & \dot{j}_{12} & \dot{j}_{13} & \dot{j}_{14} \\
\dot{j}_{21} & \dot{j}_{22} - \tilde{j}_{22} & \dot{j}_{23} & \dot{j}_{24} \\
\dot{j}_{31} & \dot{j}_{32} & \dot{j}_{33} - \tilde{j}_{33} & \dot{j}_{34} \\
\dot{j}_{41} & \dot{j}_{42} & \dot{j}_{43} & \dot{j}_{44} - \tilde{j}_{44}
\end{bmatrix}
\]

corresponding to the Jacobian components arising from the neglected reaction terms, and

\[
D - \tilde{D} = \begin{bmatrix}
\dot{j}_{55} - \tilde{j}_{55}
\end{bmatrix}
\]

is the Jacobian component arising from the neglected reaction and advection terms.

Therefore, this block diagonal preconditioner turns into:

\[
\tilde{P}^{-1} = \begin{bmatrix}
\tilde{j}_{11}^{-1} & & & \\
& \tilde{j}_{22}^{-1} & & \\
& & \tilde{j}_{33}^{-1} & \\
& & & \tilde{j}_{44}^{-1}
\end{bmatrix}
\]

4.1.2. Lower triangular preconditioner

A block lower triangular preconditioner matrix for this system would have the form

\[
P_{tri}^{-1} = \begin{bmatrix}
M \\
L & D
\end{bmatrix}^{-1} = \begin{bmatrix}
M^{-1} \\
-D^{-1}LM^{-1} & D^{-1}
\end{bmatrix}
\]

which would correspond with the left-preconditioned matrix

\[
P_{tri}^{-1}J = \begin{bmatrix}
M^{-1} \\
-D^{-1}LM^{-1} & D^{-1}
\end{bmatrix} \begin{bmatrix}
M & U \\
L & D
\end{bmatrix} = \begin{bmatrix}
I & M^{-1}U \\
L & D
\end{bmatrix}.\]
However, due to the computational costs associated with inversion of $M$ we again approximate this block lower triangular preconditioner as

$$
P^{-1}_{tri} = \begin{bmatrix}
\tilde{j}_{11}^{-1} & & \\
& \tilde{j}_{22}^{-1} & \\
& & \tilde{j}_{33}^{-1} \\
& & & \tilde{j}_{44}^{-1} \\
\hat{L} & & & \tilde{j}_{55}^{-1}
\end{bmatrix},
$$

where $\tilde{j}_{ii}^{-1}$ are the same as in the previous subsection. Here, we first approximate

$$
L = \begin{bmatrix}
\tilde{j}_{51} & \tilde{j}_{52} & \tilde{j}_{53} & \tilde{j}_{54}
\end{bmatrix}
$$

by

$$
\tilde{L} = \begin{bmatrix}
0 & 0 & \tilde{j}_{53} & 0
\end{bmatrix},
$$

where $\tilde{j}_{53}$ contains the Jacobian terms related to chemotaxis of $T$, and

$$
L - \tilde{L} = \begin{bmatrix}
\tilde{j}_{51} & \tilde{j}_{52} & \tilde{j}_{53} - \tilde{j}_{53} & \tilde{j}_{54}
\end{bmatrix}
$$

only contains the Jacobian components related to reaction terms. Then we approximate the lower triangular component $-D^{-1}LM^{-1}$ by

$$
\hat{L} = -\tilde{D}^{-1}\tilde{L}\tilde{M}^{-1} = -\begin{bmatrix}
\tilde{j}_{55}^{-1} & & \\
& 0 & 0 & \\
& & \tilde{j}_{53}^{-1} & \\
& & & \tilde{j}_{33}^{-1}
\end{bmatrix}
\begin{bmatrix}
\tilde{j}_{11}^{-1} & & \\
& \tilde{j}_{22}^{-1} & \\
& & \tilde{j}_{33}^{-1} \\
& & & \tilde{j}_{44}^{-1}
\end{bmatrix}
= \begin{bmatrix}
0 & 0 & -\tilde{j}_{55}^{-1}\tilde{j}_{53}^{-1}\tilde{j}_{33}^{-1} & 0
\end{bmatrix}.
$$

Putting these together, we have

$$
P_{tri} - \tilde{P}_{tri} = \begin{bmatrix}
M & \\
L & D
\end{bmatrix} - \begin{bmatrix}
\tilde{M} \\
\tilde{L} & \tilde{D}
\end{bmatrix}
$$
which again corresponds to only the Jacobian components related to reaction terms.

4.1.3. Schur complement

We note that for the block decomposition (4.2) of our matrix \( J_F \), the exact Schur complement is given by

\[
P_{\text{Schur}}^{-1} = \begin{bmatrix}
I & -M^{-1}U \\
I & S^{-1}
\end{bmatrix}
\begin{bmatrix}
I \\
LM^{-1}
\end{bmatrix},
\]

where \( S = D - LM^{-1}U \), which by definition gives rise to the left-preconditioned matrix

\[
P_{\text{Schur}}^{-1}J = \begin{bmatrix}
I & -M^{-1}U \\
I & S^{-1}
\end{bmatrix}
\begin{bmatrix}
I \\
LM^{-1}
\end{bmatrix}
\begin{bmatrix}
M & U \\
L & D
\end{bmatrix} = \begin{bmatrix}
I \\
I
\end{bmatrix}.
\]

Unfortunately, the cost of computing (and even storing) \( S^{-1} \) is extremely high, so we approximate the true Schur complement in two different ways. For our \( P_{\text{Schur},1} \) preconditioner, we first approximate the Schur complement as \( \tilde{S} = \tilde{D} \), where, as previously, \( \tilde{D} \) contains only the diffusion and mass matrix contributions from \( j_{55} \). And for our \( P_{\text{Schur},2} \) preconditioner, we use the slightly more costly approximation \( \hat{S} = \hat{D} - \hat{L}U \) where these \( \hat{D} \) and \( \hat{L} \) are the same as in the previous subsection. For both approaches, we again approximate \( M \) by the block-diagonal version containing only diffusion and mass-matrix contributions, \( \tilde{M} \).

With these approximations, we have:

\[
\hat{P}_{\text{Schur},1} = \begin{bmatrix}
I & -\tilde{M}^{-1}U \\
I & S^{-1}
\end{bmatrix}
\begin{bmatrix}
I \\
LM\tilde{M}^{-1}
\end{bmatrix},
\]

48
and

\[
\tilde{P}_{\text{Schur},2} = \begin{bmatrix}
I & -\tilde{M}^{-1}U \\
1 & \tilde{M}^{-1} \tilde{S}^{-1} & -L\tilde{M}^{-1} & I
\end{bmatrix},
\]

where \( \tilde{S} = \tilde{j}_{55} \), and \( \tilde{S} = \tilde{j}_{55} - \tilde{j}_{53}j_{35} \).

4.1.4. Block solvers

In the implementation, we solve each block, e.g., \( \tilde{j}_{ii}^{-1} \) in MFEM using the BoomerAMG algebraic multigrid solver from the hypre library. As we discussed previously, we analyzed the structure of our Jacobian and construct the corresponding preconditioners. MFEM allows the user to provide customized preconditioners as a derived C++ class from the generic MFEM Solver class. We can provide our Jacobian as an operator and access each block through this operator. For scalable preconditioners solving, we use BoomerAMG in hypre as the preconditioner and GMRES as the solver.

4.2. Scalability of the preconditioners and Matlab tests

We first focus on the algorithmic scalability of these preconditioning approaches, i.e., whether the number of iterations required for the preconditioned Krylov method to converge remains nearly constant as the spatial mesh is refined, or equivalently, whether the number of nonunitary eigenvalues of the preconditioned matrix is almost constant despite the size of the matrix.

It has already been proven that for spatial discretization of certain types of PDEs, multigrid methods exhibit \( h \)-independent convergence [13, 52]. However, this theory does not generally apply to block linear systems such as those encountered here. While we were unable to provide theoretical proof of algorithmic scalability for our block systems, in the following we summarize results from related work suggesting the scalability of our proposed preconditioners and perform numerical tests with similarly-structured one- and two-dimensional problems in Matlab to show that our preconditioned systems are algorithmically scalable.
4.2.1. Block preconditioners

The paper “Block preconditioners for coupled physics problems” by Howle and collaborators [34] provides a closely-related study to our work. There, under a specific set of assumptions (which we discuss in detail momentarily) on their problems, the authors analyze eigenvalue bounds on block diagonal and block upper triangular preconditioners.

