Abstract

POTTER, LAURA KAY. Physiologically based pharmacokinetic models for the systemic transport of trichloroethylene (Under the direction of H. Thomas Banks).

Three physiologically based pharmacokinetic (PBPK) models for the systemic transport of inhaled trichloroethylene (TCE) are presented. The major focus of these modeling efforts is the disposition of TCE in the adipose tissue, where TCE is known to accumulate. Adipose tissue is highly heterogeneous, with wide variations in fat cell size, lipid composition, blood flow rates and cell permeability. Since TCE is highly lipophilic, the uneven distribution of lipids in the adipose tissue may lead to an uneven distribution of TCE within the fat. These physiological characteristics suggest that the dynamics of TCE in the adipose tissue may depend on spatial variations within the tissue itself.

The first PBPK model for inhaled TCE presented here is a system of ordinary differential equations which includes the standard perfusion-limited compartmental model for each of the adipose, brain, kidney, liver, muscle and remaining tissue compartments. Model simulations predict relatively rapid decreases in TCE fat concentrations following exposure, which may not reflect the accumulation and relative persistence of TCE inside the fat tissue. The second PBPK model is identical to the first except for the adipose tissue compartment, which is modeled as a diffusion-limited compartment. Although this model yields various concentration profiles for TCE in the adipose tissue depending on the value of the permeability coefficient, this model may not be physically appropriate for TCE, which is highly lipophilic and has a low molecular weight. Moreover, neither of these two PBPK models is able to capture spatial variation of TCE concentrations in adipose tissue as suggested by the physiology.

The third model we present is a hybrid PBPK model with a dispersion-type model for the transport of TCE in the adipose tissue. The dispersion model is designed to
account for the heterogeneities within fat tissue, as well as the corresponding spatial variation of TCE concentrations that may occur. This partial differential equation model is based on the dispersion model of Roberts and Rowland for hepatic uptake and elimination, adapted here for the specific physiology of adipose tissue.

Theoretical results are given for the well-posedness of a general class of abstract nonlinear parabolic systems which includes the TCE PBPK-hybrid model as a special case. Moreover, theoretical issues related to associated general least squares estimation problems are addressed, including the standard type of deterministic problem and a probability-based identification problem that incorporates variability in parameters across a population. We also establish the theoretical convergence of the Galerkin approximations used in our numerical schemes.

The qualitative behavior of the TCE PBPK-hybrid model is studied using model simulations and parameter estimation techniques. In general, the TCE PBPK-hybrid model can generate various predictions of the dynamics of TCE in adipose tissue by varying the adipose model parameters. These predictions include simulations that are similar to the expected behavior of TCE in the adipose tissue, which involves a rapid increase of TCE adipocyte concentrations during the exposure period, followed by a slow decay of TCE levels over several hours.

Results are presented for several types of parameter estimation problems associated with the TCE PBPK-hybrid model. We test these estimation strategies using two types of simulated data: observations representing TCE concentrations from a single individual, and observations that simulate inter-individual variability. The latter type of data, which is commonly found in experiments related to toxicokinetics, assumes variability in the parameters across a population, and may include observations from multiple individuals. Using both deterministic and probability-based estimation techniques, we demonstrate that the probability-based estimation strategies that incorporate variability in the parameters may be best suited for estimating adipose model parameters that vary across the population.
PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELS FOR THE SYSTEMIC TRANSPORT OF TRICHLOROETHYLENE

BY
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CHAIR OR ADVISORY COMMITTEE
To my husband and my parents,
whose love, patience and encouragement made it all possible.
Biography

The author was born and raised in Des Moines, Iowa. In May 1991 she graduated from Valley High School in West Des Moines. She then attended Drake University in Des Moines, graduating summa cum laude with a bachelor of arts in mathematics in May 1995. She earned a master of science in applied mathematics in May 1999 and a doctor of philosophy in applied mathematics in August 2001 from North Carolina State University in Raleigh. She has accepted a postdoctoral position with the Curriculum in Toxicology, University of North Carolina at Chapel Hill, and will be conducting research at the National Health and Environmental Effects Research Laboratory of the U.S. Environmental Protection Agency in Research Triangle Park, North Carolina.
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research questions considered in this thesis.

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6.29 Parameter estimation results for $\tilde{q} = (\mu, \sigma)$ with multiple observations per time point and $t_f = 5$, $N_t = 17$.

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Chapter 1

Introduction

Many environmental and occupational toxins are lipophilic in nature, and tend to accumulate in the adipose, or fat tissue of animals and humans. These compounds vary widely in their means of uptake into, disposition through, and elimination from the body, as well as in their toxic mechanisms. A key component in understanding their specific toxicities is the characterization of their disposition. Since adipose is a storage tissue for these particular xenobiotics, their dynamics inside the adipose tissue have a major impact on their overall kinetics. Thus it is important to ascertain their absorption, distribution and accumulation properties for adipose tissue.

Numerous studies have shown that a large class of lipophilic compounds accumulates in adipose tissue. This class includes organochloride pesticides such as aldrin, dieldrin, endrin, chlordane, heptachlor and DDT [3], as well as polychlorinated biphenyls [3], [47], polychlorinated dibenzo-p-dioxins and polychlorinated dibenzo-furans [25]. Moreover, a variety of other halogenated organic compounds are known to accumulate in fat tissue [3]. This tissue accumulation is related to the lipophilicity of the compounds and the low perfusion rate of adipose tissue, although studies in [31] and [50] suggest that the tissue distribution of lipophilic compounds is also dependent on binding competition between fat tissue and well-perfused lean tissues.

Here we consider the solvent trichloroethylene (TCE), which has been used widely in industry as a metal degreasing agent, as well as in the dry cleaning industry. TCE
is now a common soil and groundwater contaminant, and can be found at Superfund sites and Department of Defense facilities across the United States [57]. Humans come into contact with TCE most often by inhaling TCE vapor in an industrial setting, or by drinking contaminated water. TCE is a highly lipophilic volatile organic compound, and is quickly distributed into the bloodstream. It is partially eliminated from the body through exhaled air and is rapidly metabolized in the liver. There are two major metabolic pathways for TCE: Cytochrome P450-mediated oxidation and glutathione conjugation [43]. Major metabolites include chloral hydrate, trichloroacetic acid (TCA), dichloroacetic acid (DCA), free trichloroethanol, trichloroethanol-glucuronide and S-(1,2-dichlorovinyl)-L-cysteine (DCVC) [30], [43], and most are eliminated in the urine [65].

Unmetabolized TCE accumulates in adipose tissue [65], but over long periods of time is not very persistent in the body because of its rapid metabolism. In a study by Bergman [16], mice were exposed to a dose of 280 mg/kg radiolabeled TCE for ten minutes, and the tissue distribution of TCE was measured using whole-body autoradiography. Within 30 minutes, there was a large accumulation of TCE in the fat tissue, with significant levels still present after four hours and traces still visible after eight hours. Moreover, Davidson and Beliles [30] have estimated the half life of TCE in adipose tissue to be about four hours.

TCE and several of its metabolites are known to produce toxic effects in humans. Acute exposure to TCE impacts the central nervous system, causing symptoms such as fatigue, headaches, dizziness and drowsiness [38]. Several of its metabolites, including TCA, DCA, DCVC and chloral hydrate, are suspected of causing toxicity in animals and/or humans [22], [51]. Evidence suggests that both TCA and DCA are hepatocarcinogens [22], [23], while chloral hydrate is associated with lung tumors in mice [39]. Moreover, a recent study shows that TCE may play a role in the development of kidney cancer in humans [21], and the metabolite DCVC has been linked to kidney tumors in rats [44]. TCE and some of its metabolites also have been associated with developmental toxicity in animals [56], including eye and cardiac malformations.
Chapter 1. Introduction

These lipophilic environmental toxins, including TCE, can have both short-term and long-term adverse health effects on the population. It is important to assess the health risks these chemicals pose, so that the public can be adequately protected from dangerous compounds, while the safer compounds can be used with greater confidence. In order to better determine how xenobiotics such as TCE cause toxic effects in humans and animals, the toxicokinetics of these compounds must be understood. Physiologically based pharmacokinetic (PBPK) models are used to describe the systemic disposition of a given chemical. By characterizing the kinetics of the compound, one can predict its transport inside the body and the specific dosage levels received by each of the tissues. This is an important step in working towards gaining a better understanding of a compound’s overall toxic effects and mechanisms.

The standard PBPK models, which make use of “perfusion-limited” and “diffusion-limited” compartments, are designed around the assumption of rapid equilibrium and uniformity within each compartment or subcompartment. This is often a reasonable assumption in physiological modeling, but may not be appropriate for tissues which have heterogeneous that impact the disposition of a given compound inside that tissue. As we discuss in Section 3.1, the nonhomogeneous composition, structure and circulation properties of adipose tissue and the chemical properties of TCE suggest that the standard “well-stirred” models may not be sufficient in this specific case. There are several modeling approaches that are designed to account for such physiological heterogeneities, including the axial dispersion model as derived by Roberts and Rowland [53] for hepatic uptake and elimination.

Here we develop toxicokinetic models to describe the behavior of inhaled trichloroethylene as it flows through and possibly accumulates in adipose tissue. We formulate and compare three physiologically based models, each with a different submodel for the adipose tissue component. The comparison of these three models lends support to the hypothesis that a spatially varying model is best able to capture the complicated dynamics of TCE in adipose tissue.
In Chapter 2 we derive the standard PBPK model with perfusion-limited compartments. Model simulations demonstrate the perfusion-limited model, which assumes rapid equilibrium in each tissue, is not able to predict the expected slow decay of TCE in adipose tissue following exposure. We then modify this model by replacing the perfusion-limited adipose tissue compartment with a diffusion-limited compartment. Although this model is better able to predict the expected behavior of TCE in adipose tissue, the chemical properties of TCE suggest that this model may not be physically appropriate in this case.

In Chapter 3 we adapt the dispersion model of Roberts and Rowland to describe the transport of TCE in adipose tissue. The geometry and fundamental assumptions for the model are based specifically on the physiology of adipose tissue and the chemistry of TCE. The resulting compartment is then coupled with the remaining perfusion-limited compartments to create a whole-body PBPK-hybrid model, which is a system of both partial and ordinary differential equations. In Chapter 4 we address issues of well-posedness related to this model and associated parameter estimation problems. We then present a computational scheme for this model and the resulting model simulations in Chapter 5, demonstrating the dependence of the model on the adipose-related parameters. Moreover, we present simulations of TCE adipocyte concentrations that suggest that the PBPK-hybrid model is better able to capture the expected behavior of TCE in adipose tissue than the two ODE models discussed in Chapter 2.

Finally, in Chapter 6 we study several types of parameter estimation problems associated with the TCE PBPK-hybrid model, including both standard deterministic and probability-based estimation techniques. We test these inverse problems using simulated data that represent observations from a single individual, as well as with data that simulate observations from multiple individuals. Moreover, we explore the performance of these various estimation strategies with the assumption that the adipose model parameters vary across the population, demonstrating that significant amounts of inter-individual variability have a negative effect on the performance of
the standard deterministic parameter estimation procedures. The probability-based estimation methods, which are specifically designed to incorporate such variability across a population, are shown to better capture variation that is seen in actual experimental data.
Chapter 2

Standard PBPK models for the systemic transport of TCE

2.1 A perfusion-limited PBPK model for TCE

Many PBPK models for lipophilic compounds include compartments for tissues such as the liver, lungs, adipose tissue, richly perfused and poorly perfused tissues. These compartments often assume a perfusion-limited model, or equivalently, a flow-limited model of disposition, meaning that the rate of uptake of the compound into the tissue is limited by the blood flow rate to the tissue rather than the rate of diffusion across the cell membranes [49]. In this case, the blood flow rate to the tissue is slow compared to the diffusion rate across cell membranes, so that the blood and tissue are in equilibrium. The equation for transport of a solute through a constant-volume, well-mixed tissue compartment is an ordinary differential equation of the form

\[ V \frac{dC}{dt} = Q(C_{in} - C_{out}), \]

where \( V \) is the volume of the tissue (in liters), \( C \) is the concentration of compound inside the tissue (in mg/liter), \( Q \) is the blood flow rate to the tissue (in liters/hour), and \( C_{in} \) and \( C_{out} \) are the compound concentrations entering and exiting the tissue, respectively. Examples of PBPK models for TCE and its metabolites that use perfusion-limited compartments can be found in [1], [34], [35], [40], [63].
Here we develop a standard PBPK model [49] for TCE with flow-limited compartments for the kidney, muscle tissue, adipose tissue, brain, liver, venous blood, and remaining non-fat tissue (see Figure 2.1). We assume uptake via inhalation, with a lung compartment subdivided into the alveolar space and lung blood subcompartments. TCE is metabolized in the liver, which is modeled with Michaelis-Menten kinetics.

In the lung, ventilation is assumed to be continuous with rate $Q_p$, and the vapor in the alveolar space is assumed to be in rapid equilibrium with the arterial lung blood. The cardiac output rate is given by $Q_c$ and the blood/air partition coefficient is denoted by $P_b$.

The variables used in the lung compartment include:

- $C_c$ = Concentration of TCE in surrounding air
- $C_x$ = Concentration of TCE in alveolar space
- $C_a$ = Concentration of TCE in arterial blood
- $C_v$ = Concentration of TCE in venous blood
- $A_i$ = Amount of TCE inhaled
- $A_x$ = Amount of TCE exhaled
- $A_L$ = Amount of TCE in lung.

In this case, the concentration $C_x$ in the alveolar air is related linearly to the concentration $C_a$ in the arterial blood:

$$C_x = \frac{C_a}{P_b}.$$

The rate of inhalation of TCE is given by $Q_p C_c$, while the rate of exhalation is given by $Q_p C_x$. Therefore we have the following equations:

$$\frac{dA_i}{dt} = Q_p C_c$$
$$\frac{dA_x}{dt} = Q_p C_x = Q_p \frac{C_a}{P_b}$$
$$\frac{dA_L}{dt} = Q_p (C_c - C_x) + Q_c (C_v - C_a). \quad (2.1)$$
PBPK Model for Inhaled TCE

Figure 2.1: PBPK model for inhaled TCE with a perfusion-limited compartment for adipose tissue.
Moreover, the assumptions of the model [49] imply that \( \frac{dA_k}{dt} = 0 \), so by substituting \( C_x = C_a/P_b \) into (2.1) we obtain

\[
C_a = \frac{Q_p C_c + Q_c C_v}{Q_c + \frac{Q_p}{P_b}}.
\]

Combining the perfusion-limited compartments with the lung compartment, we obtain

\[
V_f \frac{dC_f}{dt} = Q_f (C_a - C_vf) \tag{2.2}
\]
\[
V_v \frac{dC_v}{dt} = Q_m C_{vm} + Q_f C_vf + Q_b C_vbr + Q_l C_vl + Q_k C_vk - Q_c C_v \tag{2.3}
\]
\[
C_a = \frac{Q_c C_v + Q_p C_c}{Q_c + \frac{Q_p}{P_b}} \tag{2.4}
\]
\[
V_m \frac{dC_m}{dt} = Q_m (C_a - C_{vm}) \tag{2.5}
\]
\[
V_l \frac{dC_l}{dt} = Q_l (C_a - C_vl) \tag{2.6}
\]
\[
V_{br} \frac{dC_{br}}{dt} = Q_{br} (C_a - C_{vbr}) \tag{2.7}
\]
\[
\frac{dA_{am}}{dt} = \frac{v_{max} C_{vl}}{k_M + C_{vl}} \tag{2.8}
\]
\[
\frac{dA_{i}}{dt} = \frac{k_M + C_{vl}}{v_{max} C_{vl}} \tag{2.9}
\]
\[
\frac{dA_{k}}{dt} = Q_k (C_a - C_vk) \tag{2.10}
\]
\[
\frac{dA_{x}}{dt} = Q_p C_x. \tag{2.12}
\]

The subscripts denote the following specific tissues:

\[ v \leftrightarrow \text{Venous blood} \]
\[ k \leftrightarrow \text{Kidney} \]
\[ m \leftrightarrow \text{Muscle} \]
\[ f \leftrightarrow \text{Fat} \]
Volumes (in liters) of specific tissues are denoted by $V$, concentrations of TCE (mg/liter) are denoted by $C$ and flow rates (liters/hour) are denoted by $Q$, each with subscripts corresponding to the specific tissue. The concentration of TCE in the air is denoted by $C_{c}$, and is a specified quantity. The variables $C_{vk}, C_{vm}, C_{vf}, C_{vbr}, C_{vl}$ and $C_{vt}$ are the concentrations of TCE leaving the respective organ and entering the venous blood system. In this case, all compartments except for the lung are perfusion-limited, so the concentration of TCE leaving each of these compartments is equal to the concentration of free TCE in that compartment itself [49]. In the kidney, for example, this implies

$$C_{vk} = \frac{C_{k}}{P_{k}},$$

where $C_{k}$ is the total concentration of TCE inside the kidney compartment and $P_{k}$ is the tissue/blood partition coefficient for the kidney.

The amount of TCE metabolized in the liver is denoted by $A_{am}$, and has units in milligrams. Constants in the liver compartmental model include the Michaelis-Menten constant $k_{M}$ (mg/liters) and the metabolic constant $v_{max}$ (mg/hour).

We note that our model includes a venous blood compartment governed by the differential equation (2.3). In this type of PBPK model, the algebraic equation

$$C_{v} = \frac{1}{Q_{c}} \left( Q_{m} C_{vm} + Q_{t} C_{vt} + Q_{f} C_{vf} + Q_{br} C_{vbr} + Q_{l} C_{vl} + Q_{k} C_{vk} \right)$$

is often used and is generally sufficient to capture the behavior of a solute in the venous blood. This equation is based on a steady-state assumption for the large venous blood compartment. Here we include the more complicated model (2.3) because it will be more compatible with our modified model which uses a dispersion compartment for the adipose tissue (see Chapter 3).
Simulations were carried out using the model (2.2) – (2.12) to predict TCE concentrations in Long-Evans rats. The Matlab code for this model and the model parameters were provided by Evans et al. [32]. In their experiment, Long-Evans rats were placed in an inhalation chamber for 5, 20, 40, 60 or 120 minutes. The chamber contained a constant concentration of 200, 2000 or 4000 parts per million (ppm) TCE in the air for a total of one hour, followed by a second hour with zero TCE concentration. Following the pre-specified exposure time, the rats were immediately removed from the chamber, and samples were then collected from the blood, fat, liver and brain tissues. TCE concentrations were measured in the tissue samples using extraction followed by gas chromatography [32]. See Appendix A for a list of parameter values.

Figure 2.2 depicts an example simulation for the following input function: 2000 ppm TCE in the surrounding air for one hour, followed by 0 ppm TCE in the surrounding air for 14 hours. The concentration of unbound TCE inside the perfusion-limited fat compartment is given in Figure 2.2. Note the rapid, exponential decay of concentrations following \( t = 1 \) hour. This simulation illustrates that this type of compartmental model may not be able to capture the expected slow accumulation and release of TCE in the adipose tissue. Moreover, this type of model may result in the under-prediction of TCE in fat and of the time it takes for TCE to clear the fat tissue. This might lead to an over-prediction of TCE concentrations in the blood and lean tissue, and may also lead to an under-prediction of the total amount of time required for TCE to be removed from the body.

### 2.2 A PBPK model for TCE with a diffusion-limited adipose tissue compartment

A second type of compartment used in PBPK modeling is the diffusion-limited, or membrane-limited compartment. Unlike the perfusion-limited model, the blood flow rate to the tissue is assumed to be rapid compared to the transport of the compound
Chapter 2. Standard PBPK models for the systemic transport of TCE

Figure 2.2: Model simulation: Concentration in time of unbound TCE inside the perfusion-limited fat compartment.

across the cell membranes [49]. This compartment is divided into two subcompartments: the intracellular space and the extracellular space, which includes the vascular blood and the interstitial space. The concentration of compound within each of these subcompartments is in equilibrium, and the equations governing transport of a compound through the tissue are

\[
V_E \frac{dC_E}{dt} = Q(C_{in} - C_{out}) + \mu(C_I - C_E)
\]

\[
V_I \frac{dC_I}{dt} = \mu(C_E - C_I),
\]

where \(V_E\) and \(V_I\) are the volumes of the extracellular and intracellular compartments, respectively, and \(C_E\) and \(C_I\) are the concentrations of compound in the extracellular and intracellular compartments, respectively. Here \(\mu\) is the cell membrane permeability for the compound (in liters/hour), and \(Q, C_{in},\) and \(C_{out}\) are defined as in Section 2.1.

Now we modify the previous PBPK model for TCE to include a diffusion-limited fat compartment (see Figure 2.3). The remainder of the model is identical, but we
Figure 2.3: PBPK model for inhaled TCE with a diffusion-limited compartment for adipose tissue.
assume that the flow of blood through adipose tissue is much faster than the diffusion of solute across the cell membranes. Thus, we replace (2.2) by

\[
V_{fe} \frac{dC_{fe}}{dt} = Q_f (C_a - C_{vf}) + \mu (C_{fi} - C_{fe}) \tag{2.13}
\]

\[
V_{fi} \frac{dC_{fi}}{dt} = \mu (C_{fe} - C_{fi}) \tag{2.14}
\]

where \(C_{fe}\) and \(C_{fi}\) are the concentrations of TCE in the extracellular and intracellular spaces of the fat tissue, respectively, \(V_{fe}\) and \(V_{fi}\) are the volumes of these extracellular and intracellular spaces, and \(\mu\) is the cell membrane permeability coefficient for TCE. Our new system of equations is therefore given by (2.13), (2.14) and (2.3) – (2.12).

Model simulations were carried out for this model as before (see Appendix A for parameter values). The concentrations of TCE in the adipose subcompartments are shown in Figures 2.4 and 2.5 for varying values of \(\mu\). For \(\mu = 1\), the concentration of unbound TCE in the intracellular subcompartment as seen in Figure 2.5 is nearly identical to the concentration of unbound TCE in the perfusion-limited adipose compartment (Figure 2.2).

As \(\mu\) decreases, the peak concentration of unbound TCE in the intracellular subcompartment decreases and the decay following exposure is less rapid. The concentration profile in the intracellular space for \(\mu = 0.1\) shows a steady increase in TCE concentrations before \(t = 1\) hour, followed by a slow decrease. The dynamics for this value of \(\mu\) appear to match more closely with the expected behavior of TCE in the adipose tissue than the dynamics predicted by the perfusion-limited compartmental model.

One disadvantage with the diffusion-limited model, however, is that there is only one extra degree of freedom and there is little flexibility in obtaining both the correct concentration profile and the correct peak value in the intracellular compartment. Moreover, since TCE has a low molecular weight (131.3889) and is highly lipophilic, it diffuses easily across cell membranes. This diffusion rate will be much greater than the blood flow rate to the adipose tissue, which suggests that the diffusion-limited model may not be physically appropriate.
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Figure 2.4: Model simulation: Total concentration of TCE in time in the extracellular subcompartment of the diffusion-limited fat compartment for various values of the permeability coefficient $\mu$.