The first test problem that they consider is the Bidomain equations, that consist of a reaction-diffusion system of PDEs coupled to the Fitzhugh-Nagumo equation. This problem results in a positive semidefinite linear system:

\[
\begin{bmatrix}
K_i + \frac{1}{\Delta t} M & K_i \\
K_i & K_e + K_i
\end{bmatrix}
\begin{bmatrix}
u_1 \\
u_2
\end{bmatrix}
= \begin{bmatrix}
b_1 \\
b_2
\end{bmatrix},
\]

and they name these blocks as \( A = K_i + \frac{1}{\Delta t} M, \) \( B = C = K_i, \) and \( D = K_e + K_i. \)

For this problem the authors state that \( \exists \alpha \in (0, 1) \) such that

\[
2|(Bv, u)| \leq \alpha((Au, u) + (Dv, v)), \quad \forall \ v, \ u \in \mathbb{R}^k,
\]  

and they prove that \( \kappa(AP_D) \leq \frac{1 + \alpha}{1 - \alpha}. \) Here \( \kappa \) denotes the ratio of the maximum real parts of the eigenvalues of a given matrix to the minimum real parts of the eigenvalues, and \( P_D \) is a diagonal preconditioner. Thus with the block-diagonal preconditioner, the right-preconditioned matrix has condition number that is bounded independently of the mesh size, indicating algorithmic scalability of the method.

The second test problem considered by Howle and collaborators is the Bénard convection problem. This problem consists of the incompressible Navier-Stokes equations coupled to a convection-diffusion equation for the temperature. The system is

\[
\begin{align*}
-\Delta u + u \cdot \nabla u + \nabla p &= -\frac{R_a}{P_r} \hat{g} T \\
\nabla \cdot u &= 0 \\
-\frac{1}{P_r} \Delta T + u \cdot \nabla T &= 0,
\end{align*}
\]

with fluid velocity \( u \) and pressure \( p. \) The Rayleigh number \( R_a \) measures the ratio of energy from buoyant forces to viscous dissipation and heat conduction, the Prandtl number \( P_r \).
measures the ratio of viscosity to heat conduction, and \( \hat{g} \) denotes a unit vector along the axis in which gravity acts.

The authors prove that the real parts of the eigenvalues of the Bénard convection system with a block diagonal preconditioner are given by

\[
\Re(\lambda) \leq 1 + (C_p)^2 \sqrt{\frac{R_a}{P_r}} \| \nabla T^h_0 \|_\infty \| A^{-1} \|_{L(X_h^+,X_h)},
\]

where \( C_p \) represents the constant from Poincaré’s inequality, \( \| \nabla T^h_0 \|_\infty \) is the usual infinity norm of the initial discretized temperature gradient, and the \( \| A^{-1} \|_{L(X_h^+,X_h)} \) term has a mesh-independent bound that depends on \( \| u_0 \|_{H_0^1} \), amongst others.

If we apply the block upper triangular preconditioner to a generalized matrix \( A = \begin{bmatrix} A & B \\ C & D \end{bmatrix} \), we will have

\[
A P_T^{-1} = \begin{bmatrix} A & B \end{bmatrix} \begin{bmatrix} A & B \\ C & D \end{bmatrix}^{-1} = \begin{bmatrix} I & 0 \\ CA^{-1} & I - CA^{-1}BD^{-1} \end{bmatrix}.
\]

The authors also prove that: the eigenvalues of \( CA^{-1}BD^{-1} \) for the Bénard convection problem are bounded by

\[
\Re(\lambda) \leq 1 + (C_p)^4 \frac{R_a}{P_r} \| \nabla T^h_0 \|_\infty \| A^{-1} \|_{L(X_h^+,X_h)} \| D^{-1} \|_{L(W_h^+,W_h)}.
\]

Here, the authors prove that with the block-diagonal and block upper triangular preconditioners, the eigenvalues of the right-preconditioned matrix are bounded independently of the mesh size.

Thus in their work, Howle and collaborators prove that for two specific problems, the eigenvalues are bounded independently of the mesh size for a right-preconditioned matrix with block diagonal and block upper triangular preconditioners. As our problem is an advection-reaction-diffusion system of PDEs which is similar in structure to these two specific problems, and we also apply block diagonal and block triangular preconditioners, then their proof suggests that our preconditioned system may also be algorithmically scalable.
4.2.2. Matlab tests

As we discussed previously, we would like for our preconditioned system to be algorithmically scalable. In the absence of rigorous theory to this end, we chose to investigate this question with some numerical tests using similarly-structured one- and two-dimensional problems in Matlab. Although our target application is time-dependent, we perform these Matlab tests on steady-state problems to examine the most challenging case for these preconditioners (since the linear system becomes simpler to solve as $h_n \to 0$, whereas the steady-state problem corresponds to $h_n \to \infty$). For these tests, we compute the condition numbers of the preconditioned Jacobian matrices as the spatial mesh size is refined. If the condition number of the preconditioned matrix remains close to one with mesh refinement, then we believe that the corresponding preconditioning approach will be promising for our target application.

We tested matrices with no preconditioning and with each of the preconditioning approaches outlined in Section 4.1: block-diagonal, block lower triangular, ‘perfect’ Schur complement, and two approximations of the Schur complement.

Our target problem is an advection-diffusion-reaction model, so we should choose the test problems with advection, diffusion, and reaction term in the matrices. Our corresponding 1D Matlab test problem is:

\[
\begin{align*}
    u'' + v'^2 + uv &= 2 + e^t (e^t + t^2), & u(0) = 0, & u(1) = 1 \\
    v'' + u' - v &= 2t, & v(0) = 1, & v(1) = e.
\end{align*}
\]  

(4.4a)  

(4.4b)

In this test problem, $u''$ and $v''$ are diffusion terms, $uv$ is a reaction term, $v'^2$ and $u'$ are advection terms, and $-v$ is the mass term, thus this test problem has a similar structure to our target model. We linearized this model for our tests around $u = v = 0$. The condition numbers corresponding to each preconditioning approach are shown in Table 4.1.
Table 4.1. Condition numbers of preconditioned matrices for the 1D test problem (4.4).

<table>
<thead>
<tr>
<th>Preconditioner</th>
<th># of nodes</th>
<th>5</th>
<th>50</th>
<th>100</th>
<th>500</th>
<th>1000</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Original matrix</td>
<td></td>
<td>70.7</td>
<td>5.89e+3</td>
<td>2.33e+4</td>
<td>5.77e+5</td>
<td>2.31e+6</td>
<td>9.22e+6</td>
</tr>
<tr>
<td>Block diagonal</td>
<td></td>
<td>1.62</td>
<td>2.08</td>
<td>2.11</td>
<td>2.13</td>
<td>2.13</td>
<td>2.14</td>
</tr>
<tr>
<td>Lower triangular</td>
<td></td>
<td>1.01</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Schur (perfect)</td>
<td></td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Schur type 1</td>
<td></td>
<td>1.01</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Schur type 2</td>
<td></td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Our 2D Matlab test problem is:

\[
-\nabla^2 u + u + v = -2[x(x - 1) + y(y - 1)] + x(x - 1)y(y - 1) + \sin(\pi x)\sin(\pi y) \\
-\nabla^2 v - u - v - \nabla \cdot h(v) = 2\pi^2 \sin(\pi x)\sin(\pi y) - x(x - 1)y(y - 1) - \pi (\cos(\pi x)\sin(\pi y) + \sin(\pi x)\cos(\pi y)) ,
\]

where \( h(v) = \begin{bmatrix} v \\ v \end{bmatrix} \). Similarly, we also include diffusion, advection, and reaction terms in this test problem. The corresponding condition numbers for each preconditioned matrix are shown in Table 4.2.
Table 4.2. Condition numbers of preconditioned matrices for 2D test problem (4.5).

<table>
<thead>
<tr>
<th>preconditioner</th>
<th># of nodes</th>
<th>$26^2$</th>
<th>$74^2$</th>
<th>$994^2$</th>
<th>$3786^2$</th>
<th>$5882^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>original matrix</td>
<td></td>
<td>11.6</td>
<td>16.2</td>
<td>1.73e+2</td>
<td>7.01e+2</td>
<td>1.13e+3</td>
</tr>
<tr>
<td>block diagonal</td>
<td></td>
<td>1.03</td>
<td>1.03</td>
<td>1.03</td>
<td>1.03</td>
<td>1.03</td>
</tr>
<tr>
<td>lower triangular</td>
<td></td>
<td>1.10</td>
<td>1.17</td>
<td>1.25</td>
<td>1.26</td>
<td>1.21</td>
</tr>
<tr>
<td>Schur (perfect)</td>
<td></td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Schur type 1</td>
<td></td>
<td>1.01</td>
<td>1.00</td>
<td>1.01</td>
<td>1.01</td>
<td>1.01</td>
</tr>
<tr>
<td>Schur type 2</td>
<td></td>
<td>1.00</td>
<td>1.01</td>
<td>1.01</td>
<td>1.01</td>
<td>1.01</td>
</tr>
</tbody>
</table>

From these data, we clearly find that the condition number of the un-preconditioned matrices increase rapidly as the mesh is refined. However, for each of the proposed preconditioning approaches the condition numbers of the preconditioned matrices seem to remain bounded independently of the mesh size, indicating a potential for algorithmic scalability on our target application. We also note that even the simple block diagonal preconditioner and block triangular preconditioner perform rather well. As these are significantly less costly to construct and apply than the Schur complement approaches, we believe that these may prove to be more efficient for our application.

4.3. MFEM results

Due to the success of our preconditioning approaches on the preceding Matlab test problems, we applied the four proposed preconditioners on our target application when using GMRES as the Krylov solver. Again, to predict the effectiveness of each preconditioner on the ‘worst case’ for our time-dependent model we collect some data from the corresponding steady-state problem, where we additionally set each $rhs$ to enforce ‘manufactured’ solutions
for assessing solution error. Here the model is:

\[-\nabla \cdot (D_V \nabla V) + f_T TV + e_M MV - r_I I + d_V V = rhs_V,\]  
\[-\nabla \cdot (D_M \nabla M) + e_M MV + d_M M = rhs_M,\]  
\[-\nabla \cdot (D_c \nabla c) + \lambda c - p_c TV = rhs_c,\]  
\[-\nabla \cdot (D_I \nabla I) + \delta I - i_T VT = rhs_I,\]  
\[-\nabla \cdot (D_T \nabla T - \chi T \nabla c) + k_T TV + d_T T = rhs_T.\]  

(4.6a)  
(4.6b)  
(4.6c)  
(4.6d)  
(4.6e)

This test model is on the steady-state of our full model with extra right-hand sides. These right-hand sides come from the computation of the ‘manufactured’ method. For this model we chose the exact solution:

\[V(x, y, z) = \sin(x) \sin(y) \sin(z),\]  
\[M(x, y, z) = \cos(x) \sin(y) \sin(z),\]  
\[c(x, y, z) = \sin(x) \cos(y) \sin(z),\]  
\[I(x, y, z) = \sin(x) \sin(y) \cos(z),\]  
\[T(x, y, z) = \sin(x) \cos(y) \cos(z),\]  

(4.7a)  
(4.7b)  
(4.7c)  
(4.7d)  
(4.7e)

with nonhomogeneous Dirichlet boundary conditions derived from this exact solution (4.7)

\[d_V(x, y, z) = \sin(x) \sin(y) \sin(z), \quad (x, y, z) \in \partial \Omega\]  
\[d_M(x, y, z) = \cos(x) \sin(y) \sin(z), \quad (x, y, z) \in \partial \Omega\]  
\[d_c(x, y, z) = \sin(x) \cos(y) \sin(z), \quad (x, y, z) \in \partial \Omega\]  
\[d_I(x, y, z) = \sin(x) \sin(y) \cos(z), \quad (x, y, z) \in \partial \Omega\]  
\[d_T(x, y, z) = \sin(x) \cos(y) \cos(z), \quad (x, y, z) \in \partial \Omega,\]  

(4.8a)  
(4.8b)  
(4.8c)  
(4.8d)  
(4.8e)

over the domain \(\Omega = [-1, 1]^3\). We then constructed each right-hand side forcing term, \(rhs_*\) from (4.6) to ensure these solutions (4.7).
Table 4.3. Number of preconditioned GMRES iterations for the 3D test problem (4.6)-(4.8).

<table>
<thead>
<tr>
<th>preconditioner</th>
<th>degrees of freedom</th>
<th>6240</th>
<th>42835</th>
<th>315745</th>
<th>2420925</th>
</tr>
</thead>
<tbody>
<tr>
<td>original matrix</td>
<td>205</td>
<td>361</td>
<td>563</td>
<td>800</td>
<td></td>
</tr>
<tr>
<td>block diagonal</td>
<td>26</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>lower triangular</td>
<td>21</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Schur type 1</td>
<td>20</td>
<td>17</td>
<td>16</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Schur type 2</td>
<td>21</td>
<td>20</td>
<td>17</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

In MFEM, the problem is linearized around the exact solution since we use the ‘manufactured’ method, and we use the BoomerAMG algebraic multigrid solver for each block when evaluating our preconditioners. As before, we determined the number of GMRES iterations for the preconditioned linear systems as the mesh was refined, with results shown in Table 4.3. In this table, we see that the iteration numbers increase rapidly with mesh refinement for the un-preconditioned matrices. Meanwhile, the number of GMRES iterations for each preconditioned matrix remains almost constant. We point out that the lower triangular and Schur type 1 preconditioning approaches result in slightly smaller numbers of preconditioned iterations than the block diagonal and Schur type 2 approaches; however, all preconditioners seem to demonstrate the desired algorithmic scalability.
Chapter 5
Numerical results

In this Chapter, we discuss the various numerical tests we do as preparation for larger-scale biology tests. More specifically, in the sections that follow we discuss

- the structure of the lymph node and construction of its 3D mesh,
- simulation of chemotaxis phenomena,
- spatial convergence tests on steady state problems using manufactured solution methods,
- the effect of discontinuous diffusion coefficients on the convergence rate, and
- ODE analysis of the chemical reaction network.

5.1. Lymph node mesh

Figure 5.1 shows a diagram of the human lymph node. The lymph nodes are highly organized lymphoid structures located at the points of convergence of vessels of the lymphatic system, an extensive system of vessels that collects extracellular fluid from the tissues and returns it to the blood [36]. There are seven major subdivisions of the lymph node [43]:

- The lymph node capsule, which surrounds the lymph node [this is our sinus region, $\Omega_2$].
- The subcapsular sinus, which is the initial entryway of lymphatic fluid into the node via afferent lymphatic vessels [this forms a small portion of our sinus region, $\Omega_2$].
The lymph node cortex, which is beneath the subcortical sinus, is the location of primary and secondary lymphoid follicles [this forms a portion of our lymph node region, $\Omega_1$, with large hydraulic conductivity].

- In the absence of immune stimulation, the cortical lymphoid follicles are primary follicles, composed of small B lymphocytes which may be virgin B lymphocytes or recirculating memory B cells.

- With antigenic stimulation, antigen recognizing B cells are stimulated to replication and differentiation. This converts the primary follicle into a secondary follicle or germinal center.

The paracortex, the major site of the T-cells, is the region surrounding and beneath the germinal centers [this forms a portion of our lymph node region, $\Omega_1$, with low diffusivity].

The medulla, which is composed of medullary cords and medullary sinuses [this forms
a portion of our lymph node region, $\Omega_1$.

- Medullary vessels such as arteries and veins [these form a small portion of our sinus region, $\Omega_2$].

- Afferent and efferent lymphatic vessels [these form a small portion of our sinus region, $\Omega_2$].

It is noticeable in the diagram that there are multiple almost identical regions in the lymph node, which we call ‘nodules’. The nodules are composed of a lymphoid follicle, a paracortex and the medullary cords. Each of the nodules is surrounded by the fluid in the vessels. In this work, we model one nodule as a representative and note that several nodules could be coupled together to simulate a full lymph node.

We use the software package Gmsh ([27], see http://www.gmsh.info/) to construct our 3D geometric model of the lymph node and to generate our unstructured tetrahedral mesh for our finite element approximation.

![Figure 5.2. 2D mesh of the lymph node](image)

Figure 5.2. 2D mesh of the lymph node
We note that we generate a finer-resolution mesh close to the follicle to capture the large change in the diffusion coefficient between the inside and outside of the follicle. As opposed to just asking MFEM to perform refinement of the coarsest mesh, we construct this refinement in Gmsh directly so that finer-resolution grids capture the follicle shape.