Figure 2.5: Model simulation: Concentrations of unbound TCE in time in the intracellular subcompartment of the diffusion-limited fat compartment for various values of the permeability coefficient $\mu$. 
Chapter 3

An axial dispersion model for the transport of TCE in adipose tissue

3.1 The physiology of adipose tissue

Neither the perfusion-limited nor the diffusion-limited compartmental models are designed to account for spatial heterogeneities within the intracellular space of a given tissue. Adipose tissue is known to be widely heterogeneous in both its composition and functional properties. Its general structure includes a rich, irregular vascular bed, with capillaries in contact with each adipocyte, or fat cell [62]. The adipocytes, relatively large spherical cells containing lipid droplets that make up the bulk of each cell, are organized into a structure of lobules supported by connective tissue [62]. See Figure 3.1 for an illustration of a representative adipocyte and capillary unit, which is suspended in the surrounding interstitial fluid. An example scanning electron micrograph of adipose tissue that is on the same scale as the illustration can be found in [64], p. 92.

The major metabolic functions of adipose tissue include: the synthesis and storage of lipid in the form of triglyceride [27], the breakdown of triglyceride and the mobilization of lipid in the form of free fatty acids [27], and the uptake of fatty acids, glucose and amino acids [62].
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Figure 3.1: Representation of an adipocyte and capillary, surrounded by interstitial fluid.

Unlike many organs, the adipose “organ” is located in multiple distinct depots throughout the body. Several studies have shown that there are pronounced differences in tissue composition, blood flow and metabolic activities across these depots [27], [29], [30], [48], [66], which suggests that a single perfusion-limited or diffusion-limited compartment may be insufficient to capture the behavior of adipose tissue as a whole. A possible modification to these models is the inclusion of many separate perfusion-limited or diffusion-limited compartments, each representing a distinct adipose depot and each with its own physiological parameters.

In addition to inter-depot differences in blood flow, metabolism and tissue composition, there are heterogeneities within each adipose depot itself. The sizes of individual fat cells greatly vary, as does the amount of lipid in each adipocyte, creating an uneven distribution of lipids across the depot [42]. Since TCE and other compounds of interest are highly lipophilic, an uneven distribution of these compounds may result, leading to a spatially dependent concentration function inside the adipose tissue.

It has been shown that the metabolic activities of adipose tissue are directly linked
to its blood flow properties [27]. As the metabolic process varies in different regions of tissue and in time, the perfusion of blood to those regions changes accordingly. Moreover, the blood flow to adipose tissue is affected directly by the local concentrations of substrates and hormones used in the process of metabolizing lipids [29]. Blood flow in adipose tissue is also controlled by the central nervous system, which can alter vascular permeability, capillary density, diffusion, and the rate of transport of lipophilic compounds [54]. Together, these physiological characteristics of adipose tissue suggest that a spatially varying model may be more appropriate for describing the disposition of lipophilic xenobiotics in adipose tissue.

3.2 Modeling philosophy

An important feature of adipose tissue is that each adipocyte and connecting capillary is an individual “functional unit” within the tissue. There are millions of fat cells within adipose tissue, and it would be nearly impossible to capture the disposition of TCE specifically through each adipocyte. Rather, there are several “aggregate” modeling approaches that may be used to approximate the transport through the tissue without actually modeling each cell.

One such approach utilizes mathematical homogenization theory, as used in [60] and [61] to estimate the magnetic permeability of magnetorheological fluids. The homogenization technique involves a domain with a periodic microstructure, such as a collection of individual fat cells with capillaries immersed in interstitial fluid, resulting in an “effective” equation that approximates the overall behavior inside the domain. In the case of adipose tissue, such a model would approximate the effective concentration of TCE inside the tissue.

Another modeling approach designed to handle this type of heterogeneity makes use of probability theory. As the physiology indicates widely varying ranges for parameters such as fat cell size, blood flow rates and cell permeability coefficients inside the fat tissue, we could think of each of these quantities as a random variable. Each
of these random variables would have an unknown probability distribution that could be estimated with inverse problem techniques. See [4] and [5] for detailed descriptions of this modeling philosophy.

A third type of model sometimes used in physiological modeling is the axial dispersion model, which is designed to account for the heterogeneity of tissue. It assumes that the amount of time it takes for a compound to pass through a given tissue is not constant for each particle of compound. This dispersion model is based on the premise that the variations in these “residence times” are a result of variations in flow velocity, variations in path length, convective mixing in the direction of blood flow, and molecular diffusion.

One important feature of this model is that it is an aggregate type of model, using one representative “cell” to capture the behavior of a large collection of similar “cells” that have varying properties. The variability among these cells is accounted for in the model with an axial dispersion term, and the axial dispersion coefficient is a representative measure of the variability within the overall system. See [45] for a detailed development of the axial dispersion model.

Roberts and Rowland [53] adapted this type of dispersion model for the flow of compounds through the liver. Based on this model, Banks, Musante and Tran [13] developed a dispersion model for the transport and elimination of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the liver. The complex, heterogeneous physiology of the liver and the widely varying circulation of blood through the liver’s sinusoids both suggest this type of modeling approach, and simulations carried out in [12] illustrate the effectiveness of this model for describing TCDD transport through the liver.

Any of these three modeling approaches may be adapted to develop a model for spatially-varying concentrations of TCE in adipose tissue. The resulting adipose compartmental model may then be coupled with the PBPK whole-body model to create a TCE PBPK-hybrid model for the overall systemic transport of TCE. Examples of hybrid models that combine specialized compartmental models with whole-body PBPK models include a CFD-PBPK hybrid model for gas and vapor uptake [24],
as well as a distributed parameter PBPK hybrid model for dermal absorption and inhalation [55].

The CFD-PBPK hybrid model utilizes computational fluid dynamics to simulate vapor uptake of toxicants in the rat nose, which has been shown to vary spatially depending on the nature of flow streams within the nasal passages. The dermal absorption model includes a partial differential equation-based model for the inhalation of toxicants and for the diffusion of these compounds through the dermal layers. A key characteristic of each of these hybrid models is the use of a high-fidelity, specialized compartment for tissues which exhibit complex dynamics, combined with the standard PBPK compartmental models for the remaining tissues and organs, where the dynamics are reasonably approximated with the standard well-mixed assumptions.

3.3 A dispersion model for TCE in adipose tissue

Here we develop an axial dispersion-type model for the adipose tissue compartment, which will connect with the remaining PBPK compartmental model. These two models combine to form a PBPK-hybrid model for the systemic transport of TCE. The axial dispersion model for the adipose compartment is based on the dispersion modeling philosophy found in [45], and will be adapted for a representative geometry for adipose tissue.

3.3.1 Geometry

As we have discussed, adipose tissue is composed primarily of adipocytes, which are relatively large spherical-shaped cells. The adipocytes are supported with a network of connective tissue, and each fat cell is in contact with one or more capillaries. The interstitial space makes up about 10% of the total tissue weight of adipose tissue.

Based on these histological characteristics, we choose a representative geometry for the fat compartment that includes three subcompartments: the capillary subcompartment, the adipocyte subcompartment and the interstitial fluid subcompartment.
Figure 3.2: Adipose tissue represented geometrically: the adipocyte region (A) is a sphere, surrounded by the interstitial space (I). The capillary or blood region (B) is a cylindrical tube that wraps around the capillary. Coordinates are in spherical coordinates \((r, \theta, \phi)\).

We choose to represent the adipocyte subcompartment by a single sphere centered at the origin (see Figure 3.2). The adipocyte is in contact with a capillary, represented by a cylindrical tube with a circular cross section. The space surrounding the capillary and the adipocyte is occupied by the interstitial fluid, including the space between the capillary and adipocyte.

The adipocyte region is denoted by (A), and consists of the sphere centered at the origin with radius \(r_1\). The capillary or blood region (B) is a cylindrical tube with a circular cross-section that wraps around the capillary. This cylindrical tube (again see Figure 3.2) has a central axis \(r = r_2 + \alpha, \theta = \theta_0, \varepsilon_1 < \phi < \pi - \varepsilon_2\) in spherical coordinates.
coordinates, where $r_2 > r_1 > 0$ and $\varepsilon_1, \varepsilon_2 > 0$. The cross section of the capillary has radius $\alpha$ and area $A_B$. The domain of this cylindrical tube is denoted by $\Omega_B$. The capillary connects with the arterial blood at $\phi = \varepsilon_1$, and similarly connects with the venous blood at $\phi = \pi - \varepsilon_2$. The interstitial fluid region (I) is the space surrounding the adipocyte and the capillary, including the space between the capillary and adipocyte ($r_1 < r < r_2$).

### 3.3.2 Model assumptions

Blood flows from the arterial compartment into the capillary, carrying TCE to the adipose tissue. TCE then diffuses back and forth across the capillary endothelium into and out of the interstitial fluid, and TCE in the interstitial fluid may also diffuse back and forth across the plasma membrane of the adipocyte into and out of the fat cell. At the exit to the capillary the blood and TCE flow into the venous blood compartment. See Figure 3.2 for a schematic of the assumed geometry.

Some studies have suggested that there may be an “interfacial continuum” between capillary endothelial cells and adipocytes [18], [19], [20], [58]. That is, there is evidence of membrane continuity between the membranes of capillary endothelial cells and the plasma membranes of adipocytes. Since TCE is highly lipophilic and the cell membranes are composed of lipid bilayers [41], TCE may diffuse directly across the capillary endothelium and the adipocyte plasma membrane at these areas of membrane continuity. This would result in direct transport between the capillary and the adipocyte.

Therefore there are two feasible routes of transport between the capillary and the adipocyte: indirect transport via diffusion through the interstitial fluid, and direct transport across an “interfacial continuum.” It would be difficult to determine in vivo the exact proportions of direct and indirect transport of TCE occurring between an adipocyte and a capillary. Our model includes both of these types of transport, and the proportions of each type are parameters that may be estimated using inverse problem techniques.
Chapter 3. An axial dispersion model for the transport of TCE in adipose tissue

We do not attempt to include in our representative geometry the areas of continuity between the capillary endothelium and the adipocyte plasma membrane. Rather than modeling each of these regions individually, we include a general term in our model that will account for any direct transport that occurs.

We assume that the concentrations of TCE in the interstitial fluid are in equilibrium at points far away from the adipocyte and the capillary. Specifically, we assume that the net radial flux of TCE across the spherical shell \( r = r_3 \) is equal to zero for some \( r_3 > r_2 + 2\alpha \), where \( r_2 + 2\alpha \) is the outer radius of the capillary. We define this region of the interstitial space as

\[
\Omega_I = \{(r, \theta, \phi): r_1 \leq r \leq r_3, 0 \leq \theta \leq 2\pi, 0 \leq \phi \leq \pi\}.
\]

Similarly, since the adipocyte is large relative to the size of the capillary and nearby interstitial fluid, we assume that the net radial flux of TCE inside the adipocyte across the spherical shell \( r = r_0 \) is equal to zero for some \( 0 < r_0 < r_1 \). We thus define the adipocyte domain by

\[
\Omega_A = \{(r, \theta, \phi): r_0 \leq r \leq r_1, 0 \leq \theta \leq 2\pi, 0 \leq \phi \leq \pi\}.
\]

Here we assume that the difference between the inner radius \( r_0 \) and the outer radius \( r_3 \) is small compared to the radius \( r_1 \) of the adipocyte.

The remaining assumptions for our dispersion model are based on those used by Roberts and Rowland for the liver, adapted here for the physiology of adipose tissue.

1. Conditions in the capillary do not vary in a cross section normal to flow. This implies that the concentration \( C_B \) of TCE in the capillary depends only on \( \phi \). The basis for this assumption is that the flow in the \( r \) and \( \theta \) directions is negligible compared to the flow of the blood in the \( \phi \) direction.

2. Axial diffusion of solute is slow compared to the convection of solute in the capillary, so it may be ignored. In fact, it can be shown that without loss of generality, a separate axial diffusion term can be omitted in any axial dispersion
model. If we assume axial diffusion, then we obtain the following diffusive mass flux in the $\phi$ direction:

$$J_\phi = -D \frac{\partial C}{\partial \phi},$$

where $C$ is the concentration of solute and $D$ is the axial diffusivity coefficient. When considering axial dispersion, the dispersive mass flux in the $\phi$ direction is given by

$$J_\phi = -D \frac{\partial C}{\partial \phi},$$

where $D$ is the axial dispersivity coefficient. Since neither of these coefficients is known in general, they must be estimated using inverse problem techniques. Indeed, the dispersivity coefficient is not physical, since it is an effective coefficient which accounts for variations in residence times, path length, local geometry, etc. Therefore we can interpret the coefficient of this flux term as either the axial diffusivity, axial dispersivity, or as a net axial transport coefficient involving a combination of the two.

3. The transport of TCE between the capillary and the interstitial space is assumed to obey Fick’s law of diffusion, as are the transport between the interstitial space and the adipocyte and the transport between the capillary and the adipocyte.

4. No metabolism or elimination of solute occurs in adipose tissue. This assumption is based on the fact that TCE is metabolized by the enzyme Cytochrome P450 2E1, which is assumed to be located primarily in the liver and is not known to be present at significant levels inside adipose tissue. Moreover, TCE is eliminated only via exhalation from the lungs and via the excretion of its metabolites in the urine.

5. Only unbound solute can cross cell membranes. This is a standard assumption used in physiological modeling.

6. Concentrations of TCE in the interstitial fluid immediately surrounding the capillary and adipocyte ($r_1 < r < r_3$) are uniform with respect to $r$, depending
only on $\theta$ and $\phi$. This assumption is based on the small radial distance between $r_1$ and $r_3$.

7. Concentrations of TCE in the interstitial fluid near the capillary vary only slightly with respect to $\theta$, and the transport between the capillary and the interstitial space is approximated by the transport occurring at the arc $r = r_2$, $\theta = \theta_0, \varepsilon_1 < \phi < \pi - \varepsilon_2$.

8. Concentrations of TCE in the adipocyte near the capillary vary only slightly with respect to $\theta$, and the direct transport between the capillary and the adipocyte across an interfacial continuum is approximated by the transport occurring at the arc $r = r_2, \theta = \theta_0, \varepsilon_1 < \phi < \pi - \varepsilon_2$.

9. Concentrations of TCE inside the adipocyte between $r_0$ and the outer radius $r_1$ are uniform with respect to $r$, depending only on $\theta$ and $\phi$.

10. The ratio $f_B$ of the unbound TCE concentration to the total TCE concentration within the blood is a constant. This standard physiological assumption is based on the fact that the total and unbound concentrations of solute in the blood are in equilibrium with each other, and a linear relationship between the free and unbound concentrations is assumed. Let $C_B$ and $C_{uB}$ denote the blood concentrations of total and unbound TCE, respectively. Then

$$C_{uB} = f_B C_B$$

for some $f_B$, and the fact that these concentrations are in equilibrium implies that $f_B$ must be a constant.

11. The ratio $f_I$ of the unbound TCE concentration to the total TCE concentration within the interstitial space is a constant. This assumption is the interstitial space analog of Assumption 10.
12. The ratio $f_A$ of the unbound TCE concentration to the total TCE concentration within the adipocytes is a constant. This assumption is the adipocyte analog of Assumption 10.

### 3.3.3 Derivation of equations: Capillary region

Consider a “spherical cuboid” volume element spanning from $r$ to $r + \Delta r$, $\theta$ to $\theta + \Delta \theta$ and $\phi$ to $\phi + \Delta \phi$ (see Figure 3.3). The volume of this element is $\Delta V = r^2 \sin \phi \Delta r \Delta \phi \Delta \theta$, and we will denote its surface by $\Delta S$.

![Figure 3.3: “Spherical cuboid” volume element.](image)

In the capillary, the concentration of TCE is assumed to be uniform with respect to both $r$ and $\theta$, and we have axial dispersion in the $\phi$ direction. Moreover, we assume that $\alpha$ is small relative to $r_2$ so that we may approximate $r \approx r_2$ for $r \in \Omega_B$. This implies that the flux vector $J = (J_r, J_\theta, J_\phi)$ is given by

$$J = (0, 0, -\frac{D_B}{r_2} \frac{\partial C_B}{\partial \phi} + v C_B),$$
where \( D_B \) is the axial dispersion coefficient with units \( \text{m}^2/\text{hr} \). The velocity \( v \) is given by

\[
v = \frac{Q_f}{1000A_B} = \mathcal{F} \left( Q_f \frac{\text{liters}}{\text{hour}} \right) \left( \frac{1}{A_B \text{ meters}^2} \right) \left( \frac{1 \text{ meter}^3}{1000 \text{ liters}} \right)
\]

with units \( \text{m/hr} \), where \( Q_f \) is the blood flow rate to the fat tissue in liters/hr and \( A_B \) is the cross-sectional area of the capillary in meters\(^2\).

The dimensionless coefficient \( \mathcal{F} \) is included to account for the inversion of the Fahraeus-Lindquist effect, which is a phenomenon that involves the flow of blood as a function of the vessel diameter. To understand the phenomenon involved, consider the flow of blood from a larger vessel to a smaller vessel, with the smaller vessel ranging between 15 to 500 microns in diameter. If we assume that blood with constant hematocrit (the fraction of blood volume made up of the red blood cells) flows from the larger vessel to the smaller vessel, the hematocrit in the smaller vessel decreases as the diameter of the vessel decreases [37]. This is known as the Fahraeus effect, and is related directly to the Fahraeus-Lindquist effect, which involves a concurrent decrease in the apparent viscosity of blood in the smaller vessel as the diameter and the hematocrit decrease [37].

The apparent viscosity \( \mu_{\text{app}} \) can be expressed as a function of the vessel radius \( R \) and length \( L \), the drop in pressure \( \Delta P \) across the length of the vessel, and the volumetric flow rate \( Q \) as in [36] and [37]:

\[
\mu_{\text{app}} = \frac{\pi R^4 \Delta P}{8LQ}.
\]

A different phenomenon occurs in vessels less than about 4-6 microns in diameter. These vessels are significantly smaller than the normal 8 micron diameter of red blood cells, making it difficult for the red blood cells to enter vessels of this size [37]. This results in an increase of the flow resistance and hence an increase in the apparent viscosity of the blood as the diameter of the vessel decreases, which is the inversion of the Fahraeus-Lindquist effect [37]. This phenomenon leads to a concurrent decrease in the flow rate of the blood inside the smaller tube compared to the flow rate in the larger feed vessel.
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The capillaries in adipose tissue typically have lumen diameters measuring between 2 and 4 microns [29], which would place them in the range of vessels covered by the inversion of the Fahraeus-Lindquist effect. This implies a significant difference between the flow velocities of blood inside the arterial blood system versus the velocities inside the capillaries of the adipose tissue. Hence we include the “reverse Fahraeus-Lindquist parameter” $\mathcal{F} < 1$ to account for this decrease in blood flow rates as the blood and TCE flow from the arterial vessels to the adipose capillaries.

Now conservation of mass implies that

$$
\begin{align*}
\left( \text{Net rate of change} \right)_{\text{of TCE in blood element}} &= \left( \text{Net flow rate} \right)_{\text{of TCE within blood element}} + \left( \text{Net flow rate of TCE between blood element and interstitial space} \right) \\
&+ \left( \text{Net flow rate of TCE between blood element and adipocyte region} \right).
\end{align*}
$$

First we consider only transport from within the capillary (i.e., no exchange with the interstitial space or adipocyte region). Then

$$
\left( \text{Net flow rate of TCE within blood element} \right) = \int \int_{\Delta S} -J \cdot \hat{n} \, dS,
$$

where $\hat{n}$ is the outer unit normal to the surface $\Delta S$. Dividing by the volume $\Delta V$ of the element, we obtain

$$
\left( \text{Net flow rate of TCE within blood element per unit volume} \right) = \frac{1}{\Delta V} \int \int_{\Delta S} -J \cdot \hat{n} \, dS
$$

$$
= \frac{1}{\Delta V} \int \int \int_{\Delta V} \text{Div}(-J) \, dV
$$

by the Divergence Theorem. Taking the limit as $\Delta V \to 0$ at $r = r_2$ and $\theta = \theta_0$, we
have
\[
\left( \begin{array}{c}
\text{Net flow rate of TCE} \\
\text{in the blood element} \\
\text{per unit volume} \\
\text{at the point } (r_2, \theta_0, \phi)
\end{array} \right) = \text{Div}(-J)
\]
\[
= -\frac{1}{r_2^2} \frac{\partial}{\partial r}(r_2^2 J_r) - \frac{1}{r_2 \sin \phi} \frac{\partial J_\theta}{\partial \theta} - \frac{1}{r_2 \sin \phi} \frac{\partial}{\partial \phi} (\sin \phi J_\phi)
\]
\[
= -\frac{1}{r_2 \sin \phi} \frac{\partial}{\partial \phi} (\sin \phi J_\phi)
\]
\[
= -\frac{1}{r_2 \sin \phi} \frac{\partial}{\partial \phi} \left[ \sin \phi \left( -\frac{D_B}{r_2} \frac{\partial C_B}{\partial \phi} + v C_B \right) \right].
\]

We multiply both sides by the volume of the capillary $V_B$ to obtain
\[
\left( \begin{array}{c}
\text{Net flow rate of TCE} \\
\text{within capillary}
\end{array} \right) = \frac{V_B}{r_2 \sin \phi} \frac{\partial}{\partial \phi} \left[ \sin \phi \left( -\frac{D_B}{r_2} \frac{\partial C_B}{\partial \phi} + v C_B \right) \right].
\]

Now consider the exchange of TCE between the capillary and interstitial space. By Assumption 3, this transport is governed by Fick’s law of diffusion, so that
\[
\left( \begin{array}{c}
\text{Net flow rate of TCE} \\
\text{between blood element} \\
\text{and interstitial space}
\end{array} \right) = \lambda_I \mu_{BI} (f_I C_I(\theta_0) - f_B C_B),
\]
where $\mu_{BI}$ is the permeability coefficient for transport between the capillary and interstitial regions, with units liters/hour. The dimensionless coefficient $\lambda_I$ represents the fraction of transport that occurs between the capillary and interstitial fluid (versus the direct transport between the capillary and the adipocyte).

Similarly, we model the transport between the capillary and the adipocyte by
\[
\left( \begin{array}{c}
\text{Net flow rate of TCE} \\
\text{between blood element} \\
\text{and adipocyte}
\end{array} \right) = \lambda_A \mu_{BA} (f_A C_A(\theta_0) - f_B C_B),
\]
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where $\mu_{BA}$ is the permeability coefficient for transport between the capillary and adipocyte regions (in liters/hour), and $\lambda_A$ represents the fraction of transport that occurs between the capillary and the adipocyte. Note that we have $\lambda_I + \lambda_A = 1$.

Since the total rate of change of TCE at a point in the blood element is given by $V_B \frac{\partial C_B}{\partial t}$, we have

$$V_B \frac{\partial C_B}{\partial t} = \frac{V_B}{r_2 \sin \phi \partial \phi} \left[ \sin \phi \left( \frac{\partial C_B}{\partial \phi} - v C_B \right) \right] + \lambda_I \mu_{BI}(f_I C_I(0) - f_B C_B) + \lambda_A \mu_{BA}(f_A C_A(0) - f_B C_B)$$

for $t \geq 0$ and $(r, \theta, \phi) \in \hat{\Omega}_B$, where

$$\hat{\Omega}_B = \{(r, \theta, \phi) : r = r_2, \theta = \theta_0, \varepsilon_1 < \phi < \pi - \varepsilon_2 \} \subset \Omega_B.$$

Note that $C_B = C_B(t, \phi)$ due to uniformity in $r$ and $\theta$.