5.2. Chemotaxis

As we discussed in Chapter 3, we include a model for chemotaxis; in this section we verify that these modeling terms reproduce the correct behavior. Here, we focus on the Keller-Segel Model, modifying the relevant terms to match those from our model, and employ homogeneous Neumann boundary conditions. The reproduced model is:

\begin{align*}
\frac{du}{dt} &= \Delta u - \nabla \cdot (u \nabla v) - u, & x \in \Omega, t > 0, \\
\frac{dv}{dt} &= \Delta v - v + u, & x \in \Omega, t > 0, \\
\frac{\partial u}{\partial \nu} &= \frac{\partial v}{\partial \nu}, & x \in \partial \Omega, t > 0, \\
u(x, 0) &= u_0(x), & \quad v(x, 0) = v_0(x), & x \in \Omega.
\end{align*}

We use a simple square domain $\Omega = [-1, 1]^2$ and an initial condition for the chemoattractant given by the Gaussian distribution $v_0 = K_2 \exp (-K_1 \|x - x_c\|)$, where $K_1$ and $K_2$ correspond to the radius and height of the Gaussian function, and $x_c$ is the center of the chemoattractant region. Here we simply choose $K_1 = 4$, $K_2 = 20$, and $x_c = (0, 0)$. The
initial condition for the moving cells is given by the constant $u_0 = 10$, which means that $u$ is homogeneous throughout the domain at the beginning. We simulate for a time span of $[t_0, t_F] = [0, 0.5]$.

![Simple unstructured triangular mesh used for testing the chemotaxis phenomena.](image)

Figure 5.4. Simple unstructured triangular mesh used for testing the chemotaxis phenomena.

Here, we use GLVis ([1], see https://glvis.org/) to view the mesh and the solution. GLVis is a lightweight tool for accurate and flexible finite element visualization, and is included with the MFEM library.

Initially, the chemoattractant should display a Gaussian distribution, concentrated at the center of $\Omega$, and the attracting cells should be homogeneous throughout the domain. Since we use homogeneous Neumann boundary conditions, there is no flux of either quantity through the boundary. Therefore due to chemotaxis, we expect to see the oriented movement of $u$ toward the center of $\Omega$, followed by spreading of both fields to a homogeneous steady-state due to diffusion.

In Figure 5.5 we show the distribution of $u$ and $v$ in the square domain at the initial time $t_0 = 0$. From the initial condition, $u$ is homogeneous in the domain, and $v$ has a Gaussian distribution.
In Figure 5.5 we plot the solutions at time $t_0 = 0$, which shows that $u$ is moving oriented corresponding to the chemoattractant $v$, and so the distribution of $u$ should be similar to the distribution of $v$. The equations for $u$ and $v$ include both diffusion and reaction terms, they will spread out and decay as time goes by. We see that all of the above expected phenomena are shown in this figure.

In Figure 5.6 we plot the solutions at time $t_1 = 0.05$, which shows that $u$ is moving oriented corresponding to the chemoattractant $v$, and so the distribution of $u$ should be similar to the distribution of $v$. The equations for $u$ and $v$ include both diffusion and reaction terms, they will spread out and decay as time goes by. We see that all of the above expected phenomena are shown in this figure.
In Figure 5.7 we plot the concentrations of $u$ and $v$ at the times $t_2 = 0.1$ and $t_3 = 0.5$. As expected, the motion of $u$ is still determined through diffusion, chemotaxis and decay, while $v$ changes due to diffusion and decay. The distribution of $u$ and $v$ are becoming homogeneous quickly as time increases.

Figure 5.7. Distribution of $u$ (left) and $v$ (right) at the times $t_2 = 0.1$ (first row), $t_3 = 0.5$ (second row), respectively. The chemoattractant $v$ diffuses and decays as expected, and the attracted cells $u$ return to homogeneity as $v$ diffuses.

5.3. Convergence test

As we discussed in Chapter 2, we use an advection-reaction-diffusion system of PDEs to model dynamics of the particles (virus, medicine, chemoattractant, infected cells and lymphocytes) in the region $\Omega_1$. In this section, we study the steady-state distribution of our
model with manufactured source terms to examine the spatial convergence of our model. The corresponding steady-state version of our model (2.2) is:

\[-\nabla \cdot (D_V \nabla V) + f_T V + e_M M V - r_I I + d_V V = rhs_V, \quad (5.2a)\]
\[-\nabla \cdot (D_M \nabla M) + e_M M V + d_M M = rhs_M, \quad (5.2b)\]
\[-\nabla \cdot (D_c \nabla c) + \lambda c - p_c VT = rhs_c, \quad (5.2c)\]
\[-\nabla \cdot (D_I \nabla I) + \delta I - i_T VT = rhs_I, \quad (5.2d)\]
\[-\nabla \cdot (D_T \nabla T - \chi T \nabla c) + k_T VT + d_T T = rhs_T. \quad (5.2e)\]

To verify our implementation, we choose the system of analytical solutions:

\[V(x, y, z) = \sin(x) \sin(y) \sin(z),\]
\[M(x, y, z) = \cos(x) \sin(y) \sin(z),\]
\[c(x, y, z) = \sin(x) \cos(y) \sin(z),\]
\[I(x, y, z) = \sin(x) \sin(y) \cos(z),\]
\[T(x, y, z) = \sin(x) \cos(y) \cos(z),\]

which in turn requires the forcing functions

\[rhs_V(x, y, z) = (3D_V + d_V) \sin(x) \sin(y) \sin(z) + f_T \sin(x) \cos(y) \cos(z) \sin(x) \sin(y) \sin(z)\]
\[+ e_M \cos(x) \sin(y) \sin(z) \sin(x) \sin(y) \sin(z) - r_I \sin(x) \sin(y) \cos(z),\]
\[rhs_M(x, y, z) = (3D_M + d_M) \cos(x) \sin(y) \sin(z) + e_M \cos(x) \sin(y) \sin(z) \sin(x) \sin(y) \sin(z),\]
\[rhs_c(x, y, z) = (3D_c + \lambda) \sin(x) \cos(y) \sin(z) - p_c \sin(x) \cos(y) \cos(z) \sin(x) \sin(y) \sin(z),\]
\[rhs_I(x, y, z) = (3D_I + \delta) \sin(x) \sin(y) \cos(z) - i_T \sin(x) \cos(y) \cos(z) \sin(x) \sin(y) \sin(z),\]
\[rhs_T(x, y, z) = (3D_T + d_T) \sin(x) \cos(y) \cos(z) + k_T \sin(x) \cos(y) \cos(z) \sin(x) \sin(y) \sin(z)\]
\[+ \chi (\cos^2(x) \cos^2(y) + \sin^2(x) \sin^2(y) - 4 \sin^2(x) \cos^2(y)) \sin(z) \cos(z),\]
and nonhomogeneous Dirichlet boundary conditions

\[
\begin{align*}
  d_V(x, y, z) &= \sin(x) \sin(y) \sin(z), & (x, y, z) &\in \partial\Omega \\
  d_M(x, y, z) &= \cos(x) \sin(y) \sin(z), & (x, y, z) &\in \partial\Omega \\
  d_c(x, y, z) &= \sin(x) \cos(y) \sin(z), & (x, y, z) &\in \partial\Omega \\
  d_I(x, y, z) &= \sin(x) \sin(y) \cos(z), & (x, y, z) &\in \partial\Omega \\
  d_T(x, y, z) &= \sin(x) \cos(y) \cos(z), & (x, y, z) &\in \partial\Omega.
\end{align*}
\]

For these convergence tests, we consider:

- the computational domain \(\Omega = [-1, 1]^3\),
- constant diffusion coefficients, i.e. \(D_V = D_M = D_c = D_I = D_T = 1\),
- reaction parameters \(f_T = e_M = k_T = p_c = i_T = 1\),
- particle growth/clearance rates \(r_I = d_V = d_M = \lambda = \delta = d_T = 1\),
- chemotaxis parameter \(\chi = 1\).

In the Table 5.3 we show the convergence of each component from our model as the mesh is refined. Here, \(N\) is the total number of unknowns for \((V, M, c, I, T)\) in the mesh. We compute the error in each component using the \(L_2\) norm. With the 3D box mesh we used here, \(N\) is proportional to \(h^{-3}\). So we use \(1/\sqrt[3]{N}\) to estimate \(h\), then estimate the convergence rate with the formula \(p = \frac{\log(\text{err}_{\text{new}}/\text{err}_{\text{old}})}{\log(h_{\text{new}}/h_{\text{old}})}\), and measure the overall convergence rate by using a linear least squares fit. From these results, we estimate the rate of convergence to be approximately 2. In the Figure 5.8 we show the 3D unstructured tetrahedral mesh used in this test, corresponding to the value \(N = 1745\). Larger meshes are constructed through uniform refinement of this mesh.
Figure 5.8. Coarse \((N = 1745)\) box mesh used in steady-state convergence tests.