Boundary conditions

To obtain boundary conditions for the capillary region, we use flux balance principles. The mass flux in the capillary across the boundary $\phi = \varepsilon_1$ is given by $J_\phi|_{\phi=\varepsilon_1}$, and the mass flux in the arterial blood across $\phi = \varepsilon_1$ is $(Q_c/(1000A_B))C_a$. Therefore we have

$$-\frac{D_B}{r_2} \frac{\partial C_B}{\partial \phi}(t, \phi) + v C_B(t, \phi) \bigg|_{\phi=\varepsilon_1} = \frac{Q_c}{1000A_B} C_a(t).$$

Similarly, using flux balance at the boundary $\phi = \pi - \varepsilon_2$ between the capillary and the venous blood, we obtain

$$-\frac{D_B}{r_2} \frac{\partial C_B}{\partial \phi}(t, \phi) + v C_B(t, \phi) \bigg|_{\phi=\pi-\varepsilon_2} = \frac{Q_c}{1000A_B} C_v(t).$$

3.3.4 Derivation of equations: Interstitial space

In the interstitial space, TCE enters and exits via diffusion from the capillary region and via diffusion from the adipocyte. We assume that the interstitial space immediately surrounding the adipocyte and the capillary has a radial thickness sufficiently
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small so that diffusion in the radial direction is nearly instantaneous, i.e., the concentration of TCE in the interstitial space depends on \((t, \theta, \phi)\) but not \(r\). Therefore, we may assume that \(r \approx r_1\) in the interstitial space. Inside the interstitial fluid, TCE diffuses across the interstitial space in both the \(\theta\) and \(\phi\) directions.

Based on these assumptions, the mass flux vector for the interstitial space is given by

\[
J = (J_r, J_\theta, J_\phi) = \left(0, -\frac{D_I}{r_1 \sin \phi} \frac{\partial C_I}{\partial \theta}, -\frac{D_I}{r_1} \frac{\partial C_I}{\partial \phi}\right).
\]

The parameter \(D_I\) is the standard diffusion coefficient with units \(m^2/hr\).

Now consider an arbitrary “spherical cuboid” volume element in the interstitial space, as depicted in Figure 3.3. Using mass balance as before, we have

\[
\begin{pmatrix}
\text{Net rate of change of TCE in interstitial element}
\end{pmatrix} = \begin{pmatrix}
\text{Net flow rate of TCE within interstitial element}
\end{pmatrix} + \begin{pmatrix}
\text{Net flow rate of TCE between interstitial element and capillary}
\end{pmatrix} + \begin{pmatrix}
\text{Net flow rate of TCE between interstitial element and adipocyte}
\end{pmatrix}.
\]

First we consider the transport of TCE within the interstitial element only (i.e., no exchange with the other regions). Then

\[
\begin{pmatrix}
\text{Net flow rate of TCE within interst. element}
\end{pmatrix} = \int \int_{\Delta S} -J \cdot \hat{n} \, dS,
\]

where \(\hat{n}\) is the outer unit normal to the surface \(\Delta S\). Dividing by the volume \(\Delta V\) of the element, we obtain

\[
\begin{pmatrix}
\text{Net flow rate of TCE within interst. element per unit volume}
\end{pmatrix} = \frac{1}{\Delta V} \int \int_{\Delta S} -J \cdot \hat{n} \, dS.
\]
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Using the Divergence Theorem and taking the limit as $\Delta V \to 0$ at $r = r_1$, we have

\[
\begin{pmatrix}
\text{Net flow rate of TCE} \\
\text{within interst. element} \\
\text{per unit volume} \\
\text{at the point } (r_1, \theta, \phi)
\end{pmatrix}
=
\text{Div}(-J)
\]

\[
= -\frac{1}{r_1^2} \frac{\partial}{\partial r} (r_1^2 J_r) - \frac{1}{r_1 \sin \phi} \frac{\partial J_\theta}{\partial \theta} - \frac{1}{r_1 \sin \phi} \frac{\partial}{\partial \phi} (\sin \phi J_\phi)
\]

\[
= -\frac{1}{r_1 \sin \phi} \frac{\partial J_\theta}{\partial \theta} - \frac{1}{r_1 \sin \phi} \frac{\partial}{\partial \phi} (\sin \phi J_\phi)
\]

\[
= \frac{D_I}{r_1^2 \sin^2 \phi} \frac{\partial^2 C_I}{\partial \theta^2} + \frac{D_I}{r_1^2 \sin \phi} \frac{\partial}{\partial \phi} \left( \sin \phi \frac{\partial C_I}{\partial \phi} \right).
\]

As with the capillary, we multiply by the volume and then add in the transport with the other regions to obtain

\[
V_I \frac{\partial C_I}{\partial t} = \frac{V_I D_I}{r_1^2} \left[ \frac{1}{\sin^2 \phi} \frac{\partial^2 C_I}{\partial \theta^2} + \frac{1}{\sin \phi} \frac{\partial}{\partial \phi} \left( \sin \phi \frac{\partial C_I}{\partial \phi} \right) \right] + \delta_{\theta_0}(\theta) \chi_B(\phi) \lambda_I \mu_{BI} (f_BC_B - f_IC_I) + \mu_{IA} (f_AC_A - f_IC_I) \quad (3.1)
\]

for $t \geq 0$ and $(r, \theta, \phi) \in \hat{\Omega}_I$, where

\[
\hat{\Omega}_I = \{(r, \theta, \phi) : r = r_1, 0 \leq \theta \leq 2\pi, 0 \leq \phi \leq \pi \} \subset \Omega_I
\]

and $\chi_B$ is the following indicator function in $\phi$:

\[
\chi_B(\phi) = \begin{cases} 
  1 & \text{if } \phi \in (\varepsilon_1, \pi - \varepsilon_2) \\
  0 & \text{otherwise.}
\end{cases}
\]

This function $\chi_B$ is used with $\delta_{\theta_0}$, the Dirac delta distribution centered at $\theta = \theta_0$, to specify mathematically the location of the capillary – interstitial space transport and the capillary – adipocyte transport.

**Boundary conditions**

Since we have diffusion in the interstitial space in the $\phi$ and $\theta$ directions, we require boundary conditions in both $\phi$ and $\theta$. The geometry of the spherical shell dictates
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periodic boundary conditions in \( \theta \). That is,

\[
C_I(t, \theta, \phi) = C_I(t, \theta + 2\pi, \phi) \quad \text{for } t \geq 0, \quad 0 < \phi < \pi
\]

\[
\frac{\partial C_I}{\partial \theta}(t, \theta, \phi) = \frac{\partial C_I}{\partial \theta}(t, \theta + 2\pi, \phi) \quad \text{for } t \geq 0 \text{ and almost every } 0 < \phi < \pi.
\]

The boundary conditions in \( \phi \) are less straightforward. If we carry out separation of variables on the PDE (3.1) for the interstitial space, we obtain an equation in \( \phi \) which is a type of singular Sturm-Liouville problem (see [26], p. 324). These problems have the form

\[
(pu')' - qu + \lambda pu = 0,
\]

where the variable coefficient \( p \) vanishes at one or both of the endpoints. In our case, we have \( p(\phi) = \sin \phi \), which vanishes at both \( \phi = 0 \) and \( \phi = \pi \).

The corresponding boundary value problems require a finiteness or continuity condition at the singular endpoints, taking the place of the usual type of boundary condition [26]. Here we require the finiteness conditions

\[
C_I(t, \theta, 0) < \infty
\]

\[
C_I(t, \theta, \pi) < \infty
\]

for \( t \geq 0 \) and \( 0 \leq \theta \leq 2\pi \).

3.3.5 Derivation of equations: Adipocyte region

In the adipocyte region, TCE enters and leaves the fat cell via diffusion across the cell membrane between the adipocyte and the interstitial space, and via diffusion between the adipocyte and capillary. We assume that diffusion of TCE in the radial direction inside the adipocyte is nearly instantaneous, so that the concentrations are uniform in \( r \) for \( r_0 \leq r \leq r_1 \). Moreover, we approximate \( r \approx r_0 \) in the adipocyte region. As with the interstitial space, TCE in the adipocyte diffuses across the fat cell in the \( \theta \) and \( \phi \) directions.
Using flux balance principles as before, we obtain the equation (taking the limit $\Delta V \to 0$ at $r = r_0$)

$$V_A \frac{\partial C_A}{\partial t} = \frac{V_AD_A}{r_0^2} \left[ \frac{1}{\sin^2 \phi} \frac{\partial^2 C_A}{\partial \theta^2} + \frac{1}{\sin \phi} \frac{\partial}{\partial \phi} \left( \sin \phi \frac{\partial C_A}{\partial \phi} \right) \right] + \delta_{\theta_0}(\theta) \chi_B(\phi) \lambda_A \mu_{BA}(f_B C_B - f_A C_A) + \mu_I A(C_I - f_A C_A) \quad (3.2)$$

for $t \geq 0$ and $(r, \theta, \phi) \in \tilde{\Omega}_A$, where

$$\tilde{\Omega}_A = \{(r, \theta, \phi) : r = r_0, 0 \leq \theta \leq 2\pi, 0 \leq \phi \leq \pi \} \subset \Omega_A.$$

As before, the parameter $D_A$ is the standard diffusion coefficient with units m$^2$/hr.

**Boundary conditions**

The boundary conditions for the adipocyte region are similar to those for the interstitial space, and are derived using the same principles. We require periodic boundary conditions in $\theta$ and finiteness conditions in $\phi$:

$$C_A(t, \theta, \phi) = C_A(t, \theta + 2\pi, \phi) \quad \text{for } t \geq 0, \quad 0 < \phi < \pi$$

$$\frac{\partial C_A}{\partial \theta}(t, \theta, \phi) = \frac{\partial C_A}{\partial \theta}(t, \theta + 2\pi, \phi) \quad \text{for } t \geq 0 \text{ and almost every } 0 < \phi < \pi,$$

$$C_A(t, \theta, 0) < \infty, \quad t \geq 0 \text{ and } 0 \leq \theta < 2\pi,$$

$$C_A(t, \theta, \pi) < \infty, \quad t \geq 0 \text{ and } 0 \leq \theta < 2\pi.$$

**3.3.6 Summary of model equations**

Combining the PBPK whole-body model with the adipose dispersion model, we obtain a PBPK-hybrid TCE model:

$$V_B \frac{\partial C_B}{\partial t} = \frac{V_B}{r_2 \sin \phi} \frac{\partial}{\partial \phi} \left[ \sin \phi \left( \frac{D_B}{r_2} \frac{\partial C_B}{\partial \phi} - v C_B \right) \right] + \lambda_I \mu_{BI}(f_I C_I(\theta_0) - f_B C_B)$$
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\[
- \frac{D_B}{r_2} \frac{\partial C_B(t, \phi)}{\partial \phi} + v C_B(t, \phi) \bigg|_{\phi = \varepsilon_1} = \frac{Q_c}{1000 A_B} C_a(t) \tag{3.3}
\]

\[
- \frac{D_B}{r_2} \frac{\partial C_B(t, \phi)}{\partial \phi} + v C_B(t, \phi) \bigg|_{\phi = \pi - \varepsilon_2} = \frac{Q_c}{1000 A_B} C_v(t) \tag{3.5}
\]

\[
V_I \frac{\partial C_I}{\partial t} = \frac{V_I D_I}{r_I^2} \left[ \frac{1}{\sin^2 \phi} \frac{\partial^2 C_I}{\partial \theta^2} + \frac{1}{\sin \phi} \frac{\partial}{\partial \phi} \left( \sin \phi \frac{\partial C_I}{\partial \phi} \right) \right] + \delta_{b_0}(\theta) \chi_B(\phi) \lambda_{A} \mu_{B} (f_B C_B - f_I C_I) + \mu_{IA} (f_A C_A - f_I C_I) \tag{3.6}
\]

\[
C_I(t, \theta, \phi) = C_I(t, \theta + 2\pi, \phi) \tag{3.7}
\]

\[
\frac{\partial C_I}{\partial \theta}(t, \theta, \phi) = \frac{\partial C_I}{\partial \theta}(t, \theta + 2\pi, \phi) \tag{3.8}
\]

\[
C_I(t, \theta, 0) < \infty \tag{3.9}
\]

\[
C_I(t, \theta, \pi) < \infty \tag{3.10}
\]

\[
V_A \frac{\partial C_A}{\partial t} = \frac{V_A D_A}{r_A^2} \left[ \frac{1}{\sin^2 \phi} \frac{\partial^2 C_A}{\partial \theta^2} + \frac{1}{\sin \phi} \frac{\partial}{\partial \phi} \left( \sin \phi \frac{\partial C_A}{\partial \phi} \right) \right] + \delta_{b_0}(\theta) \chi_B(\phi) \lambda_{A} \mu_{B} (f_B C_B - f_A C_A) + \mu_{IA} (f_I C_I - f_A C_A) \tag{3.11}
\]

\[
C_A(t, \theta, \phi) = C_A(t, \theta + 2\pi, \phi) \tag{3.12}
\]

\[
\frac{\partial C_A}{\partial \theta}(t, \theta, \phi) = \frac{\partial C_A}{\partial \theta}(t, \theta + 2\pi, \phi) \tag{3.13}
\]

\[
C_A(t, \theta, 0) < \infty \tag{3.14}
\]

\[
C_A(t, \theta, \pi) < \infty \tag{3.15}
\]

\[
V_v \frac{dC_v}{dt} = Q_m C_{vm} + Q_t C_{vt} + Q_f C_{vf} + Q_{br} C_{vbr} + Q_{l} C_{vl} + Q_k C_{vk} - Q_c C_v \tag{3.16}
\]

\[
C_a = \frac{Q_c C_v + Q_p C_c}{Q_c + \frac{Q_p}{P_v}} \tag{3.17}
\]

\[
V_m \frac{dC_m}{dt} = Q_m (C_a - C_{vm}) \tag{3.18}
\]
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\[ V_t \frac{dC_t}{dt} = Q_t(C_a - C_{vt}) \]  
(3.19)

\[ V_{br} \frac{dC_{br}}{dt} = Q_{br}(C_a - C_{vbr}) \]  
(3.20)

\[ \frac{dA_{am}}{dt} = \frac{v_{max}C_{vl}}{k_M + C_{vl}} \]  
(3.21)

\[ V_l \frac{dC_l}{dt} = Q_l(C_a - C_{vl}) - \frac{v_{max}C_{vl}}{k_M + C_{vl}} \]  
(3.22)

\[ V_k \frac{dC_k}{dt} = Q_k(C_a - C_{vk}) \]  
(3.23)

\[ \frac{dA_i}{dt} = Q_pC_c \]  
(3.24)

\[ \frac{dA_x}{dt} = Q_pC_x. \]  
(3.25)
Chapter 4

Well-posedness results

In this chapter we present theoretical results for the PBPK-hybrid TCE model and associated parameter estimation problems. In the first section we establish the well-posedness of a class of abstract nonlinear parabolic equations, and further show that the PBPK-hybrid TCE model fits into this class of equations. These results guarantee the existence of a unique weak solution to the model equations under certain assumptions that we detail below.

Our TCE model is dependent on many physical, biological and chemical parameters, some of which can be explicitly measured. However, most of the adipose model parameters are unknown, and it would be impractical to measure them experimentally. Therefore, we must use inverse problem techniques to estimate these parameters. In the second portion of this chapter we present theoretical results that relate to the parameter estimation problem. Moreover, these results establish the convergence of the numerical scheme that we develop in Chapter 5 to compute solutions for the model equations and to generate simulations. This numerical scheme also will be utilized in Chapter 6, where we discuss results related to the parameter estimation problem.

Finally, we address issues related to variability that may occur in parameter values across a population. For example, it is unreasonable to expect that an entire population of rats would exhibit the same fixed value for a parameter such as a permeability
coefficient. Rather, we would expect that different rats would possess different values for this parameter. This suggests that such a parameter could be represented by a random variable, where the distribution of the parameter reflects the variability across the population. The probability distribution for the parameter would be unknown in general, and may be estimated using inverse problem techniques detailed in [5], which we outline in Section 4.3. We also present theoretical results from [5] related to the well-posedness of this type of inverse problem, and consider the special case of estimating truncated normal probability distributions for the parameters.

\section{Well-posedness of solutions}

First we present well-posedness results for a class of abstract nonlinear parabolic equations. The theoretical issues that we address here establish the existence, uniqueness and continuous dependence of solutions for the TCE-adipose dispersion model coupled with the whole-body PBPK model, as well as for a class of more general equations that may arise in more complicated models of xenobiotic transport inside the body. Moreover, these theoretical efforts lay the groundwork for computational methods used in model verification, simulation and parameter estimation.

The main result that we establish here regarding well-posedness of solutions is based on ideas presented in [10] and [2]. Banks and Musante [10] proved well-posedness results for two classes of abstract nonlinear parabolic systems. The first class they addressed requires the nonlinearity to satisfy a particular convexity condition. The second class replaces the convexity condition with an assumption that the forcing function has additional regularity with respect to time or space.

The TCE PBPK-hybrid model has a simple Michaelis-Menten nonlinearity in the liver equation, and it can be shown that this system of model equations fits into the first of these abstract classes of problems. Although this happens to be the case for TCE, which has a simple metabolic mechanism, there may be other lipophilic compounds which have more complicated kinetics (e.g., protein binding) that would
not satisfy the convexity condition.

The forcing function in our TCE model is related to the inhalation of TCE vapor in the ambient air, and does not have the necessary regularity required for the model to fit into the second class of abstract problems discussed by Banks and Musante. Transport models for other inhaled compounds would have a similar forcing function that also may lack the required regularity. Therefore, a model for an inhaled lipophilic compound with complicated nonlinear kinetics would likely fall outside both of these abstract classes of problems.

Using ideas in [2], we can improve upon the results of Banks and Musante by achieving well-posedness for a more general class of abstract nonlinear parabolic equations. Ackleh, Banks and Pintér [2] proved the well-posedness of second order elastomer problems in which the nonlinearities satisfy local Lipschitz and affine domination properties. Our result is based on their work, and will establish well-posedness for a wider class of inhaled xenobiotic transport models.

4.1.1 Problem formulation for the TCE model

Here we present the weak or variational formulation for the TCE whole-body transport model including the axial dispersion model for the adipose tissue compartment.

Consider the domains \( \tilde{\Omega}_B \), \( \tilde{\Omega}_I \) and \( \tilde{\Omega}_A \) as defined in Chapter 3:

\[
\tilde{\Omega}_B = \{(r, \theta, \phi) : r = r_2, \theta = \theta_0, \varepsilon_1 < \phi < \pi - \varepsilon_2\}
\]

\[
\tilde{\Omega}_I = \{(r, \theta, \phi) : r = r_1, 0 \leq \theta \leq 2\pi, 0 \leq \phi \leq \pi\}
\]

\[
\tilde{\Omega}_A = \{(r, \theta, \phi) : r = r_0, 0 \leq \theta \leq 2\pi, 0 \leq \phi \leq \pi\}.
\]

Recall that in Section 3.3.2, we made the assumption that the difference \( r_2 - r_0 \) is small compared to the radius \( r_1 \) of the adipocyte, where \( 0 < r_0 < r_1 < r_2 \). Here we use that assumption to approximate \( r_0 \) and \( r_2 \) by \( r_1 \), and we define the domains

\[
\tilde{\Omega}_B = \{(r, \theta, \phi) : r = r_1, \theta = \theta_0, \varepsilon_1 < \phi < \pi - \varepsilon_2\}
\]

\[
\tilde{\Omega}_{IA} = \{(r, \theta, \phi) : r = r_1, 0 \leq \theta \leq 2\pi, 0 \leq \phi \leq \pi\} = \tilde{\Omega}_I.
\]
Note that both $r$ and $\mu$ are constant in the domain $\Omega_B$, so that we may write $u = u(\phi)$ for functions $u \in \Omega_B$. Similarly, since $r$ is constant in $\Omega_{IA}$ we write $u = u(\theta, \phi)$ for $u \in \Omega_{IA}$. In both cases, $r = r_1$ is understood.

We choose the following state spaces for the regions of the adipose dispersion model:

$$H^1_B = H^1(\Omega_B)$$

in the capillary region and

$$H^1_{IA} \equiv H^1_{per}(\Omega_{IA}) = \{ u \in H^1(\Omega_{IA}) : u(\theta, \phi) = u(\theta + 2\pi, \phi) \}$$

in the interstitial region and adipocyte regions.

We now define the state space $V = H^1_B \times H^1_{IA} \times H^1_{IA} \times \mathbb{R}^6$ and the space $\mathcal{H} = L^2(\Omega_B) \times L^2(\Omega_{IA}) \times L^2(\Omega_{IA}) \times \mathbb{R}^6$.

The domain $\Omega_B$ is an arc in three-dimensional space spanning between $\phi = \varepsilon_1$ and $\phi = \pi - \varepsilon_2$ at $r = r_1$ and $\theta = \theta_0$, and accordingly we define the inner product

$$\langle u, v \rangle_B = \int_{\varepsilon_1}^{\pi - \varepsilon_2} u(\phi) v(\phi) \sin \phi \, d\phi$$

for $u, v \in L^2(\Omega_B)$ and norms

$$|u|^2_B = \int_{\varepsilon_1}^{\pi - \varepsilon_2} |u(\phi)|^2 \sin \phi \, d\phi \quad \text{for} \quad u \in L^2(\Omega_B)$$

$$|u|^2_{H^1_B} = \int_{\varepsilon_1}^{\pi - \varepsilon_2} \left( \frac{1}{r_1} \frac{\partial u(\phi)}{\partial \phi} \right)^2 + |u(\phi)|^2 \sin \phi \, d\phi \quad \text{for} \quad u \in H^1_B$$

since

$$\nabla u = \left( \frac{\partial u}{\partial r}, \frac{1}{r \sin \phi} \frac{\partial u}{\partial \theta}, \frac{1}{r_1} \frac{\partial u}{\partial \phi} \right) = \left( 0, 0, \frac{1}{r_1} \frac{\partial u}{\partial \phi} \right)$$

for all $u \in H^1_B$.

The domain $\Omega_{IA}$ is the surface of the sphere $r = r_1$, and we define the following inner product and norm for $u, v \in L^2(\Omega_{IA})$:

$$\langle u, v \rangle_{IA} = \int_0^{2\pi} \int_0^{\pi} u(\theta, \phi) v(\theta, \phi) \sin \phi \, d\phi \, d\theta$$

$$|u|^2_{IA} = \int_0^{2\pi} \int_0^{\pi} |u(\theta, \phi)|^2 \sin \phi \, d\phi \, d\theta.$$
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Moreover, for \( u \in H^1_{IA} \) we define the norm

\[
|u|^2_{H^1_{IA}} = \int_0^{2\pi} \int_0^\pi \left( \frac{1}{r_1 \sin \phi} \left| \frac{\partial u(\theta, \phi)}{\partial \theta} \right|^2 + \left| \frac{1}{r_1} \frac{\partial u(\theta, \phi)}{\partial \phi} \right|^2 + |u(\theta, \phi)|^2 \right) \sin \phi \, d\phi \, d\theta,
\]

since for \( u \in H^1_{IA} \) we have

\[
\nabla u = \left( \frac{\partial u}{\partial r}, \frac{1}{r \sin \phi} \frac{\partial u}{\partial \theta} - \frac{1}{r} \frac{\partial u}{\partial \phi} \right) = \left( 0, \frac{1}{r_1 \sin \phi} \frac{\partial u}{\partial \theta}, \frac{1}{r_1} \frac{\partial u}{\partial \phi} \right).
\]

Finally, we define the following inner product and norm on \( \mathcal{H} \):

\[
\langle u, v \rangle_{\mathcal{H}} = \langle u_1, v_1 \rangle_B + \langle u_2, v_2 \rangle_{IA} + \langle u_3, v_3 \rangle_{IA} + \sum_{j=4}^9 u_j v_j
\]

\[
|u|^2_{\mathcal{H}} = |u_1|^2_B + |u_2|^2_{IA} + |u_3|^2_{IA} + \sum_{i=4}^9 |u_i|^2
\]

for all \( u, v \in \mathcal{H} \), and the norm

\[
|u|^2_{\mathcal{V}} = |u|^2_{H^1_B} + |u|^2_{H^1_{IA}} + |u|^2_{H^1_{IA}} + \sum_{i=4}^9 |u_i|^2
\]

for all \( u \in \mathcal{V} \).

Let \( \Gamma \) denote the boundary of the domain \( \bar{\Omega}_{IA} \). Since \( \bar{\Omega}_{IA} \) is defined as a spherical shell in spherical coordinates, we can choose the boundary \( \Gamma \) to be any fixed value of \( \theta \). Therefore we define \( \Gamma = \{ (r, \theta, \phi) : r = r_1, \theta = \theta_0, 0 \leq \phi \leq \pi \} \). Moreover, we define the trace operator \( T^0_{\theta_0} : H^1(\bar{\Omega}_{IA}) \to L^2(\Gamma) \) so that

\[
T^0_{\theta_0} u = u|_{\theta = \theta_0} \tag{4.1}
\]

for any \( u \in H^1(\bar{\Omega}_{IA}) \), where

\[
|u|^2_{L^2(\Gamma)} = \int_0^\pi |u(\phi)|^2 \sin \phi \, d\phi
\]

for all \( u \in L^2(\Gamma) \), and where \( |u|^2_{H^1(\bar{\Omega}_{IA})} = |u|^2_{H^1_{IA}} \) for all \( u \in H^1(\bar{\Omega}_{IA}) \).

It follows from the Trace Theorem (see Theorem 6 in [52], p. 240) that there exists \( K_1 > 0 \) such that for every \( u \in H^1(\bar{\Omega}_{IA}) \) we have

\[
|T^0_{\theta_0} u|_{L^2(\Gamma)} \leq K_1 |u|^2_{H^1_{IA}}.
\]
so that

\[ |T_{\theta_0}^0 u|^2_B = \int_{\varepsilon_1}^{\pi - \varepsilon_2} |T_{\theta_0}^0 u(\theta, \phi)|^2 \sin \phi \, d\phi \]
\[ \leq |T_{\theta_0}^0 u|_{L^2(\Gamma)}^2 \]
\[ \leq K_1 |u|_{H^1_{\theta_0}}^2. \quad (4.2) \]

Here we are seeking a solution \( y(t) \in \mathcal{V} \) which satisfies the initial condition \( y(0) = y_0 \in \mathcal{H} \) and

\[ \langle y(t), \psi \rangle_{\mathcal{V}^*, \mathcal{V}} + \sigma(y(t), \psi) + \langle g(y(t)), \psi \rangle_{\mathcal{H}} = \langle f(t), \psi \rangle_{\mathcal{V}^*, \mathcal{V}} \quad (4.3) \]

for all \( \psi \in \mathcal{V} \), where

\[
y(t) = [C_B(t), C_1(t), C_A(t), C_v(t), C_{v_1}(t), C_{v_2}(t), C_{v_3}(t), C_4(t), C_1(t)]^T
\]

and

\[
\sigma(u, v) = \left\langle \frac{a_1}{r_1} \frac{\partial u_1}{\partial \phi} - \frac{a_2}{r_1} u_1, \frac{\partial v_1}{\partial \phi} \right \rangle_B + \left\langle a_3 u_1 - a_4 T_{\theta_0}^0 u_2, v_1 \right \rangle_B + \left\langle a_5 u_1 - a_6 T_{\theta_0}^0 u_3, v_1 \right \rangle_B
\]
\[ + \left\langle -a_7 u_4, v_1(\varepsilon_1) \right \rangle_{\mathbb{R}} + \left\langle a_8 u_4, v_1(\pi - \varepsilon_2) \right \rangle_{\mathbb{R}} + \left\langle \frac{b_1}{r_1^2 \sin^2 \phi} \frac{\partial u_2}{\partial \theta}, \frac{\partial v_2}{\partial \theta} \right \rangle_{I_A}
\]
\[ + \left\langle b_1 \frac{\partial u_2}{\partial \phi}, \frac{\partial v_2}{\partial \phi} \right \rangle_{I_A} + \left\langle \delta_{\theta_0}(\theta) \chi_B(\phi)(-b_2 u_1 + b_3 u_2) + b_4 u_2 - b_5 u_3, v_2 \right \rangle_{I_A}
\]
\[ + \left\langle \frac{c_1}{r_1^2 \sin^2 \phi} \frac{\partial u_3}{\partial \theta}, \frac{\partial v_3}{\partial \theta} \right \rangle_{I_A} + \left\langle \frac{c_1}{r_1^2 \sin^2 \phi} \frac{\partial u_3}{\partial \phi}, \frac{\partial v_3}{\partial \phi} \right \rangle_{I_A}
\]
\[ + \left\langle \delta_{\theta_0}(\theta) \chi_B(\phi)(-c_2 u_1 + c_3 u_3) + c_4 u_3 - c_5 u_2, v_3 \right \rangle_{I_A}
\]
\[ + \left\langle -d_1 u_1(\pi - \varepsilon_2) + d_2 u_4 - d_3 u_5 - d_4 u_6 - d_5 u_7 - d_6 u_8 - d_7 u_9, v_4 \right \rangle_{\mathbb{R}}
\]
\[ + \left\langle -e_1 u_4 + e_2 u_5, v_5 \right \rangle_{\mathbb{R}} + \left\langle -h_1 u_4 + h_2 u_6, v_6 \right \rangle_{\mathbb{R}} + \left\langle -\ell_1 u_4 + \ell_2 u_7, v_7 \right \rangle_{\mathbb{R}}
\]
\[ + \left\langle -p_1 u_4 + p_2 u_8, v_8 \right \rangle_{\mathbb{R}} + \left\langle -s_1 u_4 + s_2 u_9, v_9 \right \rangle_{\mathbb{R}} \quad (4.4)
\]

\[
g(y) = [0, 0, 0, 0, 0, 0, 0, 0, g_0(y_0)]^T \quad (4.5)
\]
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\[ f(t) = \begin{bmatrix} \frac{V_B Q_b Q_c}{1000 A_{\beta \tau_1} (Q_c + \frac{Q_p}{T_B})} C_c(t) \delta_{\epsilon_1} (\phi) \\ 0 \\ 0 \\ 0 \\ \frac{Q_b Q_c}{Q_c + \frac{Q_p}{T_B}} C_c(t) \\ \frac{Q_b Q_c}{Q_c + \frac{Q_p}{T_B}} C_c(t) \\ \frac{Q_b Q_c}{Q_c + \frac{Q_p}{T_B}} C_c(t) \\ \frac{Q_c Q_p}{Q_c + \frac{Q_p}{T_B}} C_c(t) \\ \frac{Q_c Q_p}{Q_c + \frac{Q_p}{T_B}} C_c(t) \end{bmatrix}, \quad (4.6) \]

where

\[ g_9(y) = \begin{cases} \frac{s_3 y_9}{1 + s_4 y_9} & \text{if } y_9 \geq 0 \\ 0 & \text{otherwise.} \end{cases} \quad (4.7) \]

Here we use the notation \( \dot{y} = \frac{\partial y}{\partial t} \), and \( \langle \cdot, \cdot \rangle_{V^*, V} \) denotes the usual duality product described in the next section. The system (4.3) belongs to a general class of abstract problems that we consider in the next section, where we address issues of well-posedness.

### 4.1.2 Well-posedness results for a class of abstract nonlinear parabolic systems

Consider the system

\[ \dot{y}(t) + A y(t) + g(y(t)) = f(t) \quad \text{in } V^* \quad (4.8) \]
\[ y(0) = y_0 \quad (4.9) \]

for \( t \in (0, T) \) with \( T < \infty \). We assume that \( V, H \) and \( V^* \) are separable real Hilbert spaces that form a Gelfand triple [67] which satisfies

\[ V \hookrightarrow H \simeq H^* \hookrightarrow V^*. \]
We denote the inner product in $\mathcal{H}$ by $\langle \cdot, \cdot \rangle$, and the norms in each of the spaces $\mathcal{V}$, $\mathcal{H}$ and $\mathcal{V}^*$ are denoted by $|\cdot|_{\mathcal{V}}$, $|\cdot|$ and $|\cdot|_{\mathcal{V}^*}$ respectively. Moreover, we assume that the embedding $\mathcal{V} \hookrightarrow \mathcal{H}$ is dense and continuous, with

$$|\psi| \leq k |\psi|_{\mathcal{V}} \quad \text{for all } \psi \in \mathcal{V}. \quad (4.10)$$

The duality product $\langle \cdot, \cdot \rangle_{\mathcal{V}^*, \mathcal{V}}$ is the extension by continuity of the inner product in $\mathcal{H}$ from $\mathcal{H} \times \mathcal{V}$ to $\mathcal{V}^* \times \mathcal{V}$ (see [67] for a complete discussion).

We define the operator $\mathcal{A}$ in terms of its corresponding sesquilinear form $\sigma : \mathcal{V} \times \mathcal{V} \rightarrow \mathbb{R}$. That is, we define $\mathcal{A} : \mathcal{V} \rightarrow \mathcal{V}^*$ by $\langle \mathcal{A}u, v \rangle_{\mathcal{V}^*, \mathcal{V}} = \sigma(u, v)$, and it follows that $\mathcal{A} \in \mathcal{L}(\mathcal{V}, \mathcal{V}^*)$.

We make the following assumptions:

(A1) The sesquilinear form $\sigma$ is bounded in $\mathcal{V}$, i.e., there exists $C_1 > 0$ such that

$$|\sigma(u, v)| \leq C_1 |u|_{\mathcal{V}} |v|_{\mathcal{V}} \quad \text{for all } u, v \in \mathcal{V}. \quad (4.11)$$

(A2) The sesquilinear form $\sigma$ is elliptic on $\mathcal{V}$. That is, there exist $k_1 > 0$ and $\lambda > 0$ such that

$$\sigma(u, u) \geq k_1 |u|_{\mathcal{V}}^2 - \lambda |u|^2 \quad \text{for all } u \in \mathcal{V}. \quad (4.12)$$

(A3) The forcing function $f$ satisfies

$$f \in L_2((0, T); \mathcal{V}^*). \quad (4.13)$$

(A4) The nonlinear function $g : \mathcal{H} \rightarrow \mathcal{H}$ satisfies the following local Lipschitz condition: let $B_r(0) = \{ u \in \mathcal{H} : |u| \leq r \}$ denote the ball of radius $r$ centered around the origin in $\mathcal{H}$. Then given $r > 0$, there exists $L_{B_r} > 0$ such that

$$|g(u) - g(v)| \leq L_{B_r} |u - v| \quad \text{for all } u, v \in B_r(0). \quad (4.14)$$

(A5) There exist positive constants $C_2$ and $C_3$ such that

$$|g(u)| \leq C_2 |u| + C_3 \quad \text{for all } u \in \mathcal{H}. \quad (4.15)$$
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We say that \( y \in L_2((0, T); \mathcal{V}) \) is a weak solution of (4.8), (4.9) if it satisfies

\[
\langle \dot{y}(t), \psi \rangle_{\mathcal{V}^*, \mathcal{V}} + \sigma(y(t), \psi) + \langle g(y(t)), \psi \rangle = \langle f(t), \psi \rangle_{\mathcal{V}^*, \mathcal{V}} \tag{4.16}
\]

\[
y(0) = y_0 \tag{4.17}
\]

for all \( \psi \in \mathcal{V} \).

**Theorem 4.1.1** Under Assumptions (A1) – (A4) and for any \( y_0 \in \mathcal{H} \), the system (4.16) – (4.17) has a unique weak solution \( y \in L_2((0, T); \mathcal{V}) \cap C([0, T]; \mathcal{H}) \) on some interval \([0, t^*] \).

**Proof:** Let \( \mathcal{P} \) denote the Hilbert space radial retraction onto the ball in \( \mathcal{H} \) with radius 1 centered at \( y_0 \), and define the nonlinear function \( \tilde{g} : \mathcal{H} \to \mathcal{H} \) by

\[
\tilde{g}(u) = g(\mathcal{P} u).
\]

Then

\[
|\tilde{g}(u) - \tilde{g}(v)| \leq L_{B_{\|y_0\|}+1} |\mathcal{P}u - \mathcal{P}v| \leq \tilde{L} |u - v| \tag{4.18}
\]

for all \( u, v \in \mathcal{H} \), where \( \tilde{L} = 2 \) (see Lemma 2.1, p. 230 in [9]). Moreover,

\[
|\tilde{g}(u)| \leq \tilde{L} |u| + c \tag{4.19}
\]

where \( c = |g(0)| \geq 0 \) since

\[
|\tilde{g}(u)| - |\tilde{g}(0)| \leq |\tilde{g}(u) - \tilde{g}(0)| \leq \tilde{L} |u|.
\]

Consider the problem

\[
\dot{y}(t) + \mathcal{A} y(t) + \tilde{g}(y(t)) = f(t) \quad \text{in } \mathcal{V}^* \tag{4.20}
\]

\[
y(0) = y_0 \tag{4.21}
\]

with corresponding weak form

\[
\langle \dot{y}(t), \psi \rangle_{\mathcal{V}^*, \mathcal{V}} + \sigma(y(t), \psi) + \langle \tilde{g}(y(t)), \psi \rangle = \langle f(t), \psi \rangle_{\mathcal{V}^*, \mathcal{V}} \tag{4.22}
\]

\[
y(0) = y_0 \tag{4.23}
\]
Suppose that there exists a solution \( y(t) \) to (4.22) \(-\) (4.23). Here we establish a priori bounds for this solution by setting \( \psi = y(t) \) in (4.22) and integrating from 0 to \( t \) for some \( t \in [0, T] \):

\[
\frac{1}{2} |y(t)|^2 + \int_0^t [\sigma(y(s), y(s)) + \langle \tilde{g}(y(s)), y(s) \rangle] \, ds = \frac{1}{2} |y(0)|^2 + \int_0^t \langle f(s), y(s) \rangle_{V^*, V} \, ds,
\]

where we have applied the identity

\[
\langle \dot{y}(t), y(t) \rangle_{V^*, V} = \frac{1}{2} \frac{d}{dt} |y(t)|^2.
\]

Moreover, (4.12) and (4.23) imply

\[
\frac{1}{2} |y(t)|^2 + k_1 \int_0^t |y(s)|_{V^*}^2 \, ds + \int_0^t \langle \tilde{g}(y(s)), y(s) \rangle \, ds \leq \frac{1}{2} |y_0|^2 + \int_0^t \langle f(s), y(s) \rangle_{V^*, V} \, ds
\]

\[
+ \lambda \int_0^t |y(s)|^2 \, ds.
\]

Using (4.19) we obtain

\[
\frac{1}{2} |y(t)|^2 + k_1 \int_0^t |y(s)|_{V^*}^2 \, ds \leq \frac{1}{2} |y_0|^2 + \int_0^t \langle f(s), y(s) \rangle_{V^*, V} \, ds
\]

\[
+ (\tilde{L} + \lambda + \frac{1}{2}) \int_0^t |y(s)|^2 \, ds + \frac{1}{2} c^2 T
\]

since

\[
\langle \tilde{g}(y(s)), y(s) \rangle \geq -|\langle \tilde{g}(y(s)), y(s) \rangle|
\]

\[
\geq -|\tilde{g}(y(s))| |y(s)|
\]

\[
\geq -(\tilde{L} |y(s)| + c) |y(s)|
\]

\[
\geq -\tilde{L} |y(s)|^2 - \frac{1}{2} c^2 - \frac{1}{2} |y(s)|^2.
\]

Now we apply the Cauchy-Schwarz inequality and the inequality \( 2ab \leq a^2 + b^2 \):

\[
|y(t)|^2 + k_1 \int_0^t |y(s)|_{V^*}^2 \, ds \leq \left[ |y_0|^2 + c^2 T + \frac{1}{k_1} \int_0^T |f(s)|_{V^*}^2 \, ds \right] + \int_0^t \tilde{L} |y(s)|^2 \, ds, \quad (4.24)
\]
where $\hat{L} = 2\tilde{L} + 2\lambda + 1$. If we ignore the second term on the left side of (4.24) and apply Gronwall’s inequality, we obtain
\[
|y(t)|^2 \leq e^{Lt} \left[ |y_0|^2 + c^2T + \frac{1}{k_1} \int_0^T |f(s)|^2_{V^*} \, ds \right]
\leq e^{\tilde{L}T} \left[ |y_0|^2 + c^2T + \frac{1}{k_1} \int_0^T |f(s)|^2_{V^*} \, ds \right]
= \tilde{C}(\hat{L}, y_0, T, k_1, f, c).
\tag{4.25}
\]
This bound (4.25) can then be substituted into the right side of (4.24):
\[
|y(t)|^2 + k_1 \int_0^t |y(s)|^2_{V^*} \, ds \leq |y_0|^2 + \frac{1}{k_1} \int_0^T |f(s)|^2_{V^*} \, ds + c^2T + \hat{L} \tilde{C}T
= \hat{C}(k_1, f, y_0, c, \tilde{L}, \tilde{C}).
\tag{4.26}
\]
This establishes an \textit{a priori} bound for the system (4.22) – (4.23).

Next we define the “Galerkin” approximations for (4.20) by
\[
y^N(t) = \sum_{k=1}^N c_k^N(t) \psi_k,
\]
where $\{\psi_k\}_{k=1}^\infty \subset V$ is a linearly independent total subset of $V$, and where $\{c_k^N(t)\}_{k=1}^N$ are chosen so that $y^N(t)$ is the unique solution of
\[
\langle \dot{y}^N(t), \psi_j \rangle + \sigma(y^N(t), \psi_j) + \langle \tilde{g}(y^N(t)), \psi_j \rangle = \langle f(t), \psi_j \rangle_{V^*, V}
\tag{4.27}
\]
for $j = 1, \ldots, N$ with $c_k^N(0) = c_{0k}^N$. Since $\{\psi_k\}_{k=1}^\infty$ is a total subset of $V$, we can and do choose the constants $\{c_{0k}^N\}$ so that
\[
y_0 = \lim_{N \to \infty} \sum_{k=1}^N y_0^N = \lim_{N \to \infty} \sum_{k=1}^N c_{0k}^N \psi_k \quad \text{in} \quad V.
\tag{4.28}
\]
Now we multiply (4.27) by $c_j^N(t)$ and sum over $j = 1, \ldots, N$:
\[
\frac{1}{2} \frac{d}{dt} \left[ |y^N(t)|^2 \right] + \sigma(y^N(t), y^N(t)) + \langle \tilde{g}(y^N(t)), y^N(t) \rangle = \langle f(t), y^N(t) \rangle_{V^*, V}
+ \frac{1}{2} \frac{d}{dt} \left[ |y^N(0)|^2 \right].
\]
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Note that $|y_0^N|_V$ is uniformly bounded by some constant $K_0$ since $y_0^N$ converges strongly to $y_0$ as in (4.28), and therefore we can use arguments similar to those above to obtain the a priori estimate

$$|y^N(t)|^2 + k_1 \int_0^t |y^N(s)|^2_V \, ds \leq \hat{c}(k_1, f, K_0, c, T, \hat{L}, \hat{C})$$

(4.29)

for some $\hat{c}$ which is independent of $N$.

Next we turn to the convergence of the Galerkin approximations. Note that (4.29) implies that $\{y^N\}$ is bounded in $L^2((0, T); V)$ and that $\{y^N(t)\}$ is bounded in $H$ for each $t \in [0, T]$. Therefore there exists $y \in L^2((0, T); V)$ and a subsequence of $\{y^N\}$ (which we will denote by $\{y^N\}$) such that

$$y^N \rightharpoonup y \quad \text{in} \quad L^2((0, T); V)$$

(4.30)

$$y^N(t) \rightharpoonup y(t) \quad \text{in} \quad H \quad \text{for each} \quad t \in [0, T].$$

(4.31)

Moreover, (4.19) and (4.29) imply

$$\int_0^t |\tilde{g}(y^N(s))|^2 \, ds \leq \int_0^t \left( \tilde{L} |y^N(s)| + c \right)^2 \, ds$$

$$= \int_0^t \left( \tilde{L}^2 |y^N(s)|^2 + 2\tilde{L} c |y^N(s)| + c^2 \right) \, ds$$

$$\leq T(\tilde{L}^2 \hat{c}^2 + 2\tilde{L} \hat{c} + c^2)$$

and hence $\{\tilde{g}(y^N)\}$ is bounded in $L_2((0, T); H)$. Therefore there exists $h \in L_2((0, T); H)$ such that

$$\tilde{g}(y^N) \rightharpoonup h \quad \text{in} \quad L_2((0, T); H).$$

(4.32)

Next we establish that $y$ is a solution to (4.22), (4.23). Let $P_M$ be the class of functions $\eta \in L_2((0, T); V)$ that can be represented in the form

$$\eta(t) = \sum_{k=1}^M a_k(t) \psi_k,$$
where $a_k \in C^1[0, T]$. Moreover, we define $P = \bigcup_{M=1}^{\infty} P_M$, which implies that $P$ is dense in $L_2((0, T); \mathcal{V})$.

Multiply (4.27) by $a_j(t)$, then sum from 1 to $M$ and integrate over $[0, t]$, integrating by parts in the first term:

$$
\int_0^t [ - \langle y^N(s), \dot{\eta}(s) \rangle + \sigma(y^N(s), \eta(s)) + \langle g(y^N(s)), \eta(s) \rangle ] ds + \langle y^N(t), \eta(t) \rangle
= \langle y^N(0), \eta(0) \rangle + \int_0^t \langle f(s), \eta(s) \rangle_{\mathcal{V}^*, \mathcal{V}} ds \\
(4.33)
$$

for all $\eta \in P_M$ with $M \leq N$.

Now fix $\eta \in P_M$ for $M \leq N$, and take the limit as $N \to \infty$ in (4.33) to obtain

$$
\int_0^t [ - \langle y(s), \dot{\eta}(s) \rangle + \sigma(y(s), \eta(s)) + \langle h(s), \eta(s) \rangle ] ds + \langle y(t), \eta(t) \rangle
= \langle y_0, \eta(0) \rangle + \int_0^t \langle f(s), \eta(s) \rangle_{\mathcal{V}^*, \mathcal{V}} ds \\
(4.34)
$$

for any $t \in [0, T]$. Note that we may pass to the limit $N \to \infty$ in the first term since we have the weak convergence of $y^N \rightharpoonup y$ in $L_2((0, T); \mathcal{H})$. In considering the second term, we note that for fixed $\eta \in \mathcal{V}$, Assumption (A1) implies that the mapping $y \to \int_0^t \sigma(y(s), \eta(s)) ds$ is a bounded linear functional with domain $L_2((0, T); \mathcal{V})$, and hence this mapping is weakly continuous. Therefore the convergence of $y^N$ in (4.30) allows us to pass to the limit in the second term. Moreover, we may pass to the limit in the third and fourth terms because of the convergences (4.32) and (4.31), respectively. Finally, the strong convergence of $y^N(0) \to y_0$ as in (4.28) allows us to pass to the limit in the first term on the right side of (4.34).