Table 5.1. Computed errors in each solution component for the steady-state model (5.2) as the mesh is refined. We estimate the overall rate of convergence to be approximately 2.18.

<table>
<thead>
<tr>
<th>absolute error</th>
<th>N</th>
<th>1745</th>
<th>10370</th>
<th>69575</th>
<th>504905</th>
<th>3836045</th>
<th>con. rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(|V_h - V_ex|)</td>
<td></td>
<td>1.99e-2</td>
<td>5.07e-3</td>
<td>1.30e-3</td>
<td>3.24e-4</td>
<td>8.04e-5</td>
<td>2.14</td>
</tr>
<tr>
<td>(|M_h - M_ex|)</td>
<td></td>
<td>2.81e-2</td>
<td>7.08e-3</td>
<td>1.83e-3</td>
<td>4.60e-4</td>
<td>1.15e-4</td>
<td>2.13</td>
</tr>
<tr>
<td>(|c_h - c_ex|)</td>
<td></td>
<td>2.83e-2</td>
<td>7.14e-3</td>
<td>1.83e-3</td>
<td>4.60e-4</td>
<td>1.15e-4</td>
<td>2.14</td>
</tr>
<tr>
<td>(|I_h - I_ex|)</td>
<td></td>
<td>2.93e-2</td>
<td>7.10e-3</td>
<td>1.80e-3</td>
<td>4.51e-4</td>
<td>1.12e-4</td>
<td>2.16</td>
</tr>
<tr>
<td>(|T_h - T_ex|)</td>
<td></td>
<td>4.85e-2</td>
<td>1.14e-2</td>
<td>2.81e-3</td>
<td>6.97e-4</td>
<td>1.12e-4</td>
<td>2.32</td>
</tr>
</tbody>
</table>
5.4. Discontinuous diffusion coefficient

The lymph node is composed of a number of nearly identical regions which are called nodules, and the diffusion coefficient is discontinuous in the nodule [12]. We can roughly separate the nodule into two parts based upon the diffusivity, the T-cell zone inside the follicle with diffusion coefficient $D_{\text{in}}$, and the rest of the compartment with diffusion coefficient $D_{\text{out}}$. These diffusion coefficients are such that $D_{\text{out}} \gg D_{\text{in}}$.

To test the influence of this discontinuity in the diffusion coefficient, we performed numerical experiments on a single diffusion equation with discontinuous diffusion coefficient. The test problem is:

$$-\nabla \cdot (D \nabla u) = f$$  \hspace{1cm} (5.3)

with diffusion coefficient

$$D = \begin{cases} 
D_{\text{in}} = 1, & \text{if } 0 \leq r^2 < 1, \\
D_{\text{out}} = \frac{1}{\alpha}, & \text{if } 1 \leq r^2,
\end{cases}$$

for varying values of $\alpha$, and right hand side $f = -4$. Here the jump is at the boundary of the circle with radius 1, $r = \sqrt{x^2 + y^2}$, and $u$ is a general variable which can represent the virus, immune cells or infected cells. In these tests we used nonhomogeneous Dirichlet boundary conditions corresponding to the manufactured solution

$$u = \begin{cases} 
r^2, & \text{if } 0 \leq r^2 < 1, \\
\alpha(r^2) - (\alpha - 1), & \text{if } 1 \leq r^2.
\end{cases}$$

The test problem is performed on the square domain $\Omega = [-2, 2]^2$ with an interior circle of radius 1. The mesh is separated into two sub-divisions, inside and outside of this circle, and mesh nodes are placed on the boundary of this circle to better catch the jump.

We may examine the effects of a jump in the diffusion coefficient by changing the magnitude of $\alpha$. If $\alpha = 1$ then there is no jump of the diffusion coefficient, and we would expect second-order spatial convergence as the mesh is refined. The purpose of this test is to inves-
tigate whether second-order convergence will deteriorate as $\alpha$ is decreased and the jump in diffusion coefficient grows.

Since we use a 2D mesh in which $N$ is proportional to $h$, we use $1/\sqrt{N}$ to estimate $h$. Convergence results for this test with values of $\alpha \in \{1, 0.5, 0.1, 0.05, 0.01\}$ are provided in Table 5.2. Here, we give the $L_2$ error as the mesh size increases using uniform refinement of the triangular mesh. From these results, we observe the expected quadratic convergence with $\alpha = 1$. Furthermore, even as the jump in diffusion coefficient grows to a factor of 100, we retain quadratic convergence of the method. We note that a key requirement we found in this test was that the mesh needed to be refined to match the geometry of the circular region; if instead we merely refined the original triangular mesh, the convergence rate deteriorated to 1.

Figure 5.9. Two-dimensional mesh for discontinuous diffusion coefficient test using $N = 266$ spatial nodes.
### Table 5.2. Convergence results for diffusion equation with discontinuous diffusion coefficient.

<table>
<thead>
<tr>
<th>N</th>
<th>α</th>
<th>1.0</th>
<th>0.5</th>
<th>0.1</th>
<th>0.05</th>
<th>0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>266</td>
<td></td>
<td>2.01e-1</td>
<td>1.04e-1</td>
<td>2.91e-2</td>
<td>2.15e-2</td>
<td>1.70e-2</td>
</tr>
<tr>
<td>946</td>
<td></td>
<td>5.22e-2</td>
<td>2.70e-2</td>
<td>7.49e-3</td>
<td>5.50e-3</td>
<td>4.35e-3</td>
</tr>
<tr>
<td>3635</td>
<td></td>
<td>1.30e-2</td>
<td>6.73e-3</td>
<td>1.88e-3</td>
<td>1.38e-3</td>
<td>1.09e-3</td>
</tr>
<tr>
<td>14409</td>
<td></td>
<td>3.27e-3</td>
<td>1.69e-3</td>
<td>4.75e-4</td>
<td>3.46e-4</td>
<td>2.73e-4</td>
</tr>
<tr>
<td>57377</td>
<td></td>
<td>8.19e-4</td>
<td>4.23e-4</td>
<td>1.18e-4</td>
<td>8.66e-5</td>
<td>6.84e-5</td>
</tr>
<tr>
<td>conv. rate</td>
<td>2.05</td>
<td>2.05</td>
<td>2.05</td>
<td>2.05</td>
<td>2.05</td>
<td></td>
</tr>
</tbody>
</table>

5.5. **ODE analysis of the chemical reaction network**

We now examine our model for the reaction network in the region $\Omega_1$, to study its ability to capture the correct interactions between virus, medication, chemoattractant, and healthy/infected T-cells. To focus on only the reaction network, we use the model

\[
\begin{align*}
\frac{\partial}{\partial t}V - \nabla \cdot (D_V \nabla V) &= -f_T VT - e_M VM + r_I I - d_V V, \\
\frac{\partial}{\partial t}M - \nabla \cdot (D_M \nabla M) &= -e_M VM - d_M M, \\
\frac{\partial}{\partial t}c - \nabla \cdot (D_c \nabla c) &= -\lambda c + p_c VT, \\
\frac{\partial}{\partial t}I - \nabla \cdot (D_I \nabla I) &= i_T VT - \delta I, \\
\frac{\partial}{\partial t}T - \nabla \cdot (D_T \nabla T - \chi T \nabla c) &= -k_T VT - d_T T + g_T,
\end{align*}
\]

with continuous diffusion coefficients, spatially-constant initial conditions, and homogeneous Neumann boundary conditions. Thus since there is no flux through the boundary, and all spatial gradients are initially zero, the only ‘active’ terms in the model are those corre-
sponding to reactions within and between components. All of the tests in this section are performed on the relatively coarse two-dimensional mesh shown in Figure 5.10.