Note that the $M$ we chose above was arbitrary, so for each $j$ we may replace $\eta$ in (4.34) by $\eta_j(t) = a(t) \psi_j$, where $a \in C^\infty_0[0, T]$, and then integrate from 0 to $T$:

$$
\int_0^T \dot{a}(s) \langle -y(s), \psi_j \rangle ds + \int_0^T a(s) \left[ \sigma(y(s), \psi_j) + \langle h(s), \psi_j \rangle - \langle f(s), \psi_j \rangle_{\mathcal{V}^*, \mathcal{V}} \right] ds = 0.
$$

Since $\{\psi_j\}$ is total in $\mathcal{V}$, we have

$$
\int_0^T \dot{a}(s) \langle -y(s), \psi \rangle ds + \int_0^T a(s) \left[ \sigma(y(s), \psi) + \langle h(s), \psi \rangle - \langle f(s), \psi \rangle_{\mathcal{V}^*, \mathcal{V}} \right] ds = 0
$$
for every $\psi \in \mathcal{V}$. This equation holds for every $a \in C^0_0[0,T]$, which implies that

$$\dot{y} \in L_2((0,T);\mathcal{V}^*) \simeq L_2((0,T);\mathcal{V}^*)$$

and

$$\langle \dot{y}(t), \psi \rangle_{\mathcal{V}^{*},\mathcal{V}} + \sigma(y(t), \psi) + \langle h(t), \psi \rangle = \langle f(t), \psi \rangle_{\mathcal{V}^{*},\mathcal{V}}$$

(4.35)

for each $\psi \in \mathcal{V}$ and for almost every $t \in [0,T]$. Moreover, since $y \in L_2((0,T);\mathcal{V})$ and $\dot{y} \in L_2((0,T);\mathcal{V}^*)$, it follows from Theorem 3.1 in [46, p. 19] that $y \in C([0,T];\mathcal{H})$.

To show that $y(0) = y_0$, consider (4.34) with $\eta = \eta_j = a(t)\psi_j$, $a \in C^1[0,T]$ and $a(0) \neq 0$, integrating by parts in the first term:

$$\int_0^t [\langle \dot{y}(s), \eta(s) \rangle_{\mathcal{V}^{*},\mathcal{V}} + \sigma(y(s), \eta(s)) + \langle h(s), \eta(s) \rangle]ds + \langle y(t), \eta(t) \rangle$$

$$+ \langle -y(s), \eta(s) \rangle|_{s=0}^{s=t} = \langle y_0, \eta(0) \rangle + \int_0^t \langle f(s), \eta(s) \rangle_{\mathcal{V}^{*},\mathcal{V}} ds.$$

With (4.35) we obtain

$$\langle y(t), \eta(t) \rangle + \langle -y(s), \eta(s) \rangle|_{s=0}^{s=t} = \langle y_0, \eta(0) \rangle,$$

and hence

$$\langle y(0), \psi_j \rangle a(0) = \langle y_0, \psi_j \rangle a(0)$$

for all $j$. Therefore $y(0) = y_0$.

Finally, we show that $h = \tilde{g}(y)$. If we let $z^N(t) = y^N(t) - y(t) \in L_2((0,T);\mathcal{V}) \cap C([0,T];\mathcal{H})$, and combine (4.27) with $\psi_j = y^N(t)$ and (4.35) with $\psi = y(t)$, integrating from 0 to $t$ and adding, we obtain

$$|z^N(t)|^2 + 2 \int_0^t \sigma(z^N(s), z^N(s))ds = |y^N(0) - y_0|^2 + 2 \int_0^t \langle f(s), z^N(s) \rangle_{\mathcal{V}^{*},\mathcal{V}} ds - 2 \int_0^t \langle \tilde{g}(y^N(s)) - h(s), z^N(s) \rangle ds - 2 \int_0^t \langle h(s), y^N(s) \rangle ds - 2 \int_0^t \langle \tilde{g}(y^N(s)), y(s) \rangle ds - 2 \langle y(t), y^N(t) \rangle + 2 \langle y_0, y^N(0) \rangle$$
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\[ - 2 \int_0^t \sigma(y^N(s), y(s)) ds \\
- 2 \int_0^t \sigma(y(s), y^N(s)) ds \\
+ 4 \int_0^t \langle f(s), y(s) \rangle_{\mathcal{V}^*, \mathcal{V}} ds. \]  \hspace{1cm} (4.36)

Note that

\[ 2 \int_0^t \langle \tilde{g}(y^N(s)) - h(s), z^N(s) \rangle ds = 2 \int_0^t \langle \tilde{g}(y^N(s)) - \tilde{g}(y(s)), z^N(s) \rangle ds \\
+ 2 \int_0^t \langle \tilde{g}(y(s)) - h(s), z^N(s) \rangle ds \]

and applying (4.18) we have

\[ \left| 2 \int_0^t \langle \tilde{g}(y^N(s)) - \tilde{g}(y(s)), z^N(s) \rangle ds \right| \leq 2 \int_0^t \tilde{L} |y^N(s) - y(s)| |z^N(s)| ds \\
= 2\tilde{L} \int_0^t |z^N(s)|^2 ds. \]

Therefore (4.36) becomes

\[ |z^N(t)|^2 + 2 \int_0^t \sigma(z^N(s), z^N(s)) ds \leq |y^N(0) - y_0|^2 + 2\tilde{L} \int_0^t |z^N(s)|^2 ds \\
+ |X^N(t)| + |Y^N(t)|, \] \hspace{1cm} (4.37)

where

\[ X^N(t) = 2 \left[ -\langle y(t), y^N(t) \rangle - \int_0^t \sigma(y(s), y^N(s)) ds \right. \\
- \int_0^t \sigma(y^N(s), y(s)) ds + \langle y_0, y^N(0) \rangle \\
- \int_0^t \langle \tilde{g}(y^N(s)), y(s) \rangle ds - \int_0^t \langle h(s), y^N(s) \rangle ds + 2 \int_0^t \langle f(s), y(s) \rangle_{\mathcal{V}^*, \mathcal{V}} ds \right], \]

\[ Y^N(t) = 2 \int_0^t \langle \tilde{g}(y(s)) - h(s), z^N(s) \rangle ds + 2 \int_0^t \langle f(s), z^N(s) \rangle_{\mathcal{V}^*, \mathcal{V}} ds. \]

Next we use (4.12) in (4.37) to obtain

\[ |z^N(t)|^2 + 2 \int_0^tk_1 |z^N(s)|^2_{\mathcal{V}} ds \leq |y^N(0) - y_0|^2 + 2(\tilde{L} + \lambda) \int_0^t |z^N(s)| ds \\
+ |X^N(t)| + |Y^N(t)|. \] \hspace{1cm} (4.38)
Note that (4.28) and (4.30) imply that \( |y^N(0) - y_0|^2 \to 0 \) and \( |Y^N(t)| \to 0 \) respectively. It can also be shown that \( |X^N(t)| \to 0 \) by taking the limit as \( N \to \infty \) and using the convergences (4.31), (4.30), (4.28) and (4.32):

\[
X^N(t) \to 2 \left[ -|y(t)|^2 - 2 \int_0^t \sigma(y(s), y(s))ds + |y_0|^2 \right]
- 2 \int_0^t \langle h(s), y(s) \rangle ds + 2 \int_0^t \langle f(s), y(s) \rangle_{\mathcal{V}^*, \mathcal{V}} ds,
\]

which is two times the integrated form of (4.35) with \( \psi = y \). Therefore \( |X^N(t)| \to 0 \) and (4.38) becomes

\[
|z^N(t)|^2 + 2 \int_0^t k_1 |z^N(s)|_V^2 ds \leq \hat{L} \int_0^t |z^N(s)|_V^2 ds + W^N(t),
\]

where \( \hat{L} = 2(\bar{L} + \lambda) \), and where \( W^N(t) = |y^N(0) - y_0|^2 + |X^N(t)| + |Y^N(t)| \to 0 \) as \( N \to \infty \). Using Gronwall’s inequality we obtain

\[
|z^N(t)|^2 \leq W^N(t) + \int_0^t \hat{L} W^N(s)e^{\hat{L}t - \hat{L}s} ds
\]

\[
\leq W^N(t) + \hat{L} e^{\hat{L}t} \int_0^t W^N(s) ds
\]

\[
\to 0,
\]

which implies that \( |z^N(t)|^2 \to 0 \) for \( t \in [0, T] \) and hence \( y^N(t) \to y(t) \) in \( \mathcal{H} \) for each \( t \). It follows that

\[
\int_0^t |\tilde{g}(y^N(s)) - \tilde{g}(y(s))|^2 ds \leq \bar{L}^2 \int_0^t |y^N(s) - y(s)|^2 ds \to 0
\]

and hence \( \tilde{g}(y^N) \to \tilde{g}(y) \) in \( L_2((0, T); \mathcal{H}) \). Since (4.32) implies that \( \tilde{g}(y^N) \overset{\text{w}}{\to} h \) in \( L_2((0, T); \mathcal{H}) \), we have \( h = \tilde{g}(y) \) in \( L_2((0, T); \mathcal{H}) \) and therefore

\[
\langle h, \psi \rangle = \langle \tilde{g}(y), \psi \rangle
\]

for every \( \psi \in \mathcal{V} \). This establishes that \( y \) is a weak solution of (4.22), (4.23).

Next we address the uniqueness of weak solutions. Let \( y, \tilde{y} \) be weak solutions of (4.22), (4.23) on \([0, T]\) with \( y_0 \) and \( f \). Then \( w = y - \tilde{y} \) satisfies

\[
\langle \dot{w}(t), \psi \rangle_{\mathcal{V}^*, \mathcal{V}} + \sigma(w(t), \psi) + \langle \tilde{g}(y(t)), \psi \rangle - \langle \tilde{g}(\tilde{y}(t)), \psi \rangle = 0 \quad (4.39)
\]

for every \( \psi \in \mathcal{V} \).
for $\psi \in \mathcal{V}$, with $w(0) = 0$. Note that (4.39) also holds for $\psi \in L_2((0,T);\mathcal{V})$.

Now let $\Delta \tilde{g} = \tilde{g}(y) - \tilde{g}(\tilde{y})$, and let $\psi = w(t)$ in (4.39), integrating from $0$ to $t$:

$$
\int_0^t [\langle \tilde{w}(s), w(s) \rangle_{\mathcal{V}^*, \mathcal{V}} + \sigma(w(s), w(s)) + \langle \Delta \tilde{g}(s), w(s) \rangle] ds = 0,
$$

and hence

$$
|w(t)|^2 + 2 \int_0^t [\sigma(w(s), w(s)) + \langle \Delta \tilde{g}(s), w(s) \rangle] ds = 0.
$$

We then apply (4.12) and (4.18) to obtain the bound

$$
|w(t)|^2 + 2k_1 \int_0^t |w(s)|_{\mathcal{V}}^2 ds \leq 2 \int_0^t -\langle \Delta \tilde{g}(s), w(s) \rangle ds + 2\lambda \int_0^t |w(s)|^2 ds \\
\leq 2 \int_0^t |\Delta \tilde{g}(s)| |w(s)| ds + 2\lambda \int_0^t |w(s)|^2 ds \\
\leq 2 \int_0^t (\tilde{L} + \lambda) |w(s)|^2 ds.
$$

It follows from Gronwall’s inequality that

$$
|w(t)|^2 \leq 0
$$

and therefore the weak solution $y$ of (4.22), (4.23) is unique.

Finally, we show the existence of a weak solution for the original problem (4.16), (4.17) on some interval in time. Since the weak solution $y$ of (4.22), (4.23) satisfies $y \in C([0,T];\mathcal{H})$, there exists $t^* \in [0,T]$ such that

$$
|y(t) - y_0| \leq 1
$$

for all $t \in [0,t^*]$. Therefore $y(t) \in B_1(y_0)$ for all $t \in [0,t^*]$, which further implies that $\tilde{g}(y(t)) = g(\mathcal{P}y(t)) = g(y(t))$ for all $t \in [0,t^*]$. It follows that $y$ is a weak solution of (4.16), (4.17) on the interval $[0,t^*]$. The uniqueness of the solution $y$ can be shown as above. This completes the proof of the theorem.

The existence of a unique global weak solution to (4.16), (4.17) can now be shown using the additional assumption (A5).
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Theorem 4.1.2 Under Assumptions (A1) - (A5) with \( y_0 \in \mathcal{H} \), the system (4.16), (4.17) has a unique global weak solution \( y \in L_2((0,T); \mathcal{V}) \cap C([0,T]; \mathcal{H}) \) which depends continuously on the data \( (y_0, f) \).

Proof: Let \( y^N(t) = \sum_{k=1}^N c_k^N(t) \psi_k \), where \( \{c_k^N(t)\} \) are chosen so that \( y^N(t) \) is a solution of the finite dimensional system of equations derived from (4.16), (4.17) with \( \psi_k \) as test functions. Moreover, we choose the constants \( c_{0k}^N \) so that

\[
y_0 = \lim_{N \to \infty} \sum_{k=1}^N y_0^N \equiv \lim_{N \to \infty} c_{0k}^N \psi_k \quad \text{in } \mathcal{V}.
\]  

As before we obtain

\[
|y^N(t)|^2 + 2 \int_0^t \sigma(y^N(s), y^N(s))ds + 2 \int_0^t \langle g(y^N(s)), y^N(s) \rangle ds = 2 \int_0^t \langle f(s), y^N(s) \rangle_{\mathcal{V}^*, \mathcal{V}} + |y^N(0)|^2 ds,
\]

and (4.12) and (4.15) imply

\[
|y^N(t)|^2 + 2k_1 \int_0^t |y^N(s)|_{\mathcal{V}}^2 ds \leq -2 \int_0^t \langle g(y^N(s)), y^N(s) \rangle ds
\]

\[
+ 2 \int_0^t \langle f(s), y^N(s) \rangle_{\mathcal{V}^*, \mathcal{V}} ds + |y^N(0)|^2
\]

\[
+ 2 \lambda \int_0^t |y^N(s)|^2 ds
\]

\[
\leq 2 \int_0^t |g(y^N(s))| |y^N(s)| ds
\]

\[
+ 2 \int_0^t |f(s)|_{\mathcal{V}^*} |y^N(s)|_{\mathcal{V}} ds + |y_0^N|^2
\]

\[
+ 2 \lambda \int_0^t |y^N(s)|^2 ds
\]

\[
\leq 2 \int_0^t (C_2 |y^N(s)| + C_3) |y^N(s)| ds
\]

\[
+ 2 \int_0^t |f(s)|_{\mathcal{V}^*} |y^N(s)|_{\mathcal{V}} ds + |y_0^N|^2
\]

\[
+ 2 \lambda \int_0^t |y^N(s)|^2 ds
\]
Therefore
\[
|y^N(t)|^2 + k_1 \int_0^t |y^N(s)|_V^2 \, ds \leq |y_0^N|^2 + \int_0^t \frac{1}{k_1} |f(s)|_V^2 \, ds + C_3^2 T
\]
\[
+ \int_0^t (2C_2 + 1 + 2\lambda) |y^N(s)|^2 \, ds.
\]

Note that (4.40) implies that $|y_0^N|^2$ is uniformly bounded by some constant $C_0$ independent of $N$, and it follows from Gronwall’s inequality that
\[
|y^N(t)|^2 \leq \hat{C}(y_0, k_1, C_3, T, C_2, \lambda, f, C_0)
\]  
and as before
\[
|y^N(t)|^2 + k_1 \int_0^t |y^N(s)|_V^2 \, ds \leq \hat{C}_1
\]
for $t \in [0, T]$, where $T$ is arbitrary.

This implies that there exists $y \in L_2((0,T);\mathcal{V})$ and a subsequence of $\{y^N\}$ such that
\[
y^N \overset{w}{\rightharpoonup} y \quad \text{in} \ L_2((0,T);\mathcal{V})
\]
\[
y^N(t) \rightharpoonup y(t) \quad \text{in} \ \mathcal{H}
\]
\[
g(y^N) \overset{w}{\rightharpoonup} h \quad \text{in} \ L_2((0,T);\mathcal{H}).
\]

In addition, we use the weak lower semicontinuity of norms to obtain
\[
|y(t)|^2 \leq \liminf_{N \to \infty} |y^N(t)|^2 \leq \hat{C}
\]  
for $t \in [0, T]$. Therefore $y(t) \in B_{\sqrt{\hat{C}}(0)}$ in $\mathcal{H}$, and the arguments of Theorem 4.1.1 imply that $y$ is the unique global weak solution to (4.16), (4.17).
To prove continuous dependence, we consider solutions $y$ and $\tilde{y}$ in $L_2((0,T);V)$ to (4.16), (4.17) with initial conditions $y_0$ and $\tilde{y}_0$ and forcing functions $f$ and $\tilde{f}$, respectively. Note that since $y \in L_2((0,T);V)$ satisfies (4.16) with $y(0) = y_0$, we can use arguments similar to those used earlier in this proof for $y^N(t)$ to obtain the bound

$$|y(t)|^2 + k_1 \int_0^t |y(s)|_V^2 \, ds \leq |y_0|^2 + \int_0^t \frac{1}{k_1} |f(s)|_{V^*}^2 \, ds + C_3^2 T$$

and hence

$$|y(t)|^2 \leq \hat{C}(y_0, k_1, C_3, T, C_2, f, \lambda) = \hat{C}_2.$$ Similarly,

$$|	ilde{y}(t)|^2 \leq \hat{C}(|\tilde{y}_0|, k_1, C_3, T, C_2, \tilde{f}, \lambda) = \hat{C}_3.$$ Therefore $y(t) \in B_{\sqrt{\hat{C}_2}}$ and $\tilde{y}(t) \in B_{\sqrt{\hat{C}_3}}$, which imply that

$$|g(y(t)) - g(\tilde{y}(t))| \leq L_{B_{\hat{C}_4}} |y(t) - \tilde{y}(t)|,$$ (4.43)

where $\hat{C}_4 = \max\{\sqrt{\hat{C}_2}, \sqrt{\hat{C}_3}\}$.

Now consider $w(t) \equiv y(t) - \tilde{y}(t)$, which satisfies $w(0) = y_0 - \tilde{y}_0$ and

$$\langle \dot{w}(t), \psi \rangle_{V^*,V} + \sigma(w(t), \psi) + \langle \Delta g(t), \psi \rangle = \langle \hat{f}(t), \psi \rangle_{V^*,V}$$ (4.44)

for all $\psi \in V$, where $\Delta g(t) = g(y(t)) - g(\tilde{y}(t))$ and $\hat{f}(t) = f(t) - \tilde{f}(t)$. Note that (4.44) is also satisfied for all $\psi \in L_2((0,T);V)$.

For fixed $t \in [0,T]$ we choose $\psi = w(t) \in V$ in (4.44) and integrate from 0 to $t$:

$$\int_0^t [\langle \dot{w}(s), w(s) \rangle_{V^*,V} + \sigma(w(s), w(s)) + \langle \Delta g(s), w(s) \rangle] \, ds = \int_0^t \langle \hat{f}(s), w(s) \rangle_{V^*,V} \, ds.$$ The conditions (4.12) and (4.43) imply that

$$|w(t)|^2 + 2k_1 \int_0^t |w(s)|_V^2 \, ds \leq |w(0)|^2 + \int_0^t \langle \Delta g(s), w(s) \rangle \, ds \quad + \quad 2 \int_0^t \langle \hat{f}(s), w(s) \rangle_{V^*,V} \, ds + 2\lambda \int_0^t |w(s)|^2 \, ds$$
\[ \leq |w(0)|^2 + \int_0^t 2(L_{Bc_4} + \lambda) |w(s)|^2 \, ds \\
+ \frac{1}{k_1} \int_0^t \left| \hat{f}(s) \right|^2_{V^*} \, ds + k_1 \int_0^t |w(s)|^2_{V^*} \, ds \]

and hence
\[ |w(t)|^2 + k_1 \int_0^t |w(s)|^2_{V^*} \, ds \leq |w(0)|^2 + \int_0^t 2(L_{Bc_4} + \lambda) |w(s)|^2 \, ds \\
+ \frac{1}{k_1} \int_0^T \left| \hat{f}(s) \right|^2_{V^*} \, ds. \]

The application of Gronwall’s inequality then yields
\[ |w(t)|^2 \leq e^{2(L_{Bc_4} + \lambda)T} \left( |w(0)|^2 + \frac{1}{k_1} \int_0^T \left| \hat{f}(s) \right|^2_{V^*} \, ds \right) \]
for all \( t \in [0, T] \). Therefore we have shown continuous dependence in \( C([0, T]; \mathcal{H}) \) on the initial data \((y_0, f)\). This completes the proof of Theorem 4.1.2.

### 4.1.3 Well-posedness for the TCE model

In this section we verify that the TCE model fits into the class of abstract nonlinear parabolic systems discussed in the previous section. This will establish the well-posedness of the TCE model.

Consider the weak formulation (4.3) of the TCE model with the definitions of \( \mathcal{V}, \mathcal{H} \) and the inner products as outlined in Section 4.1.1. The spaces \( \mathcal{V} \) and \( \mathcal{H} \) form a Gelfand triple as discussed in Section 4.1.2 with the duality product \( \langle \cdot, \cdot \rangle_{\mathcal{V}^*, \mathcal{V}} \). We use
the following norms as defined in Section 4.1.1:

\[
|u|_B^2 = \int_{1}^{\pi-\varepsilon_2} |u(\phi)|^2 \sin \phi \, d\phi \quad \text{for } u \in L^2(\Omega_B),
\]

\[
|u|_{H^1_B}^2 = \int_{1}^{\pi-\varepsilon_2} \left( |\nabla u(\phi)|^2 + |u(\phi)|^2 \right) \sin \phi \, d\phi \quad \text{for } u \in H^1(\Omega_B),
\]

\[
|u|_{H^1_A}^2 = \int_{0}^{2\pi} \int_{0}^{\pi} |u(\theta, \phi)|^2 \sin \phi \, d\phi \, d\theta \quad \text{for } u \in L^2(\Omega_A),
\]

\[
|u|_{H^1_{IA}}^2 = \int_{0}^{2\pi} \int_{0}^{\pi} \left( |\nabla u(\theta, \phi)|^2 + |u(\theta, \phi)|^2 \right) \sin \phi \, d\phi \, d\theta \quad \text{for } u \in H^1_{per}(\Omega_A),
\]

\[
|u|_{V}^2 = |u|_{H^1_B}^2 + |u|_{H^1_A}^2 + |u|_{H^1_{IA}}^2 + \sum_{i=4}^{9} |u_i|^2 \quad \text{for } u \in V,
\]

\[
|u|_{H}^2 = |u|_{B}^2 + |u|_{IA}^2 + |u|_{IA}^2 + \sum_{i=4}^{9} |u_i|^2 \quad \text{for } u \in H.
\]

The forcing function \( f \) given by (4.6) satisfies \( f \in L^2((0, T); V^*) \) and hence Assumption (A3) holds for the TCE model.

It can be shown that the nonlinear function \( g \) satisfies Assumption (A4). Let \( r > 0 \) and \( u, v \in B_r(0) \). If \( u_9, v_9 \in \mathbb{R} \) are both nonnegative, then

\[
|g(u) - g(v)|_H = |g_9(u_9) - g_9(v_9)|_\mathbb{R} = \frac{s_3 u_9 - s_3 v_9}{1 + s_4 u_9 - 1 + s_4 v_9} |_{\mathbb{R}}
\]

\[
= \left| \frac{s_3 (u_9 - v_9)}{(1 + s_4 u_9)(1 + s_4 v_9)} \right|_{\mathbb{R}} 
\]

\[
\leq \frac{|s_3 (u_9 - v_9)|_{\mathbb{R}}}{(1 + s_4 u_9)(1 + s_4 v_9)} 
\]

\[
\leq s_3 |u_9 - v_9|_{\mathbb{R}} 
\]

since \( u_9, v_9 \geq 0 \) implies that \( (1 + s_4 u_9) \geq 1 \) and \( (1 + s_4 v_9) \geq 1 \). Now suppose that \( u_9 \geq 0 \) and \( v_9 < 0 \), then

\[
|g(u) - g(v)|_H = |g_9(u_9) - g_9(v_9)|_\mathbb{R} = \left| \frac{s_3 u_9}{1 + s_4 u_9} - 0 \right|_{\mathbb{R}}
\]
A similar argument can be used for the case $u_9 < 0$ and $v_9 \geq 0$. Finally, if $u_9, v_9 < 0$, then

$$|g(u) - g(v)|_{\mathcal{H}} = |g_9(u_9) - g_9(v_9)|_{\mathcal{H}}$$

$$= 0$$

$$\leq s_3 |u - v|_{\mathcal{H}}.$$ 

Therefore Assumption (A4) is satisfied for the nonlinear function $g$.

The nonlinearity $g$ also satisfies Assumption (A5) since for $u \in \mathcal{H}$ with $u_9 \geq 0$, we have

$$|g(u)|_{\mathcal{H}} = \frac{s_3 u_9}{1 + s_4 u_9}$$

$$\leq s_3 u_9$$

$$\leq s_3 |u|_{\mathcal{H}}$$

and for $u \in \mathcal{H}$ with $u_9 < 0$ we have

$$|g(u)|_{\mathcal{H}} = 0$$

$$\leq |u|_{\mathcal{H}}.$$ 

Finally, we address the conditions imposed on the sesquilinear form $\sigma$. Specifically, we prove that $\sigma$ satisfies the conditions of Assumptions (A1) and (A2).

**Lemma 4.1.1** The form $\sigma$ in (4.4) is sesquilinear form on $\mathcal{V}$ satisfying (A1) and (A2).

**Proof:** Recall that for $u \in H^1(\bar{\Omega}_B)$ we have

$$\nabla u = \left( \frac{\partial u}{\partial r}, \frac{1}{r \sin \phi} \frac{\partial u}{\partial \theta}, \frac{1}{r} \frac{\partial u}{\partial \phi} \right) = \left( 0, 0, \frac{1}{r_1} \frac{\partial u}{\partial \phi} \right),$$
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and for \( u \in H^1(\Omega_{IA}) \) we have

\[
\nabla u = \left( \frac{\partial u}{\partial r}, \frac{1}{r} \frac{\partial u}{\partial \phi} \right) = \left( 0, \frac{1}{r_1} \frac{\partial u}{\partial \phi} \right).
\]

Moreover, the definitions of the norms \(| \cdot |_B\), \(| \cdot |_{H^1_B}\), \(| \cdot |_{IA}\) and \(| \cdot |_{H^1_{IA}}\) imply that

\[
|u|_B \leq |u|_{H^1_B} \tag{4.45}
\]

\[
|u|_{IA} \leq |u|_{H^1_{IA}}. \tag{4.46}
\]

Now consider the trace operator \( T^0_{\theta_0} : H^1(\Omega_{IA}) \to L^2(\Gamma) \) as in (4.1), where

\[
T^0_{\theta_0} u(\theta, \phi) = u(\theta, \phi)|_{\theta = \theta_0} \tag{4.47}
\]

for \( u \in H^1_{IA} \). As in Section 4.1.1, the Trace Theorem implies that there exists \( K_1 > 0 \) such that

\[
|T^0_{\theta_0} u|_B \leq K_1 |u|_{H^1_{IA}} \tag{4.48}
\]

for any \( u \in H^1_{IA} \). It can also be shown that every \( u \in H^1(\Omega_B) \) is absolutely continuous, and that

\[
|u(\varepsilon_1)|_R \leq K_2 |u|_{H^1_B} \tag{4.49}
\]

\[
|u(\pi - \varepsilon_2)|_R \leq K_2 |u|_{H^1_B} \tag{4.50}
\]

for some \( K_2 > 0 \).

Clearly \( \sigma \) is a sesquilinear form on \( V \), and using the inequalities (4.45), (4.46) and (4.48) – (4.50) we obtain

\[
|\sigma(u, v)|_R \leq \left| \langle a_1 \frac{\partial u_1}{r_1 \partial \phi}, \frac{1}{r_1} \frac{\partial v_1}{\partial \phi} \rangle \right|_R + \left| \langle a_2 u_1, \frac{1}{r_1} \frac{\partial v_1}{\partial \phi} \rangle \right|_R + \left| \langle a_3 u_1 - a_4 T^0_{\theta_0} u_2, v_1 \rangle \right|_R
\]

\[
+ \left| \langle b_1 \frac{\partial u_2}{r_1 \sin \phi \partial \theta}, \frac{1}{r_1 \sin \phi} \frac{\partial v_2}{\partial \theta} \rangle \right|_{IA} + \left| \langle b_1 \frac{\partial u_2}{r_1 \partial \phi}, \frac{1}{r_1} \frac{\partial v_2}{\partial \phi} \rangle \right|_{IA}
\]

\[
+ \left| \langle -b_2 u_1 + b_3 T^0_{\theta_0} u_2, T^0_{\theta_0} v_2 \rangle \right|_R + \left| \langle b_4 u_2 - b_5 u_3, v_2 \rangle \right|_{IA}
\]

\[
+ \left| \langle c_1 \frac{\partial u_3}{r_1 \sin \phi \partial \theta}, \frac{1}{r_1 \sin \phi} \frac{\partial v_3}{\partial \theta} \rangle \right|_{IA} + \left| \langle c_1 \frac{\partial u_3}{r_1 \partial \phi}, \frac{1}{r_1} \frac{\partial v_3}{\partial \phi} \rangle \right|_{IA}
\]
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\[ + \left| -c_2 u_1 + c_3 T_0^0 u_3, T_0^0 v_3 \right|_B + \left| c_4 u_3 - c_5 u_2, v_3 \right| \left| T_0^0 v_3 \right|_B \]

\[ + \left| -d_1 u_1 (\pi - \varepsilon_2) + d_2 u_4 - d_3 u_5 - d_4 u_6 - d_5 u_7 - d_6 u_8 - d_7 u_9 \right| v_4 \left| v_3 \right|_B \]

\[ + \left| -e_1 u_4 + e_2 u_5 \right| v_5 \left| v_3 \right|_B + \left| -h_1 u_4 + h_2 u_6 \right| v_6 \left| v_3 \right|_B + \left| -\ell_1 u_4 + \ell_2 u_7 \right| v_7 \left| v_3 \right|_B \]

\[ + \left| -p_1 u_4 + p_2 u_8 \right| v_8 \left| v_3 \right|_B + \left| -s_1 u_4 + s_2 u_9 \right| v_9 \left| v_3 \right|_B \]

\[ \leq a_1 \left| \frac{1}{r_1} \frac{\partial u_1}{\partial \phi} \right|_{r_1} + \frac{1}{r_1} \frac{\partial v_1}{\partial \phi} + a_2 \left| u_1 \right|_{r_1} + a_3 \left| u_1 \right|_{r_1} \left| v_1 \right|_{r_1} \]

\[ + a_4 \left| T_0^0 u_2 \right|_{r_1} \left| v_1 \right|_{r_1} + a_5 \left| u_1 \right|_{r_1} + a_6 \left| T_0^0 u_3 \right|_{r_1} \left| v_1 \right|_{r_1} \]

\[ + a_7 \left| u_4 \right|_{r_1} + \left| v_1 (\pi - \varepsilon_2) \right|_{r_1} + a_8 \left| u_4 \right|_{r_1} \left| v_1 (\pi - \varepsilon_2) \right|_{r_1} \]

\[ + b_1 \left( \frac{1}{r_1} \frac{\partial u_2}{\partial \phi} + \frac{1}{r_1} \frac{\partial v_2}{\partial \phi} \right)_{r_1} + b_1 \left| u_2 \right|_{r_1} + b_4 \left| u_2 H^1 \right|_{r_1} \left| v_2 H^1 \right|_{r_1} \]

\[ + b_5 \left| u_3 H^1 \right|_{r_1} \left| v_2 H^1 \right|_{r_1} + C_1 \left| \frac{1}{r_1} \frac{\partial u_3}{\partial \phi} \right|_{r_1} + \left| \frac{1}{r_1} \frac{\partial v_3}{\partial \phi} \right|_{r_1} \]

\[ + c_1 \left| \frac{1}{r_1} \frac{\partial u_3}{\partial \phi} \right|_{r_1} + \left| \frac{1}{r_2} \frac{\partial v_3}{\partial \phi} \right|_{r_1} \]

\[ + c_4 \left| u_3 H^1 \right|_{r_1} \left| v_3 H^1 \right|_{r_1} + c_5 \left| u_2 H^1 \right|_{r_1} \left| v_3 H^1 \right|_{r_1} + d_1 \left| u_1 (\pi - \varepsilon_2) \right|_{r_1} \left| v_4 \right|_{r_1} \]

\[ + d_2 \left| u_4 \right|_{r_1} \left| v_4 \right|_{r_1} + d_3 \left| u_5 \right|_{r_1} \left| v_4 \right|_{r_1} + d_4 \left| u_6 \right|_{r_1} \left| v_4 \right|_{r_1} + d_5 \left| u_7 \right|_{r_1} \left| v_4 \right|_{r_1} \]

\[ + d_6 \left| u_8 \right|_{r_1} \left| v_4 \right|_{r_1} + d_7 \left| u_9 \right|_{r_1} \left| v_4 \right|_{r_1} + e_1 \left| u_4 \right|_{r_1} \left| v_5 \right|_{r_1} + e_2 \left| u_5 \right|_{r_1} \left| v_5 \right|_{r_1} \]

\[ + h_1 \left| u_4 \right|_{r_1} \left| v_6 \right|_{r_1} + h_2 \left| u_5 \right|_{r_1} \left| v_6 \right|_{r_1} + \ell_1 \left| u_4 \right|_{r_1} \left| v_7 \right|_{r_1} + \ell_2 \left| u_7 \right|_{r_1} \left| v_7 \right|_{r_1} \]

\[ + p_1 \left| u_4 \right|_{r_1} \left| v_8 \right|_{r_1} + p_2 \left| u_8 \right|_{r_1} \left| v_8 \right|_{r_1} + s_1 \left| u_4 \right|_{r_1} \left| v_9 \right|_{r_1} + s_2 \left| u_9 \right|_{r_1} \left| v_9 \right|_{r_1} \]

\[ \leq a_1 \left| u_1 H^1 \right|_{r_1} \left| v_1 H^1 \right|_{r_1} + a_2 \left| u_1 H^1 \right|_{r_1} \left| v_1 H^1 \right|_{r_1} + a_3 \left| u_1 \right|_{r_1} \left| v_1 \right|_{r_1} \]

\[ + a_4 K_1 \left| u_2 H^1 \right|_{r_1} \left| v_1 H^1 \right|_{r_1} + a_5 \left| u_1 H^1 \right|_{r_1} \left| v_1 H^1 \right|_{r_1} + a_6 \left| u_3 H^1 \right|_{r_1} \left| v_1 H^1 \right|_{r_1} \]

\[ + a_7 K_2 \left| u_4 \right|_{r_1} \left| v_1 H^1 \right|_{r_1} + a_8 K_2 \left| u_4 \right|_{r_1} \left| v_1 H^1 \right|_{r_1} \]

\[ + 2b_1 \left| u_2 H^1 \right|_{r_1} \left| v_2 H^1 \right|_{r_1} + \left( b_2 \left| u_1 H^1 \right|_{r_1} + b_3 K_1 \left| u_2 H^1 \right|_{r_1} \right) K_1 \left| v_2 H^1 \right|_{r_1} \]

\[ + \left( b_4 \left| u_2 H^1 \right|_{r_1} + b_5 \left| u_3 \right|_{H^1} \right) \left| v_2 H^1 \right|_{r_1} + 2c_1 \left| u_3 H^1 \right|_{r_1} \left| v_3 H^1 \right|_{r_1} \]

\[ + \left( c_2 \left| u_1 H^1 \right|_{r_1} + c_3 K_1 \left| u_3 \right|_{H^1} \right) K_1 \left| v_3 H^1 \right|_{r_1} \]
for all $u, v \in \mathcal{V}$. Therefore $\sigma$ satisfies (A1).

To prove that $\sigma$ satisfies (4.12), note that for $u \in \mathcal{V}$ we have

\[
\sigma(u, u) = \left( c_1 |u_3|_{H^1_{x}} + c_5 |u_2|_{H^1_{x}} \right) |v_3|_{H^1_{x}} \\
+ \left( c_4 |u_3|_{H^1_{x}} + c_5 |u_2|_{H^1_{x}} \right) |v_3|_{H^1_{x}} \\
+ d_1 K_2 |u_1|_{H^1_{x}} |v_4|_{\mathbb{R}} + d_2 |u_4|_{\mathbb{R}} |v_4|_{\mathbb{R}} + d_3 |u_5|_{\mathbb{R}} |v_4|_{\mathbb{R}} + d_4 |u_6|_{\mathbb{R}} |v_4|_{\mathbb{R}} \\
+ d_5 |u_7|_{\mathbb{R}} |v_4|_{\mathbb{R}} + d_6 |u_8|_{\mathbb{R}} |v_4|_{\mathbb{R}} + d_7 |u_9|_{\mathbb{R}} |v_4|_{\mathbb{R}} \\
+ e_1 |u_4|_{\mathbb{R}} |v_5|_{\mathbb{R}} + e_2 |u_5|_{\mathbb{R}} |v_5|_{\mathbb{R}} + h_1 |u_4|_{\mathbb{R}} |v_6|_{\mathbb{R}} + h_2 |u_6|_{\mathbb{R}} |v_6|_{\mathbb{R}} \\
+ \ell_1 |u_4|_{\mathbb{R}} |v_7|_{\mathbb{R}} + \ell_2 |u_7|_{\mathbb{R}} |v_7|_{\mathbb{R}} + p_1 |u_4|_{\mathbb{R}} |v_8|_{\mathbb{R}} + p_2 |u_8|_{\mathbb{R}} |v_8|_{\mathbb{R}} \\
+ s_1 |u_4|_{\mathbb{R}} |v_9|_{\mathbb{R}} + s_2 |u_9|_{\mathbb{R}} |v_9|_{\mathbb{R}} \\
\leq (a_1 + a_2 + a_3 + a_4 K_1 + a_5 + a_6 K_1 \\
+ a_7 K_2 + a_8 K_2 + 2b_1 + b_2 K_1 + b_3 K_1^2 + b_4 \\
+ b_5 + 2c_1 + c_2 K_1 + c_3 K_1^2 + c_4 + c_5 \\
+ d_1 K_2 + d_2 + d_3 + d_4 + d_5 + d_6 + d_7 + e_1 + e_2 \\
+ h_1 + h_2 + \ell_1 + \ell_2 + p_1 + p_2 + s_1 + s_2 ) |u|_{\mathcal{V}} |v|_{\mathcal{V}} \\
= C_1 |u|_{\mathcal{V}} |v|_{\mathcal{V}}
\]
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\[\begin{align*}
= a_1 \left| \frac{1}{r_1} \frac{\partial u_1}{\partial \phi} \right|^2_B - a_2 \langle u_1, \frac{1}{r_1} \frac{\partial u_1}{\partial \phi} \rangle_B + a_3 |u_1|^2_B - a_4 \langle T^0_{\theta_0} u_2, u_1 \rangle_B \\
+ a_5 |u_1|^2_B - a_6 \langle T^0_{\theta_0} u_3, u_1 \rangle_B - a_7 u_4(u_1(\varepsilon_1)) + a_8 u_4(u_1(\pi - \varepsilon_2)) \\
+ b_1 \left[ \left( \frac{1}{r_1 \sin \phi} \frac{\partial u_2}{\partial \theta}, \frac{1}{r_1 \sin \phi} \frac{\partial u_2}{\partial \theta} \right)_{IA} + \left( \frac{1}{r_1 \sin \phi} \frac{\partial u_2}{\partial \phi} \right)_{IA} \right] \\
- b_2 \langle u_1, T^0_{\theta_0} u_2 \rangle_B + b_3 |T^0_{\theta_0} u_2|^2_B + b_4 |u_2|^2_{IA} - b_5 \langle u_3, u_2 \rangle_{IA} \\
+ c_1 \left[ \left( \frac{1}{r_1 \sin \phi} \frac{\partial u_3}{\partial \theta}, \frac{1}{r_1 \sin \phi} \frac{\partial u_3}{\partial \theta} \right)_{IA} + \left( \frac{1}{r_1 \sin \phi} \frac{\partial u_3}{\partial \phi} \right)_{IA} \right] \\
- c_2 \langle u_1, T^0_{\theta_0} u_3 \rangle_B + c_3 |T^0_{\theta_0} u_3|^2_B + c_4 |u_3|^2_{IA} - c_5 \langle u_2, u_3 \rangle_{IA} \\
- d_1(u_1(\pi - \varepsilon_2))u_4 + d_2 |u_4|^2_{R} - d_3 u_5 u_4 - d_4 u_5 u_4 - d_5 u_7 u_4 \\
- d_6 u_4 - d_7 u_5 - e_1 u_5 + e_2 |u_5|^2_{R} - h_1 u_4 u_6 + h_2 |u_6|^2_{R} - \ell_1 u_4 u_7 \\
+ \ell_2 |u_7|^2_{R} - p_1 u_4 u_8 + p_2 |u_8|^2_{R} - s_1 u_4 u_9 + s_2 |u_9|^2_{R}.
\end{align*}\]

Moreover,

\[a_1 \left| \frac{1}{r_1} \frac{\partial u_1}{\partial \phi} \right|^2_B + a_3 |u_1|^2_B = a_1 |\nabla u_1|^2_B + a_3 |u_1|^2_B \geq \min\{a_1, a_3\} |u_1|^2_{H^1_B} \equiv \tilde{a}_1 |u_1|^2_{H^1_B} \]

\[b_1 \left[ \left( \frac{1}{r_1 \sin \phi} \frac{\partial u_2}{\partial \theta}, \frac{1}{r_1 \sin \phi} \frac{\partial u_2}{\partial \theta} \right)_{IA} + \left( \frac{1}{r_1 \sin \phi} \frac{\partial u_2}{\partial \phi} \right)_{IA} \right] = b_1 \int_0^\pi \int_0^{2\pi} \left( \left( \frac{1}{r_1 \sin \phi} \frac{\partial u_2}{\partial \theta} \right)^2 + \left( \frac{1}{r_1 \sin \phi} \frac{\partial u_2}{\partial \phi} \right)^2 \right) \sin \phi d\phi d\theta \]

\[= b_1 |\nabla u_2|^2_{IA} \]

\[b_1 |\nabla u_2|^2_{IA} + b_4 |u_2|^2_{IA} \geq \min\{b_1, b_4\} |u_2|^2_{H^1_{IA}} \equiv \tilde{b}_1 |u_2|^2_{H^1_{IA}} \]

\[c_1 \left[ \left( \frac{1}{r_1 \sin \phi} \frac{\partial u_3}{\partial \theta}, \frac{1}{r_1 \sin \phi} \frac{\partial u_3}{\partial \theta} \right)_{IA} + \left( \frac{1}{r_1 \sin \phi} \frac{\partial u_3}{\partial \phi} \right)_{IA} \right] + c_4 |u_3|^2_{IA} \geq \min\{c_1, c_4\} |u_3|^2_{H^1_{IA}} \equiv \tilde{c}_1 |u_3|^2_{H^1_{IA}} \]
for all $u \in \mathcal{V}$.