![Figure 5.10. Square mesh for reaction network tests.](image)

5.5.1. No medicine stage

We first test the chemical reaction network without medication and an initially small virus concentration, which is indicative of a new HIV infection. So we use the model:

\[
\begin{align*}
\frac{\partial}{\partial t} V - \nabla \cdot (D_V \nabla V) &= -f_T VT + r_I I - d_V V, \\
\frac{\partial}{\partial t} c - \nabla \cdot (D_c \nabla c) &= -\lambda c + p_v VT, \\
\frac{\partial}{\partial t} I - \nabla \cdot (D_I \nabla I) &= i_T VT - \delta I, \\
\frac{\partial}{\partial t} T - \nabla \cdot (D_T \nabla T - \chi T \nabla c) &= -k_T VT - d_T T + g_T,
\end{align*}
\]

(5.5a) (5.5b) (5.5c) (5.5d)

For the implementation, we use:

- time span (days) \([0, t_F] = [0, 25]\),
- constant diffusion coefficients \(D_V = D_c = D_I = D_T = 1\),
• reaction parameters $f_T = 1.0$, $k_T = 0.8$, $p_c = 0.1$, and $i_T = 1.1$,
• particle growth/clearance rates $r_I = 20$, $d_V = 23$, $\lambda = 0.5$, $\delta = 0.39$, and $d_T = 0.01$,
• chemotaxis parameter $\chi = 0$, and T-cell source $g_T = 2$,
• spatially-constant initial conditions $V_0 = 2$, $c_0 = 1$, $I_0 = 1$, and $T_0 = 2$.

Figure 5.11. Average concentration of virus, chemoattractant, infected and healthy T-cells as functions of time for the ‘no medicine’ reaction test (Section 5.5.1).

Results from this test are shown in Figure 5.11, where we plot the time history of the spatially-averaged quantities of each variable. Here, we can see a rapid increase of virus load and then the decrease of viral load caused due to the expected immune response. Also, we see the decrease of healthy T-cells caused by infection and immune response. We note that here the overall quantity in T-cells does not eventually succumb, due to the generation term $g_T$. As in [21, 53, 59], this infection progress based on our model resembles the actual viral infection progression with the damped oscillations.

5.5.2. Initial HIV treatment stage
We now test our ODE reaction network with an initially high virus load, but now in the presence of medicine, which corresponds to the phase where a patient is undergoing HIV treatment. Hence we use model 5.4 with:

- time span (days) \([0, t_F] = [0, 25]\),
- constant diffusion coefficients \(D_V = D_M = D_c = D_I = D_T = 1\),
- reaction parameters \(f_T = 1.0, e_M = 0.5, k_T = 0.8, p_c = 0.1\), and \(i_T = 1.1\),
- particle growth/clearance rates \(r_I = 20, d_V = 23, d_M = 0.3, \lambda = 0.5, \delta = 0.39\), and \(d_T = 0.01\),
- chemotaxis parameter \(\chi = 0\), medicine source \(h_M = 4\), T-cell source \(g_T = 1\),
- spatially-constant initial conditions \(V_1 = 5, M_1 = 5, c_1 = 0.5, I_1 = 1\), and \(T_1 = 2\).

We highlight two of these parameters in particular. Since as the infection progresses the patient keeps losing CD4 T-cells, we have reduced the T-cells generation rate to \(g_T = 1\). Moreover, since the patient takes medicine daily in this stage, we add the medicine source, \(h_M = 4\).

![Figure 5.12. Average concentration of virus, medicine, chemoattractant, infected and healthy T-cells as functions of time for the ‘Initial HIV treatment’ reaction test (Section 5.5.2).](image)
Results from this test, where we again plot the time history of the average values for each variable, are shown in Figure 5.12. We note two key items in this Figure. First, the concentration of virus decreases to near-zero levels as treatment proceeds. Second, we see a notable decrease in the concentration of infected T-cells. Both of these effects accurately model the course of HIV under appropriate treatment.

5.5.3. End of HIV treatment stage

We finally test what happens in our chemical reaction network when HIV treatment ends. Even though the concentration of virus is essentially zero, the presence of a reservoir of infected T-cells in the body should cause the virus to rebound after medication is halted. For this test, we return to the model 5.5, this time using the parameters:

- time span (days) \([0, t_F] = [0, 25]\),
- constant diffusion coefficients \(D_V = D_c = D_I = D_T = 1\),
- reaction parameters \(f_T = 1.0, k_T = 0.8, p_c = 0.1, \) and \(i_T = 1.1\),
- particle growth/clearance rates \(r_I = 20, d_V = 23, \lambda = 0.5, \delta = 0.39, \) and \(d_T = 0.01\),
- chemotaxis parameter \(\chi = 0\), and T-cell source \(g_T = 2\),
- spatially-constant initial conditions \(V_2 = 0, c_2 = 0.5, I_2 = 0.1, \) and \(T_2 = 2\).

We again point out a few key parameters for this test. To model an ‘undetectable’ virus load in the body, we begin with an initial virus concentration \(V_2 = 0\). Moreover, with this lack of HIV in the body, we anticipate that the T-cell growth rate may return to normal \((g_T = 2)\). Lastly, to model the reservoir of infected T-cells, we begin with a very small concentration of infected cells, \(I_2 = 0.1\).
Figure 5.13. Average concentration of virus, chemoattractant, infected and healthy T-cells as functions of time for the ‘End of HIV treatment’ reaction test (Section 5.5.3).

Figure 5.13 shows the results from this test. As expected, we see a quick rebound of both the virus and infected T-cell concentrations, along with the corresponding decrease in concentration of healthy T-cells, even with only the very small initial concentration of infected cells.

Based on this suite of chemical reaction network tests, we conclude that these terms and corresponding parameters in our chemical reaction network are able to correctly model the qualitative behavior of HIV infections.
In this Chapter, we will analyze our model biologically. Instead of measuring convergence and scalability using manufactured solutions and idealized parameters, we will use the physical parameters from Table 2.1.2 and compare model predictions against the clinical course of HIV infection.

For each of these investigations we tested with both the backward Euler ODE solver and ARKODE solver; the results shown here are produced using the implicit ARKODE solvers with the relative tolerance to be 10^{-6} and the absolute tolerance to 10^{-8}. For the choice of preconditioner, we tested with both the block diagonal preconditioner and the lower triangular preconditioner. These results utilize the block diagonal preconditioner as it is simple, efficient, and proved to be very effective for the wide range of tests in this chapter. And all these tests are produced with 16 MPI tasks.

6.1. Infection in the absence of medication

As with our reaction network test in Section 5.5.1, at the beginning of infection, the patient may not know about the virus and will not use medicine. Thus in this stage, there will be only immune cells to combat with virus. So we apply the same model (5.5) as in Section 5.5.1:

\[
\begin{align*}
\frac{\partial}{\partial t} V - \nabla \cdot (D_V \nabla V) &= -f_T VT + r_I I - d_V V, \\
\frac{\partial}{\partial t} c - \nabla \cdot (D_c \nabla c) &= -\lambda c + p_c VT, \\
\frac{\partial}{\partial t} I - \nabla \cdot (D_I \nabla I) &= i_T VT - \delta I, \\
\frac{\partial}{\partial t} T - \nabla \cdot (D_T \nabla T - \chi T \nabla c) &= -k_T VT - d_T T + g_T.
\end{align*}
\]
We now perform the test on the two-dimensional domain with unstructured triangular grid shown in Figure 6.1,

Figure 6.1. Coarse (N=943) two-dimensional lymph domain $\Omega_1$ used for testing the model (6.1).

We use the refinement mesh which is constructed in Gmsh when we perform the test in the following subsections. Now, we use the biological parameters

- $D_{v_{out}} = 1.0$, $D_{v_{in}} = 0.1$
- $D_c = 0.8$
- $D_{I_{out}} = D_{T_{out}} = 0.1$, $D_{I_{in}} = D_{T_{in}} = 0.01$,
- $f_T = 1.0$, $r_I = 20$, $d_V = 23$,
- $\lambda = 0.5$, $p_c = 0.1$,
- $i_T = 1.1$, $\delta = 0.39$,
- $\chi = 1$, $k_T = 0.8$, $d_T = 0.01$, and $g_T = 2$. 

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At the beginning of infection, the virus load is low, so we set the initial condition of virus to be \( V_0 = 2 \) [53]. At this point we assume that the immune system has just recognized the infection, producing the chemoattractant \( c \) to request more T-cells as part of the adaptive immune response. Thus we set the initial conditions \( c_0 = 1.0 \) and \( T_0 = 2 \) [9]. Also, considering the infection rate of T-cells, we set the initial condition of infected T-cells to be \( I_0 = 1 \). The existence of chemoattractant \( c \) is local to the lymph node, so we use homogeneous Neumann boundary conditions. We also apply homogeneous Neumann boundary conditions for the virus, infected and healthy T-cells because of the low lymphatic circulation rate. We test this period with 25 days, so the time span is \([t_0, t_1] = [0, 25]\).