We apply the Cauchy-Schwarz inequality, the inequalities (4.45), (4.46), (4.48), (4.49) and the relation $ab \leq \frac{1}{2}a^2 + \frac{1}{2}b^2$ for all $a, b \in \mathbb{R}$ to obtain

$$a_2 \langle u_1, \frac{1}{r_1} \frac{\partial u_1}{\partial \phi} \rangle_B \leq \left( \sqrt{\frac{a_2}{2\beta_1}} |u_1|_B \right) \left( \sqrt{2a_2\beta_1} |\nabla u_1|_B \right)$$

$$\leq \left( \sqrt{\frac{a_2}{2\beta_1}} |u_1|_B \right) \left( \sqrt{2a_2\beta_1} |u_1|_{H^1_B} \right)$$

$$\leq \frac{a_2}{4\beta_1} |u_1|^2_B + a_2 \beta_1 |u_1|^2_{H^1_B}$$

$$a_4 \langle T^0_{b_0} u_2, u_1 \rangle_B \leq a_4 |T^0_{b_0} u_2|_B |u_1|_B$$

$$\leq a_4 K_1 |u_2|_{H^1_{i_A}} |u_1|_B$$

$$\leq \frac{a_4 K_1}{4\beta_2} |u_1|^2_B + a_4 K_1 \beta_2 |u_2|^2_{H^1_{i_A}}$$

$$a_6 \langle T^0_{b_0} u_3, u_1 \rangle_B \leq \frac{a_6 K_1}{4\beta_3} |u_1|^2_B + a_6 K_1 \beta_3 |u_3|^2_{H^1_{i_A}}$$

$$a_7 u_4(u_1(\varepsilon_1)) \leq a_7 |u_4|_{\mathbb{R}} |u_1(\varepsilon_1)|_{\mathbb{R}}$$

$$\leq a_7 K_2 |u_4|_{\mathbb{R}} |u_1|_{H^1_B}$$

$$\leq \frac{a_7 K_2}{4\beta_4} |u_4|^2_{\mathbb{R}} + a_7 K_2 \beta_4 |u_1|^2_{H^1_B}$$

and hence

$$-a_2 \langle u_1, \frac{1}{r_1} \frac{\partial u_1}{\partial \phi} \rangle_B \geq -\frac{a_2}{4\beta_1} |u_1|^2_B - a_2 \beta_1 |u_1|^2_{H^1_B}$$

$$-a_4 \langle T^0_{b_0} u_2, u_1 \rangle_B \geq -\frac{a_4 K_1}{4\beta_2} |u_1|^2_B - a_4 K_1 \beta_2 |u_2|^2_{H^1_{i_A}}$$

$$-a_6 \langle T^0_{b_0} u_3, u_1 \rangle_B \geq -\frac{a_6 K_1}{4\beta_3} |u_1|^2_B - a_6 K_1 \beta_3 |u_3|^2_{H^1_{i_A}}$$

$$-a_7 u_4(u_1(\varepsilon_1)) \geq -\frac{a_7 K_2}{4\beta_4} |u_4|^2_{\mathbb{R}} - a_7 K_2 \beta_4 |u_1|^2_{H^1_B}$$

for all $u \in \mathcal{V}$. Similarly,

$$a_8 u_4(u_1(\pi - \varepsilon_2)) \geq -a_8 |u_4|_{\mathbb{R}} |u_1(\pi - \varepsilon_2)|_{\mathbb{R}}$$
\[ \sigma(u, u) \geq \bar{a}_1 |u_1|_{H^1_b}^2 - \frac{a_2}{4\beta_1} |u_1|_B^2 - a_2 \beta_1 |u_1|_{H^1_b}^2 - \frac{a_4 K_1}{4\beta_2} |u_1|_B^2 - a_4 K_1 \beta_2 |u_2|_{H^1_{IA}}^2 \]

\[ - \frac{a_6 K_3}{4\beta_3} |u_1|_B^2 - a_6 K_3 \beta_3 |u_3|_{H^1_{IA}}^2 - \frac{a_7 K_4}{4\beta_4} |u_4|_B^2 - a_7 K_4 \beta_4 |u_1|_{H^1_b}^2 \]

\[ - \frac{a_6 K_3}{4\beta_3} |u_1|_B^2 - a_6 K_3 \beta_3 |u_3|_{H^1_{IA}}^2 - \frac{a_7 K_4}{4\beta_4} |u_4|_B^2 - a_7 K_4 \beta_4 |u_1|_{H^1_b}^2 \]

\[ - \frac{a_2}{4\beta_1} |u_1|_B^2 - a_2 \beta_1 |u_1|_{H^1_b}^2 - \frac{a_4 K_1}{4\beta_2} |u_1|_B^2 - a_4 K_1 \beta_2 |u_2|_{H^1_{IA}}^2 \]

\[ - \frac{a_6 K_3}{4\beta_3} |u_1|_B^2 - a_6 K_3 \beta_3 |u_3|_{H^1_{IA}}^2 - \frac{a_7 K_4}{4\beta_4} |u_4|_B^2 - a_7 K_4 \beta_4 |u_1|_{H^1_b}^2 \]

\[ - \frac{a_6 K_3}{4\beta_3} |u_1|_B^2 - a_6 K_3 \beta_3 |u_3|_{H^1_{IA}}^2 - \frac{a_7 K_4}{4\beta_4} |u_4|_B^2 - a_7 K_4 \beta_4 |u_1|_{H^1_b}^2 \]

\[ - \frac{a_2}{4\beta_1} |u_1|_B^2 - a_2 \beta_1 |u_1|_{H^1_b}^2 - \frac{a_4 K_1}{4\beta_2} |u_1|_B^2 - a_4 K_1 \beta_2 |u_2|_{H^1_{IA}}^2 \]

\[ - \frac{a_6 K_3}{4\beta_3} |u_1|_B^2 - a_6 K_3 \beta_3 |u_3|_{H^1_{IA}}^2 - \frac{a_7 K_4}{4\beta_4} |u_4|_B^2 - a_7 K_4 \beta_4 |u_1|_{H^1_b}^2 \]

\[ - \frac{a_2}{4\beta_1} |u_1|_B^2 - a_2 \beta_1 |u_1|_{H^1_b}^2 - \frac{a_4 K_1}{4\beta_2} |u_1|_B^2 - a_4 K_1 \beta_2 |u_2|_{H^1_{IA}}^2 \]

\[ - \frac{a_6 K_3}{4\beta_3} |u_1|_B^2 - a_6 K_3 \beta_3 |u_3|_{H^1_{IA}}^2 - \frac{a_7 K_4}{4\beta_4} |u_4|_B^2 - a_7 K_4 \beta_4 |u_1|_{H^1_b}^2 \]

\[ - \frac{a_2}{4\beta_1} |u_1|_B^2 - a_2 \beta_1 |u_1|_{H^1_b}^2 - \frac{a_4 K_1}{4\beta_2} |u_1|_B^2 - a_4 K_1 \beta_2 |u_2|_{H^1_{IA}}^2 \]

\[ - \frac{a_6 K_3}{4\beta_3} |u_1|_B^2 - a_6 K_3 \beta_3 |u_3|_{H^1_{IA}}^2 - \frac{a_7 K_4}{4\beta_4} |u_4|_B^2 - a_7 K_4 \beta_4 |u_1|_{H^1_b}^2 \]
Chapter 4. Well-posedness results

We choose the constants

\[ b_1 \beta_6 |u_2|^2_{H^1_{IA}} - \frac{b_5}{4\beta_7} |u_2|^2_{IA} - b_5 \beta_7 |u_3|^2_{IA} + \tilde{c}_1 |u_3|^2_{H^1_{IA}} \]

\[ c_2 K_1 \frac{1}{4\beta_8} |u_1|^2_B - c_2 K_1 \beta_8 |u_3|^2_{H^1_{IA}} - \frac{c_5}{4\beta_9} |u_3|^2_{IA} - c_5 \beta_9 |u_2|^2_{IA} \]

\[ d_1 K_2 \frac{1}{4\beta_{10}} |u_4|^2_{\mathbb{R}} - d_1 K_2 \beta_{10} |u_1|^2_{H^1_{IA}} + d_2 |u_4|^2_{\mathbb{R}} - \frac{d_3}{4\beta_{11}} |u_5|^2_{\mathbb{R}} \]

\[ d_4 \frac{1}{4\beta_{12}} |u_6|^2_{\mathbb{R}} - \frac{d_5}{4\beta_{13}} |u_7|^2_{\mathbb{R}} - \frac{d_6}{4\beta_{14}} |u_8|^2_{\mathbb{R}} - \frac{d_7}{4\beta_{15}} |u_9|^2_{\mathbb{R}} \]

\[ (d_3 \beta_{11} + d_4 \beta_{12} + d_5 \beta_{13} + d_6 \beta_{14} + d_7 \beta_{15}) |u_4|^2_{\mathbb{R}} - \frac{c_1}{4\beta_{16}} |u_4|^2_{\mathbb{R}} - e_1 \beta_{16} |u_5|^2_{\mathbb{R}} \]

\[ e_2 |u_5|^2_{\mathbb{R}} - \frac{h_1}{4\beta_{17}} |u_4|^2_{\mathbb{R}} - h_1 \beta_{17} |u_6|^2_{\mathbb{R}} + h_2 |u_6|^2_{\mathbb{R}} - \frac{\ell_1}{4\beta_{18}} |u_4|^2_{\mathbb{R}} - \ell_1 \beta_{18} |u_7|^2_{\mathbb{R}} \]

\[ \ell_2 |u_7|^2_{\mathbb{R}} - \frac{p_1}{4\beta_{19}} |u_4|^2_{\mathbb{R}} - p_1 \beta_{19} |u_8|^2_{\mathbb{R}} + p_2 |u_8|^2_{\mathbb{R}} - \frac{s_1}{4\beta_{20}} |u_4|^2_{\mathbb{R}} - s_1 \beta_{20} |u_9|^2_{\mathbb{R}} \]

\[ + s_2 |u_9|^2_{\mathbb{R}} \]

\[ = (\tilde{a}_1 - a_2 \beta_1 - a_7 K_2 \beta_4 - a_8 K_2 \beta_5 - d_1 K_2 \beta_{10}) |u_1|^2_{H^1_B} \]

\[ + (\tilde{b}_1 - a_4 K_1 \beta_2 - b_2 K_1 \beta_6) |u_2|^2_{H^1_{IA}} + (\tilde{c}_1 - a_6 K_1 \beta_3 - c_2 K_1 \beta_8) |u_3|^2_{H^1_{IA}} \]

\[ + d_2 |u_4|^2_{\mathbb{R}} + e_2 |u_5|^2_{\mathbb{R}} + h_2 |u_6|^2_{\mathbb{R}} + \ell_2 |u_7|^2_{\mathbb{R}} + p_2 |u_8|^2_{\mathbb{R}} + s_2 |u_9|^2_{\mathbb{R}} \]

\[ - \left( \left( \frac{a_2}{4\beta_1} + \frac{a_4 K_1}{4\beta_2} + \frac{a_6 K_1}{4\beta_3} + \frac{b_2 K_1}{4\beta_6} + \frac{c_2 K_1}{4\beta_8} \right) |u_1|^2_{H^1_{IA}} \right. \]

\[ + \left. \left( \frac{b_5}{4\beta_7} + c_5 \beta_9 \right) |u_2|^2_{H^1_{IA}} + \left( \frac{b_5 \beta_7 + c_5}{4\beta_9} \right) |u_3|^2_{H^1_{IA}} \right) \]

\[ + \left( \frac{a_7 K_2}{4\beta_4} + \frac{a_8 K_2}{4\beta_5} + \frac{d_1 K_2}{4\beta_{10}} + d_3 \beta_{11} + d_4 \beta_{12} + d_5 \beta_{13} + d_6 \beta_{14} + d_7 \beta_{15} \right) \]

\[ + \left( \left( \frac{e_1}{4\beta_{16}} + \frac{h_1}{4\beta_{17}} + \frac{\ell_1}{4\beta_{18}} + \frac{p_1}{4\beta_{19}} + \frac{s_1}{4\beta_{20}} \right) |u_4|^2_{\mathbb{R}} + \left( \frac{d_3}{4\beta_{11}} + e_1 \beta_{16} \right) |u_5|^2_{\mathbb{R}} \right) \]

\[ + \left( \frac{d_4}{4\beta_{12}} + h_1 \beta_{17} \right) |u_6|^2_{\mathbb{R}} + \left( \frac{d_5}{4\beta_{13}} + \ell_1 \beta_{18} \right) |u_7|^2_{\mathbb{R}} \]

\[ + \left( \frac{d_6}{4\beta_{14}} + p_1 \beta_{19} \right) |u_8|^2_{\mathbb{R}} + \left( \frac{d_7}{4\beta_{15}} + s_1 \beta_{20} \right) |u_9|^2_{\mathbb{R}} \]

for all \( u \in \mathcal{V} \). We choose the constants \( \beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6, \beta_8 \) and \( \beta_{10} \) so that

\[ \tilde{a} = \bar{a}_1 - a_2 \beta_1 - a_7 K_2 \beta_4 - a_8 K_2 \beta_5 - d_1 K_2 \beta_{10} > 0 \]

\[ \tilde{b} = \bar{b}_1 - a_4 K_1 \beta_2 - b_2 K_1 \beta_6 > 0 \]
\[ \tilde{c} = \tilde{c}_1 - a_6 K_1 \beta_3 - c_2 K_1 \beta_8 > 0. \]

Then for \( u \in V \) we have
\[ \sigma(u, u) \geq k_1 |u|_V^2 - \lambda |u|_H^2, \]
where
\[ k_1 = \min\{\tilde{a}, \tilde{b}, \tilde{c}, d_2, e_2, h_2, \ell_2, p_2, s_2\} \]
\[ \lambda = \max\{\tilde{a}, \tilde{b}, \tilde{c}, \tilde{d}, \tilde{e}, \tilde{h}, \tilde{\ell}, \tilde{p}, \tilde{s}\}, \]
where
\[
\begin{align*}
\tilde{a} &= \frac{a_2}{4 \beta_1} + \frac{a_4 K_1}{4 \beta_2} + \frac{a_6 K_1}{4 \beta_3} + \frac{b_2 K_1}{4 \beta_6} + \frac{c_2 K_1}{4 \beta_8}, \\
\tilde{b} &= \frac{b_5}{4 \beta_7} + c_5 \beta_9, \\
\tilde{c} &= b_5 \beta_7 + \frac{c_5}{4 \beta_9}, \\
\tilde{d} &= \frac{a_7 K_2}{4 \beta_4} + \frac{a_8 K_2}{4 \beta_5} + \frac{d_1 K_2}{4 \beta_{10}} + d_3 \beta_{11} + d_4 \beta_{12} + d_5 \beta_{13} + d_6 \beta_4 + d_7 \beta_{15} \\
&\quad + \frac{e_1}{4 \beta_{16}} + \frac{h_1}{4 \beta_{17}} + \frac{\ell_1}{4 \beta_{18}} + \frac{p_1}{4 \beta_{19}} + \frac{s_1}{4 \beta_{20}}, \\
\tilde{e} &= \frac{d_3}{4 \beta_{11}} + e_1 \beta_{16}, \\
\tilde{h} &= \frac{d_4}{4 \beta_{12}} + h_1 \beta_{17}, \\
\tilde{\ell} &= \frac{d_5}{4 \beta_{13}} + \ell_1 \beta_{18}, \\
\tilde{p} &= \frac{d_6}{4 \beta_{14}} + p_1 \beta_{19}, \\
\tilde{s} &= \frac{d_7}{4 \beta_{15}} + s_1 \beta_{20}.
\end{align*}
\]

This completes the proof of Lemma 4.1.1.

We have therefore established the existence, uniqueness and continuous dependence of a global weak solution for the TCE model given by (4.3) – (4.6).
4.2 Estimation of parameters and convergence of Galerkin approximations

In this section we address theoretical issues related to the standard parameter estimation problem associated with the TCE PBPK-hybrid model, and we establish the theoretical convergence of our numerical approximation scheme. These results are based on the work of Banks and Kunisch [9], who developed results for a general parameter estimation problem. Banks and Musante [11] applied these results to the abstract class of nonlinear parabolic systems discussed in [10]. Here we extend the ideas presented in [9] and [11] to the TCE model and the abstract class of nonlinear parabolic systems discussed in the previous section.

Consider the abstract problem

\[
\dot{y}(t) + A(q)y(t) + g(q)(y(t)) = f(t; q) \quad (4.51)
\]

\[
y(0) = y_0 \quad (4.52)
\]

which is a parameterized formulation of the system (4.8), (4.9). Specifically, the sesquilinear form \(\sigma\), the nonlinearity \(g\) and the forcing function \(f\) are now functions of a vector \(q\) of parameters which must be estimated using data.

The parameter vector \(q\) belongs to a set \(Q\) of admissible parameters, where \(Q\) may be an infinite dimensional space. In the case of our TCE model, the physiology of adipose tissue (see Section 3.1) suggests that many of the adipose model parameters may be dependent on time and/or space. This includes parameters such as the volumetric blood flow rate \(Q_f\) to adipose tissue and the permeability coefficients \(\mu_{BA}, \mu_{BI}\) and \(\mu_{IA}\). Such a dependency on time and/or space would lead to infinite dimensional parameters and an infinite dimensional parameter space \(Q\).

Using arguments outlined in Section 4.1, we establish the existence of a unique weak solution to the system

\[
\langle \dot{y}(t), \psi \rangle_{V^*, V} + \langle A(q)y(t), \psi \rangle_{V^*, V} + \langle g(q)(y(t)), \psi \rangle = \langle f(t; q), \psi \rangle_{V^*, V} \quad (4.53)
\]

\[
y(0) = y_0 \quad (4.54)
\]
for $\psi \in \mathcal{V}$. These solutions $y(t)$ to the parameterized problem can be used with experimental data to estimate the parameters $q$ by solving the least squares parameter estimation problem given by

$$
\min_{q \in Q} J(q, z) = \sum_{i=1}^{N_t} |\mathcal{O}y(t_i, \cdot; q) - z_i|^2, \tag{4.55}
$$

where $z_i, i = 1, \ldots, N_t$ are observations taken at time $t_i$, and $|\cdot|$ is an appropriately chosen Euclidean norm. The solutions $y(t_i, \cdot; q)$ belong to an infinite dimensional state space $\mathcal{H}$. As discussed in [9], the observation operator $\mathcal{O}$ is determined by the type of data that is being collected. Examples appropriate for the TCE model and related experiments include observations of concentrations taken in time at a given point, or observations in time of an average concentration over a region. This latter type of observation may be used when concentrations are measured from homogenized tissue samples.

As in [9], [14] and [11], we address the parameter estimation problem (4.55) by studying the convergence properties of the finite dimensional parameter estimation problems

$$
\min_{q \in Q^M} J^N(q) = \sum_{i=1}^{N_t} |\mathcal{O}y^N(t_i, \cdot; q) - z_i|^2, \tag{4.56}
$$

where the sets $Q^M$ are a sequence of finite dimensional sets that approximate $Q$, and $y^N(t) \in \mathcal{H}^N \subset \mathcal{H}$ is the solution to the following finite dimensional approximation of (4.53), (4.54):

$$
\langle y^N(t), \psi \rangle + \langle \mathcal{A}(q)y^N(t), \psi \rangle_{\mathcal{V}^*, \mathcal{V}} + \langle g(q)(y^N(t)), \psi \rangle = \langle f(t; q), \psi \rangle_{\mathcal{V}^*, \mathcal{V}} \tag{4.57}
$$

$y^N(0) = P^N y_0 \tag{4.58}$

for $\psi \in \mathcal{H}^N$. The set $\mathcal{H}^N$ is a finite dimensional subspace of the state space $\mathcal{H}$, and $P^N$ is the orthogonal projection of $\mathcal{H}^N$ onto $\mathcal{H}$.

Assuming certain compactness conditions that we detail below, for each $M$ and $N$ there exists a minimizer $\tilde{q}^{M,N}$ for the finite dimensional estimation problem (4.56).
Chapter 4. Well-posedness results

In this section we address the convergence properties of this sequence of minimizers as \( M, N \to \infty \), and the circumstances for which we can guarantee convergence to a minimizer for the infinite dimensional parameter estimation problem (4.55). The results we prove below for the abstract class of systems in Section 4.1 are adaptations and extensions of results for the general estimation problem discussed in [9] and the estimation problem for the class of nonlinear parabolic systems presented in [11]. We also show that the results established here apply specifically to the TCE PBPK-hybrid model, which is a member of the class of systems described above.

Finally, we demonstrate the convergence of solutions for the finite dimensional approximations (4.57), (4.58) to the solution for the infinite dimensional system (4.53), (4.54). This establishes the convergence of the numerical scheme that we discuss in Chapter 5.

4.2.1 Well-posedness of solutions for the parameterized system

In this section we address the well-posedness of solutions for (4.51), (4.52). That is, using the arguments detailed in Section 4.1, we may prove the existence of a unique weak solution for this abstract system which depends continuously on the initial data.

As in Section 4.1.2, we define the state spaces \( \mathcal{V} \) and \( \mathcal{H} \) which form the Gelfand triple

\[
\mathcal{V} \hookrightarrow \mathcal{H} \hookrightarrow \mathcal{V}^*,
\]

where \( \mathcal{V} \) is continuously and densely embedded in \( \mathcal{H} \). Moreover, there exists \( k > 0 \) such that

\[
|\psi| \leq k |\psi|_\mathcal{V}
\]

for all \( \psi \in \mathcal{V} \), where \(|\cdot|_\mathcal{V}\) is the norm on \( \mathcal{V} \) and \(|\cdot|\) denotes the norm on \( \mathcal{H} \). We continue to use the notation \( \langle \cdot, \cdot \rangle_{\mathcal{V}^*, \mathcal{V}} \) to represent the duality product, which is the extension by continuity of the inner product \( \langle \cdot, \cdot \rangle \) in \( \mathcal{H} \) (see Section 4.1.2).
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Here we consider the system

\[
\begin{align*}
\langle \dot{y}(t), \psi \rangle_{V^*, V} + \sigma(q)(y(t), \psi) + \langle g(q)(y(t)), \psi \rangle &= \langle f(t, q), \psi \rangle_{V^*, V} \\
y(0) &= y_0
\end{align*}
\]  

(4.60)

(4.61)

for \( \psi \in V \), where the sesquilinear form \( \sigma(q) : V \times V \to \mathbb{R} \) is associated with the operator \( A(q) : V \to V^* \) so that \( \sigma(q)(u, v) = \langle A(q)u, v \rangle_{V^*, V} \) for all \( u, v \in V \).

We make the following assumptions for the parameterized system, which are the same assumptions as those made in Section 4.1.2 with the extra requirement of uniformity in \( q \in Q \):

(A1') The sesquilinear form \( \sigma(q) \) is uniformly bounded in \( V \), i.e., there exists \( C_1 > 0 \) independent of \( q \in Q \) such that

\[
|\sigma(q)(u, v)| \leq C_1 |u|_V |v|_V \quad \text{for all} \quad u, v \in V.
\]  

(4.62)

(A2') The sesquilinear form \( \sigma(q) \) is uniformly strictly coercive on \( V \). That is, there exist \( k_1, \lambda > 0 \) independent of \( q \in Q \) such that

\[
\sigma(q)(u, u) \geq k_1 |u|^2_V - \lambda |u|^2 \quad \text{for all} \quad u \in V.
\]  

(4.63)

(A3') The forcing function \( f(\cdot; q) \) satisfies

\[
f(\cdot; q) \in L_2((0, T); V^*)
\]  

(4.64)

for each \( q \in Q \).

(A4') The nonlinear function \( g(q) : \mathcal{H} \to \mathcal{H} \) satisfies the following uniform local Lipschitz condition: let \( B_r(0) = \{ u \in \mathcal{H} : |u| \leq r \} \) denote the ball of radius \( r \) centered around the origin in \( \mathcal{H} \). Then given \( r > 0 \), there exists \( L_{B_r} > 0 \) independent of \( q \in Q \) such that

\[
|g(q)(u) - g(q)(v)| \leq L_{B_r} |u - v| \quad \text{for all} \quad u, v \in B_r(0).
\]  

(4.65)

(A5') There exist positive constants \( C_2 \) and \( C_3 \) independent of \( q \in Q \) such that

\[
|g(q)(u)| \leq C_2 |u| + C_3 \quad \text{for all} \quad u \in \mathcal{H}.
\]  

(4.66)
Under these assumptions we can prove the existence of a unique weak solution to the parameterized system. The proof of this theorem is similar to the proof for Theorem 4.1.2.

**Theorem 4.2.1** Under Assumptions (A1') - (A5') and for any $y_0 \in \mathcal{H}$, the system (4.60) - (4.61) has a unique global weak solution $y \in L_2((0,T);\mathcal{V}) \cap C([0,T];\mathcal{H})$ which depends continuously on the initial data, with $\dot{y} \in L_2((0,T);\mathcal{V}^*)$.

### 4.2.2 The general parameter estimation problem

In this section we present theorems related to convergence for the general parameter estimation problem

$$
\min_{q \in Q} J(q,z) = \sum_{i=1}^{N_t} |\mathcal{O}y(t_i, \cdot; q) - z_i|^2,
$$

given the observations $z_i, i = 1, \ldots, N_t$ taken at time $t_i$ and the observation operator $\mathcal{O}$. Moreover, $y(t_i, \cdot; q)$ are the solutions of the parameterized system (4.60), (4.61).

As in Section 4.1.2, we use Galerkin type approximations applied to the parameterized system (4.51), (4.52).