As we mentioned in Chapter 2, CD4 T lymphocytes are a target of HIV, and loss of T-cells will ultimately lead to AIDS. While in the earliest stages of HIV infection, there is still a difference between the number of peripheral T-cells actually infected and the spreading paralysis of CD4 T-cell function. Homoeostasis is maintained in the early stage of infection, since the increase of CD8 T-cells balances the loss of CD4 T-cells. However, infection of HIV will kill plenty of memory T-cells and lead to an increase in naive T-cells to keep homoeostasis, approximately 80 times above the concentration in normal adults. There is a theory called “tap and drain” to describe this balance between CD4 and CD8 T-cells caused by HIV infection [54]. In Figure 6.2, we can see this balance intuitively.
Figure 6.2. “Tap and drain” model describes the balance of CD4 and CD8 T-cells caused by HIV infection [54].

Figure 6.3. Average concentration of virus, chemoattractant, infected cells and healthy T-cells throughout $\Omega_1$ as functions of time for the “Infection in the absence of medication” test from Section 6.1.
In Figure 6.3 we plot the average concentration of each species (virus, T-cells and infected cells) throughout the domain as functions of time. From this figure, we can see that the model correctly reproduces the clinical course of HIV infection – we see an initially rapid increase, followed by a decrease in viral load, corresponding with an eventual loss of healthy immune cells by the end of the 25-day time period.

6.2. Effects of medication on HIV infection

Similar to our test with the idealized reaction network including medicine from Section 5.5.2, after the patient has become aware of the infection, antiretroviral medication would be supplied. Hence, we can use the full model to do the analysis. As derived in Chapter 2, we use the model (2.2),

\[
\begin{align*}
\frac{\partial}{\partial t} V &- \nabla \cdot \left( D_V \nabla V \right) = -f_T VT - e_M VM + r_I I - d_V V, \quad (6.2a) \\
\frac{\partial}{\partial t} M &- \nabla \cdot \left( D_M \nabla M \right) = -e_M VM - d_M M, \quad (6.2b) \\
\frac{\partial}{\partial t} c &- \nabla \cdot \left( D_c \nabla c \right) = -\lambda c + p_c VT, \quad (6.2c) \\
\frac{\partial}{\partial t} I &- \nabla \cdot \left( D_I \nabla I \right) = i_T VT - \delta I, \quad (6.2d) \\
\frac{\partial}{\partial t} T &- \nabla \cdot \left( D_T \nabla T - \chi T \nabla c \right) = -k_T VT - d_T T + g_T. \quad (6.2e)
\end{align*}
\]

with biological parameters

- \( D_{v_{out}} = 1.0, D_{v_{in}} = 0.1 \)
- \( D_c = 0.8 \)
- \( D_M = 2 \)
- \( D_{I_{out}} = D_{T_{out}} = 0.1, D_{I_{in}} = D_{T_{in}} = 0.01, \)
- \( f_T = 1.0, r_I = 20, d_V = 23, \)
- \( e_M = 0.5, d_M = 0.3, \)
- \( \lambda = 0.5, p_c = 0.1, \)
\[ i_T = 1.1, \delta = 0.39, \]
\[ \chi = 1, k_T = 0.8, d_T = 0.01, \text{ and } g_T = 2. \]

For this stage, we set these initial conditions from the final average solutions of the previous test, i.e., \( V_1 = 0.59, M_1 = 5.0, c_1 = 0.05, I_1 = 0.69, T_1 = 0.41. \) for the chemoattractant \( c. \) However, we now apply nonhomogeneous Neumann boundary conditions for \( V, M, I \) and \( T. \) Specifically, antiretroviral medication is typically administered orally, and it must enter the lymph node though the boundary as a constant source, so we use \( \nabla M \cdot \mathbf{n} = 5.0 \) at \( \partial \Omega_1. \) Similarly, the virus, lymphocytes and infected cell particles enter the lymph node though its boundary as the infection develops, so we set \( \nabla V \cdot \mathbf{n} = 0.15, \nabla I \cdot \mathbf{n} = 0.1, \) and \( \nabla T \cdot \mathbf{n} = 3.0 \) on the boundary \( \partial \Omega_1. \) We perform this test using a 25 day period, so the time span is \([t_1, t_2] = [25, 50].\)

Following our discussion of working mechanisms for antiretroviral drugs in Chapter 2, the antiretroviral drugs take effect by diminishing the virus’s ability to infect susceptible cells through reducing the infection rate \( f_T, \) i.e., \( f_{TM} = \frac{f_T}{1 + \Phi M}, \) or diminishing virus replication by reducing the number of new virus particles generated by infected cells, i.e., \( r_M = \frac{r}{1 + \Psi M}. \) In this section, we explore the effects of different medication combinations on the HIV infection by modifying these parameters \( \Phi \) and \( \Psi. \)

### 6.2.1. \( \Phi = 1 \) and \( \Psi = 1 \)

We first test the case where both types of antiretroviral medication are administered. Since there should be spatial variation in the distribution of species inside \( \Omega_1 \) due to the nonhomogeneous boundary conditions, we separately plot time histories of the spatially-averaged concentrations of each species in Figure 6.4, followed by plots in Figure 6.5 of the spatial distribution of virus, medicine, chemoattractant, infected cells and healthy T-cells at time \( t = 50. \)
Figure 6.4. Average concentration of virus, medicine, chemoattractant, infected cells and healthy T-cells throughout $\Omega_1$ as functions of time, using the medication parameters with $\Phi = \Psi = 1$ from Section 6.2.1.
Figure 6.5. Distribution of virus (upper left), medicine (upper right), chemoattractant (middle left), infected cells (middle right) and healthy T-cells (bottom) throughout $\Omega_1$ at the time $t = 50$, using the medication parameters with $\Phi = \Psi = 1$ from Section 6.2.1.

Here we can see the decrease in viral load with the supply of medicine, especially inside...
of B-cell zone. However, the concentration of infected cells remains relatively high, since neither medicine nor healthy T-cells kill the infected cells directly. This may explain why most patients must take antiretroviral drugs indefinitely, and we cannot currently cure HIV infection entirely.

6.2.2. $\Phi = 0.5$ and $\Psi = 1$

We now test the case where both types of antiretroviral medication are administered but a larger quantity of $\Psi$ is present, corresponding to medication that reduces the virus replication rate, but only partially inhibits the virus’s ability to infect susceptible cells. We again plot time histories of the spatially-averaged concentrations of each species in Figure 6.6, followed by plots in Figure 6.7 of the spatial distribution of virus, medicine, chemoattractant, infected cells and healthy T-cells at time $t = 50$.

![concentration of virus and T_cells versus time](image)

**Figure 6.6.** Average concentration of virus, medicine, chemoattractant, infected cells and healthy T-cells throughout $\Omega_1$ as functions of time, using the medication parameters with $\Phi = 0.5$ and $\Psi = 1$ (from Section 6.2.2).
Figure 6.7. Distribution of virus (upper left), medicine (upper right), chemoattractant (middle left), infected cells (middle right) and healthy T-cells (bottom) throughout $\Omega$ at the time $t = 50$, using the medication parameters with $\Phi = 0.5$ and $\Psi = 1$ (from Section 6.2.2).

Here we obtain a similar result with as in Section 6.2.1 with $\Phi = \Psi = 1$. The only notable difference between this test and the one previous is that here, the density of virus and infected T-cells are slightly higher.
6.2.3. $\Phi = 1$ and $\Psi = 0.5$

We now test the case where both types of antiretroviral medication are administered but a larger quantity of $\Phi$ is present, corresponding to medication that inhibits the virus’s ability to infect susceptible cells, but only partially reduces the virus replication rate. We plot time histories of the spatially-averaged concentrations of each species in Figure 6.8, and the spatial distribution of virus, medicine, chemoattractant, infected cells and healthy T-cells at time $t = 50$ in Figure 6.9.

![concentration of virus and T_cells versus time](image)

**Figure 6.8.** Average concentration of virus, medicine, chemoattractant, infected cells and healthy T-cells throughout $\Omega_1$ as functions of time, using the medication parameters with $\Phi = 1$ and $\Psi = 0.5$ (see Section 6.2.3).
Figure 6.9. Distribution of virus (upper left), medicine (upper right), chemoattractant (middle left), infected cells (middle right) and healthy T-cells (bottom) throughout $\Omega_1$ at the time $t = 50$, using the medication parameters with $\Phi = 1$ and $\Psi = 0.5$ (see Section 6.2.3).

In this scenario, we also observe the decrease in viral load with this combination of medications, along with the relatively high final concentration of infected cells. All species have higher density at the boundary because of inside flow. We note, that here the density of virus and infected T-cells are higher than the previous two scenarios, thus we conclude
that the full dosage of both $\Phi = 1$ and $\Psi = 1$ works best.

6.3. The lymph node as an HIV reservoir

At the final stage, we’d like to test the reservoir effects of the lymph node. The virus load in the blood will be undetectable after a period of therapy. At this point if the patient is removed from therapy, the infection can rebound. It has been hypothesized that lymph nodes may act as reservoirs of virus due to the slower time scales for fluid flow in these organs. To test this we initialize the model with zero virus level, $V_2 = 0$, low concentration of infected cells, $I_2 = 0.2$, zero concentration of medicine, $M_2 = 0$, low concentration of chemoattractant $c_2 = 0.05$, and a relatively high level of healthy $T$-cells, $T_2 = 2.5$, which we can see from the previous medicine test. We again use the model 6.1 on the two-dimensional domain 6.1 with the biological parameters:

- $D_{v_{out}} = 1.0$, $D_{v_{in}} = 0.1$
- $D_c = 0.8$
- $D_{I_{out}} = D_{I_{in}} = 0.1$, $D_{T_{out}} = D_{T_{in}} = 0.01$,
- $f_T = 1.0$, $r_I = 20$, $d_V = 23$,
- $\lambda = 0.5$, $p_c = 0.1$,
- $i_T = 1.1$, $\delta = 0.39$,
- $\chi = 1$, $k_T = 0.8$, $d_T = 0.01$, and $g_T = 2$,

To test the reservoir effect, we apply homogeneous Neumann boundary conditions so that there is no outside influence, and we use the time period $[t_0, t_1] = [50, 75]$ day.
Figure 6.10. Average concentration of virus, chemoattractant, infected cells and healthy T-cells throughout $\Omega_1$ as functions of time, testing the reinfection of HIV when medication is discontinued (Section 6.3).

In Figure 6.10 we plot the average concentration of each species throughout the domain as a function of time for this test. Here, we can see the similar infection process as shown in Figure 6.3 for initial infection of HIV – an initially low virus load or low infected concentration will lead to a rapid rebound of HIV virus. The low lymphatic circulation rate, along with results of this test, imply that the lymph nodes could indeed serve as the reservoir of the HIV infection.
Chapter 7
Discussion and Future Work

There have been several different phases of the development of antiretroviral therapy in the history of HIV. In the early years from 1987-1990, monotherapy brought great hope as well as depression, due to the ineffectiveness of Zidovudine or the nucleoside analogs zalcitabine, didanosine and stavudine. Then in September 1997, it was found that combination therapy with two nucleoside analogs was more effective than monotherapy.

It has been forty years since AIDS was first detected. With the advent of anti-HIV drugs developed in the 90’s, HIV has been changed to a chronic disease from a terminal one. However, it has still not been completely eradicated. By modeling the concentration of the ART drugs (medicine) entering and passing through a lymph node, we wish to learn more about the biology process of HIV infection and the corresponding immune response, as well as whether the slower circulation rate within the lymph nodes renders them as potential HIV reservoirs.

This thesis discusses our construction and solution of a mathematical model to perform these analyses. In Chapter 1, we briefly introduced the history of HIV, and discussed some hypotheses about the difficulty in finding an ultimate cure for AIDS.

In Chapter 2, we discussed some of the basic biology related to this thesis. We introduced the anatomy of human lymph nodes and their functionality, notably how these organs play a key role in lymph circulation and immune response. T lymphocytes are responsible for the cell-mediated immune responses of adaptive immunity, and HIV is a retrovirus which attacks the immune system and leads to loss of immune control. Also, we introduced the concept of latently-infected cells, which is a group of infected T-cells that are not yet actively producing HIV, and that represent long-living cellular reservoirs for HIV. With all these
biological concepts, we then focused on constructing a mathematical model of the lymph node.

Most of the previous mathematical models of these processes treat the lymph node as a homogeneous vessel, ignoring its complex architecture. In our framework, we instead construct a more realistic 3D lymph node model to study the more realistic spatio-temporal dynamics of virus, immune cells and medicine.

We presented results from previous work and found three types of models that we leveraged within our model. Bocharov and collaborators [12] proposed a reaction-diffusion PDE model that realized the importance of lymphatic structure for understanding particle dynamics in lymph nodes. Dunia and collaborators [21] focused on the reaction network responsible for HIV infection, introducing models with the flexibility to consider the significant variety of infection cases step by step, including some ideas about the usage of medicine throughout the clinical course of infection. Finally, we introduced the classical Keller-Segel model of chemotaxis, which is used to model the immune response of T-cells to a localized infection.

Building off of this previous work, we construct a mathematical model consisting of the following variables: virus ($V$), medicine ($M$), chemoattractant ($c$), infected cells ($I$), and healthy T-cells ($T$). We consider the anatomy of the lymph node as consisting of two parts, an inner part $\Omega_1$ which we model by an advection-reaction-diffusion system of partial differential equations, and an outer part $\Omega_2$ where we utilize a modified diffusion-reaction model combined with the Navier-Stokes equations.

Then in Chapter 3, we presented the numerical methods we use to approximate solutions to the model (2.2) for the region $\Omega_1$. We used the finite element method to discretize the spatial domain, and constructed the corresponding nonlinear system of ODEs. For the time integration, we described approaches based on Backward Euler, singly diagonal implicit Runge-Kutta (SDIRK) and Backward Differentiation formula (BDF). We solved the corresponding systems of implicit algebraic equations using Newton’s method. We approximated the lymph node geometry using an unstructured tetrahedral 3D mesh produced using the Gmsh package. We finally implemented the resulting mathematical model using the MFEM
finite-element infrastructure.

In Chapter 4, we presented a detailed discussion of the preconditioner we used for the Jacobian system. We constructed four different types of block preconditioners: block diagonal, lower triangular, and two approximate Schur complements. Then we presented related work suggesting that our preconditioners should be scalable. We also presented numerical tests in Matlab to predict the scalability numerically. Afterwards, we applied these four types of preconditioners to a steady-state version of our model and found that the number of iterations of the preconditioned GMRES solver remained relatively constant (for each preconditioning approach), numerically verifying the algorithmic scalability of our solution approach.

In Chapter 5, we performed four different types of tests to verify our computational implementation before solving the target biological model. In section one, we discussed the structure of the lymph node and constructed its 2D and 3D mesh. Since the lymph node is composed of almost identical regions called nodules, we constructed a discretization of one nodule for our spatial model. Then in section two, we did a small test to verify the chemotaxis phenomenon using the classical Keller-Segel model and modified corresponding term extracted from our model. In section three, we checked the convergence of our model on a steady-state version of our model with a manufactured solution. In section four, we tested the influence of the discontinuous diffusion coefficient.

Finally, in Chapter 6, we analyzed our model biologically. We used biological parameters and compared our model predictions with the clinical course of HIV infection. First, the patient did not know about the infection, thus we modeled the initial phase of the infection without any medicine supplied. We computed the model with virus \((V)\), chemoattractant \((c)\), infected cells \((I)\) and healthy T-cells \((T)\) which showed the growth in both the viral load and infected cell concentrations, along with the corresponding decrease in healthy T-cell concentration. Then we supplied the medicine to the patient. Since different medications work using different mechanisms, we tested different combinations of medicines. Finally, to test the ‘reservoir’ hypothesis from Chapter 1, we performed tests that examined the effects
of spatial inhomogeneity on viral dynamics.

In the future, we will continue these efforts to include the model in the sinus region $\Omega_2$, coupling it with the model in region $\Omega_1$. This coupling of the two models will proceed in multiple different stages.

- Spatially couple the model for different interfaces. We just construct one nodule right now. We need to couple several nodules together to get the whole lymph node.

- Couple the model in the different time scale. The model in region $\Omega_1$ is an advection-diffusion-reaction model while there is a transport model in region $\Omega_2$. The fluid transports in different way and with a faster time scale.

Based on the complexity of the problem, to properly handle this multi-domain, multi-physics, multi-rate PDEs system it will require more robust and flexible numerical methods.
Bibliography


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