Proceeding as in [11], we make the following assumptions about the state and parameter spaces $\mathcal{H}, Q, \mathcal{H}^N$ and $Q^M$:

1. **(B1)** The sets $Q$ and $Q^M$ each lie in a metric space $\tilde{Q}$ with metric $d$. We assume that $Q$ and $Q^M$ are compact in this metric, and that there is a mapping $i^M : Q \to Q^M$ such that $Q^M = i^M(Q)$. Moreover, for each $q \in Q$ we have $i^M(q) \to q$ in $Q$, where the convergence is uniform in $q \in Q$.

2. **(B2)** The finite dimensional subspaces $\mathcal{H}^N$ satisfy $\mathcal{H}^N \subset \mathcal{V}$ for all $N$.

3. **(B3)** For each $\psi \in \mathcal{V}$, $|\psi - P^N\psi|_{\mathcal{V}} \to 0$ as $N \to \infty$, where $P^N$ is the orthogonal projection operator of $\mathcal{H}$ onto $\mathcal{H}^N$.

Moreover, we assume that $\mathcal{A}(q), g(q)$ and $f(\cdot; q)$ depend continuously on the parameters $q \in Q$, so that

1. **(C1)** $|\sigma(q)(u,v) - \sigma(\tilde{q})(u,v)| \leq d_1(q,\tilde{q}) |u|_{\mathcal{V}} |v|_{\mathcal{V}}$, for all $u, v \in \mathcal{V}$, where $d_1(q,\tilde{q}) \to 0$ as $d(q,\tilde{q}) \to 0$. 

(C2) \(|g(q)(u) - g(\tilde{q})(u)| \leq d_2(q, \tilde{q})|u|\) for all \(u \in \mathcal{H}\), where \(d_2(q, \tilde{q}) \to 0\) as \(d(q, \tilde{q}) \to 0\).

(C3) The mapping \(q \mapsto f(\cdot; q)\) is continuous from \(Q\) to \(L_2((0, T); \mathcal{V}^*)\).

Note that the compactness conditions of Assumption (B1) guarantee the existence of a minimizer \(\tilde{q}^{M,N}\) to the finite dimensional estimation problem (4.56). The following theorem from [14] (Theorem 5.1, p. 124) establishes conditions for which the sequence of minimizers \(\tilde{q}^{M,N}\) converges to a minimizer for the infinite dimensional estimation problem (4.55).

**Theorem 4.2.2** To obtain convergence of at least a subsequence of \(\{\tilde{q}^{M,N}\}\) to a solution \(\tilde{q}\) of minimizing (4.55) subject to (4.53), (4.54), it suffices, under Assumption (B1), to argue that for arbitrary sequences \(\{q^{M,N}\}\) in \(Q\) with \(q^{M,N} \to q\) in \(Q\), we have

\[
\mathcal{O}y^N(t; q^{M,N}) \to \mathcal{O}y(t; q). \tag{4.67}
\]

The condition (4.67) implies that the original sequence of Galerkin approximations in Section 4.1.2 converges, which is stronger than the subsequential convergence proven there. This stronger result is important for establishing the convergence of the numerical scheme that we detail in Chapter 5.

Now we verify the conditions of Theorem 4.2.2 for the general estimation problem described in this section.

**Theorem 4.2.3** Assume that Assumptions (B1) – (B3) and (C1) – (C3) are satisfied, in addition to the conditions of Theorem 4.2.1. Let \(q^N\) be any sequence in \(Q^N\) satisfying \(q^N \to q \in Q\). Then

\[
y^N(t; q^N) \to y(t; q) \quad \text{in } \mathcal{H} \text{ uniformly on } [0, T]
\]

\[
y^N(t; q^N) \to y(t; q) \quad \text{in } \mathcal{V} \text{ for almost all } t > 0,
\]

where \(y^N\) satisfies

\[
\langle g^N(t), \psi \rangle + \sigma(q^N)(y^N(t), \psi) + \langle g(q^N)(y^N(t)), \psi \rangle = \langle f(t; q^N), \psi \rangle_{\mathcal{V}^*, \mathcal{V}} \tag{4.68}
\]

\[
y^N(0) = P^N y_0 \tag{4.69}
\]
for all \( \psi \in \mathcal{H}^N \), and \( y \) satisfies (4.60) – (4.61) for all \( \psi \in \mathcal{V} \).

**Proof:** It follows from Theorem 4.2.1 that \( y(t) \in \mathcal{H} \) for every \( t \in [0, T] \) and \( y(t) \in \mathcal{V} \) for almost every \( t \in [0, T] \). Moreover,

\[
|y^N(t; q^N) - y(t; q)| \leq |y^N(t; q^N) - P^N y(t; q)| + |P^N y(t; q) - y(t; q)|.
\]

By Assumption (B3), we have \( |\psi - P^N \psi|_{\mathcal{V}} \to 0 \) for each \( \psi \in \mathcal{V} \) as \( N \to \infty \). Note that \( y \in C([0, T]; \mathcal{H}) \) implies that \( \{y(t) : t \in [0, T]\} \) is compact in \( \mathcal{H} \), which along with (4.59) and the dense embedding \( \mathcal{V} \hookrightarrow \mathcal{H} \) further implies that

\[
|P^N y(t; q) - y(t; q)| \to 0
\]

uniformly in \( t \in [0, T] \). Therefore it suffices to show that

\[
|y^N(t; q^N) - P^N y(t; q)| \to 0
\]

uniformly on \([0, T]\) as \( N \to \infty \).

As in [11], we define

\[
\begin{align*}
y^N &= y^N(t; q^N) \\
y &= y(t; q) \\
\Delta^N &= y^N(t; q^N) - P^N y(t; q) = y^N - P^N y.
\end{align*}
\]

It follows that

\[
\dot{\Delta}^N = \dot{y}^N - \frac{d}{dt} P^N y.
\]

Hence for all \( \psi \in \mathcal{H}^N \) we have

\[
\langle \dot{\Delta}^N, \psi \rangle_{\mathcal{V}^*, \mathcal{V}} = \langle \dot{y}^N - \frac{d}{dt} P^N y, \psi \rangle_{\mathcal{V}^*, \mathcal{V}} = \langle \dot{y}^N - \dot{y} + \dot{y} - \frac{d}{dt} P^N y, \psi \rangle_{\mathcal{V}^*, \mathcal{V}} = \langle \dot{y}^N, \psi \rangle_{\mathcal{V}^*, \mathcal{V}} + \langle \dot{y} - \frac{d}{dt} P^N y, \psi \rangle_{\mathcal{V}^*, \mathcal{V}}.
\]
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It follows from (4.60) and (4.68) that

\[
\langle \Delta^N, \psi \rangle_{V', V} = \langle f(t; q^N), \psi \rangle_{V', V} - \sigma(q^N)(y^N, \psi) - \langle g(q^N)(y^N), \psi \rangle \\
- \langle f(t; q), \psi \rangle_{V', V} + \sigma(q)(y, \psi) + \langle g(q)(y), \psi \rangle \\
+ \langle \dot{y} - \frac{d}{dt} P^N y, \psi \rangle_{V', V}
\]

where we have added and subtracted \( \sigma(q^N)(y - P^N y, \psi) \). Moreover, using the definition of \( \Delta^N \) we obtain

\[
\langle \Delta^N, \psi \rangle_{V', V} + \sigma(q^N)(\Delta^N, \psi) = \langle \dot{y} - \frac{d}{dt} P^N y, \psi \rangle_{V', V} + \langle f(t; q^N) - f(t; q), \psi \rangle_{V', V} \\
+ \sigma(q)(y, \psi) - \sigma(q^N)(y, \psi) \\
+ \sigma(q^N)(y - P^N y, \psi) \\
+ \langle g(q)(y) - g(q^N)(y^N), \psi \rangle - \sigma(q^N)(y^N - P^N y)(\psi),
\]

for all \( \psi \in H^N \). Now we set \( \psi = \Delta^N \in H^N \) in (4.70) and use the identity

\[
\langle \Delta^N, \Delta^N \rangle_{V', V} = 1/2 \frac{d}{dt} \left[ |\Delta^N|^2 \right]
\]

to arrive at the equation

\[
\frac{1}{2} \frac{d}{dt} \left[ |\Delta^N|^2 \right] + \sigma(q^N)(\Delta^N, \Delta^N) \\
= \langle \dot{y} - \frac{d}{dt} P^N y, \Delta^N \rangle_{V', V} \\
+ \langle f(t; q^N) - f(t; q), \Delta^N \rangle_{V', V} \\
+ \sigma(q)(y, \Delta^N) - \sigma(q^N)(y, \Delta^N) \\
+ \sigma(q^N)(y - P^N y, \Delta^N) + \langle g(q)(y) - g(q^N)(y^N), \Delta^N \rangle
\]

for almost all \( t \in [0, T] \). We integrate the left side of (4.71) and apply Assumption (A2') and the initial condition

\[
\Delta^N(0) = y^N(0) - P^N y(0) = y^N(0) - P^N y_0 = 0
\]
to obtain the inequality
\[
\int_0^t \frac{1}{2} \frac{d}{dt} |\Delta^N(s)|^2 ds + \int_0^t \sigma(q^N)(\Delta^N(s), \Delta^N(s))ds \\
= \frac{1}{2} |\Delta^N(t)|^2 - \frac{1}{2} |\Delta^N(0)|^2 \\
+ \int_0^t \sigma(q^N)(\Delta^N(s), \Delta^N(s))ds \\
\geq \frac{1}{2} |\Delta^N(t)|^2 + k_1 \int_0^t |\Delta^N(s)|_V^2 ds \\
- \lambda \int_0^t |\Delta^N(s)|_V^2 ds
\]
(4.72)
for all \( t \in [0, T] \).

Next we integrate the right side of (4.71) from 0 to \( t \). Note that the first term is equal to zero, which follows from the fact that \( P^N \) is the orthogonal projection from \( \mathcal{H} \) onto \( \mathcal{H}^N \). Indeed, for all \( \psi \in \mathcal{H}^N \) we have
\[
\langle \dot{y} - \frac{d}{dt} P^N y, \psi \rangle_{V^*, V} = \langle \frac{d}{dt} (y - P^N y), \psi \rangle_{V^*, V} \\
= \frac{d}{dt} (y - P^N y, \psi)_{V^*, V} \\
= \frac{d}{dt} (y - P^N y, \psi)
\]
since \( y - P^N y \in \mathcal{H} \). Moreover,
\[
\langle \dot{y} - \frac{d}{dt} P^N y, \psi \rangle_{V^*, V} = \frac{d}{dt} (y - P^N y, \psi) = 0
\]
(4.73)
for all \( \psi \in \mathcal{H}^N \) since \( P^N \) is the orthogonal projection of \( \mathcal{H} \) onto \( \mathcal{H}^N \), which implies that \( (I - P^N)y \) is orthogonal to all elements in \( \mathcal{H}^N \) (including \( \Delta^N(s) \) for all \( s \in [0, T] \)).

Integrating the second term on the right side of (4.71), we use the inequality \( ab \leq (1/2)a^2 + (1/2)b^2 \) to obtain
\[
\int_0^t \langle f(s; q^N) - f(s; q), \Delta^N(s) \rangle_{V^*, V} ds \leq \int_0^t |f(s; q^N) - f(s; q)|_{V^*} |\Delta^N(s)|_V ds \\
\leq \frac{1}{2\beta} \int_0^t |f(s; q^N) - f(s; q)|^2_{V^*} ds \\
+ \frac{\beta}{2} \int_0^t |\Delta^N(s)|_V^2 ds,
\]
(4.74)
where $\beta > 0$. We proceed in a similar manner with the third and fourth terms on the right side of (4.71), applying Assumption (C1):

$$
\int_0^t \left[ \sigma(q)(y(s), \Delta^N(s)) - \sigma(q^N)(y(s), \Delta^N(s)) \right] ds \leq \int_0^t d_1(q, q^N) |y(s)| V |\Delta^N(s)| V ds \\
\leq \frac{d_1^2(q, q^N)}{2\beta} \int_0^t |y(s)|^2 V ds \\
+ \frac{\beta}{2} \int_0^t |\Delta^N(s)|^2 V ds. \quad (4.75)
$$

The integral of the fifth term on the right side of (4.71) can be bounded using Assumption (A1'):

$$
\int_0^t \sigma(q^N)(y(s)) - P^N(y(s), \Delta^N(s)) ds \leq C_1 \int_0^t |y(s) - P^N(y(s)| V |\Delta^N(s)| V ds \\
\leq \frac{C_1^2}{2\beta} \int_0^t |y(s) - P^N(y(s)|^2 V ds \\
+ \frac{\beta}{2} \int_0^t |\Delta^N(s)|^2 V ds. \quad (4.76)
$$

Finally, we integrate the sixth term from 0 to $t$, obtaining

$$
\int_0^t \langle g(q)(y(s)) - g(q^N)(y^N(s)), \Delta^N(s) \rangle ds \\
\leq \int_0^t \langle g(q)(y(s)) - g(q^N)(y(s)), \Delta^N(s) \rangle ds \\
+ \int_0^t \langle g(q^N)(y(s)) - g(q^N)(y^N(s)), \Delta^N(s) \rangle ds. \quad (4.77)
$$

The first term on the right side of (4.77) can be estimated using Assumption (C2) and (4.59):

$$
\int_0^t \langle g(q)(y(s)) - g(q^N)(y(s)), \Delta^N(s) \rangle | ds \\
\leq \int_0^t |g(q)(y(s)) - g(q^N)(y(s))| |\Delta^N(s)| ds \\
\leq \int_0^t d_2(q, q^N) |y(s)| |\Delta^N(s)| ds
$$
We obtain a bound for the second term on the right side of (4.77) using Assumption (A4) applied to \( y(s) \) and \( P_N y(s) \). In the proof of Theorem 4.1.2, we showed that the solution \( y \in L_2((0,T);\mathcal{V}) \cap C([0,T];\mathcal{H}) \) to the system (4.16), (4.17) is bounded by the constant \( \hat{C} \) as in (4.42). It is easily seen that for each \( s \in [0,T] \), the same bound

\[
|y(s)|^2 \leq \hat{C}
\]

applies for the solution \( y \in L_2((0,T);\mathcal{V}) \cap C([0,T];\mathcal{H}) \) to the system (4.60), (4.61) which is guaranteed by Theorem 4.2.1. Moreover, for each \( s \in [0,T] \) we have

\[
|P_N y(s)| \leq \|P_N\| |y(s)| = |y(s)|,
\]

which implies that both \( y(s) \) and \( P_N y(s) \) are in the ball \( B_{\sqrt{\hat{C}}} \) in \( \mathcal{H} \). Using the same arguments and the bound (4.41), we can show that \( y^N(s) \) is in \( B_{\sqrt{\hat{C}}} \). Hence we may apply Assumption (A4') and (4.59) to obtain

\[
\begin{align*}
\int_0^t & |\langle g(q^N)(y(s)) - g(q^N)(y^N(s)), \Delta^N(s) \rangle| ds \\
& \leq \int_0^t |\langle g(q^N)(y(s)) - g(q^N)(P_N y(s)), \Delta^N(s) \rangle| ds \\
& + \int_0^t |\langle g(q^N)(P_N y(s)) - g(q^N)(y^N(s)), \Delta^N(s) \rangle| ds \\
& \leq \int_0^t L_{B_{\sqrt{\hat{C}}}} |y(s) - P_N y(s)| |\Delta^N(s)| ds \\
& + \int_0^t L_{B_{\sqrt{\hat{C}}}} |P_N y(s) - y^N(s)| |\Delta^N(s)| ds \\
& \leq \frac{k^2 L_{B_{\sqrt{\hat{C}}}}^2}{2\beta} \int_0^t |y(s) - P_N y(s)|^2 ds
\end{align*}
\]
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\[ + \frac{k^2 \beta}{2} \int_0^t |\Delta^N(s)|^2_\mathcal{V} \, ds \]
\[ + LB_{\sqrt{\mathcal{C}}} \int_0^t |\Delta^N(s)|^2 \, ds. \tag{4.79} \]

Now we combine the terms in (4.72) – (4.79) and use (4.71) to arrive at the estimate

\[ \frac{1}{2} |\Delta^N(t)|^2 + \left( k_1 - (3 + 2k^2) \frac{\beta}{2} \right) \int_0^t |\Delta^N(s)|^2_\mathcal{V} \, ds \]
\[ \leq \frac{1}{2\beta} \int_0^t \left| f(s; q^N) - f(s; q) \right|^2_\mathcal{V}, \, ds + \frac{d_1(q, q^N)}{2\beta} \int_0^t |y(s)|^2_\mathcal{V} \, ds \]
\[ + \frac{C_1^2}{2\beta} \int_0^t |y(s) - P^N y(s)|^2_\mathcal{V} \, ds + \frac{k^2 d_2(q, q^N)}{2\beta} \int_0^t |y(s)|^2_\mathcal{V} \, ds \]
\[ + \frac{k^2 L_B^{\sqrt{\mathcal{C}}}}{2\beta} \int_0^t |y(s) - P^N y(s)|^2_\mathcal{V} \, ds \]
\[ + (L_{B_{\sqrt{\mathcal{C}}}} + \lambda) \int_0^t |\Delta^N(s)|^2 \, ds \]
\[ \equiv \delta^N(t) + (L_{B_{\sqrt{\mathcal{C}}}} + \lambda) \int_0^t |\Delta^N(s)|^2 \, ds \]
\[ \leq \delta^N(T) + (L_{B_{\sqrt{\mathcal{C}}}} + \lambda) \int_0^t |\Delta^N(s)|^2 \, ds \tag{4.80} \]

for \( t \in [0, T] \). Note that as \( N \to \infty \) we have \( \delta^N(t) \to 0 \) for each \( t \in [0, T] \). This is because \( f \) satisfies Assumption (C3), \( q^N \to q, y \in L_2((0, T); \mathcal{V}) \), and Assumption (B3) is satisfied.

Now we choose \( \beta > 0 \) in (4.80) so that \( k_1 - (3 + 2k^2) \frac{\beta}{2} > 0 \). This implies that

\[ \frac{1}{2} |\Delta^N(t)|^2 \leq \delta^N(T) + (L_{B_{\sqrt{\mathcal{C}}}} + \lambda) \int_0^t |\Delta^N(s)|^2 \, ds. \]

By Gronwall’s lemma, we have

\[ |\Delta^N(t)|^2 \leq 2e^{2(L_B^{\sqrt{\mathcal{C}}+\lambda})T} \delta^N(T) \to 0, \tag{4.81} \]

which implies that \( \Delta^N \to 0 \) in \( C([0, T]; \mathcal{H}) \) as \( N \to \infty \). Moreover, combining (4.80) with (4.81) we have

\[ \left( k_1 - (3 + 2k^2) \frac{\beta}{2} \right) \int_0^t |\Delta^N(s)|^2_\mathcal{V} \, ds \leq \delta^N(T) + (L_{B_{\sqrt{\mathcal{C}}}} + \lambda) \int_0^t |\Delta^N(s)|^2 \, ds \]
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\[ \Delta^N \to 0 \text{ in } L_2((0,T);\mathcal{V}). \]

Therefore

\[ y^N(t; q^N) \to y(t; q) \text{ in } \mathcal{H} \text{ uniformly on } [0,T] \]

\[ y^N(t; q^N) \to y(t; q) \text{ in } \mathcal{V} \text{ for almost all } t > 0, \]

which completes the proof of the theorem.

4.2.3 Parameter estimation for the TCE model

The TCE PBPK-hybrid model presented in Chapter 3 includes several physical parameters, each of which is positive and bounded below some maximum admissible value. This implies that the parameters for this model lie in a compact subset of Euclidean space. Therefore we set \( Q^M = Q \) for all \( M \).

Using arguments in Section 4.1.3, it can be shown that Assumptions (A1') – (A5') are satisfied for the TCE PBPK-hybrid model. We state without proof that Assumptions (C1) – (C3) are also satisfied for the TCE model. Moreover, it is seen that Assumptions (B1) – (B3) hold for our choice of state spaces \( \mathcal{V}, \mathcal{H} \) and \( \mathcal{H}^N \) defined in Section 4.1.1. It follows that the theoretical results presented in Section 4.2.2 apply to the TCE PBPK-hybrid model.

Experimental observations collected in the experiments of Evans et al. [32] include measurements of TCE concentrations in the venous blood, as well as unbound concentrations in the fat, liver and brain tissue. The tissue concentrations are collected from homogenized tissue samples, leading to a measurement of an effective average tissue concentration. For the liver and brain tissues our model assumes well-mixed compartments, which implies that the average tissue concentration is equal to the concentration at any point in that tissue. Therefore the observation operators for the venous blood and the brain and liver tissues are given by

\[ \mathcal{O}y(t_i; \cdot; q) = C_j(t_i; q), \quad (4.82) \]
where \( C_j = C_v, C_{ebr} \) and \( C_{vl} \) respectively.

In the adipose tissue our model assumes spatially-varying concentrations, so that an effective average concentration is calculated by taking an average of concentrations over the adipocyte region. This implies an observation operator of the form

\[
O_y(t_i, \cdot, q) = \frac{1}{2\pi} \int_0^\pi \int_0^{2\pi} f_A C_A(t_i, \theta, \phi) d\theta d\phi.
\]  

(4.83)

Each of these observation operators will be utilized in Chapter 6, where we present parameter estimation results for the TCE model.

### 4.3 Uncertainty in parameter estimation

In the previous sections of this chapter we have assumed that each parameter of interest is a fixed constant or function. In many cases this is a reasonable assumption, but it may not be appropriate for problems that involve certain types of variability. Two types of variability that are often inherent in biological models and are well-known in the statistical literature are intra-individual and inter-individual variability.

Variability that occurs within one individual is known as *intra-individual* variability. An example relevant to the TCE model is the variability that occurs within a single individual’s adipose tissue. As we discussed in Chapter 3, it is known that physiological parameters such as cell volumes, blood flow rates and permeability coefficients have widely varying values throughout the adipose tissue. Therefore we would expect each adipocyte/capillary unit to have its own set of values for these physiological parameters, which further suggests that estimates of constant parameter values may not be appropriate in this case.

Note that in our dispersion model, we partially address this type of intra-individual variability by including the dispersion term in the capillary region. As discussed in Section 3.2, this term is designed to account for variations in path length, residence times, and flow velocities. The dispersion coefficient \( \mathcal{D}_B \) is an aggregate parameter that reflects the degree of this variability, with larger values of \( \mathcal{D}_B \) corresponding to
more variation. Note, however, that the dispersion term does not entirely account for intra-individual variability within adipose tissue. For example, the variation of permeability coefficients across the population of fat cells (as suggested by the physiology) is not specifically incorporated into the dispersion term. Therefore one must develop additional techniques to more completely account for intra-individual variability, which would then yield a truly “aggregate” model.

One approach that is commonly used to account for this type of variability is mathematical homogenization theory, as discussed in Section 3.2. Homogenization techniques could be applied, for example, on the membrane permeability coefficients in the adipose model, yielding “effective” permeability coefficients for the entire tissue. An alternative approach discussed in Section 3.2 makes use of probability-based methods. In this case we assume that each “cellular” parameter (e.g., a permeability coefficient) is a random variable with a probability distribution that may be estimated using inverse problem techniques. This probability distribution is a representation of the variability in the parameter across the entire adipose tissue, and can be used to arrive at an estimate for an “effective” value of that parameter.

A second type of variability that is commonly found in biological modeling is inter-individual variability. In this case, we assume that model parameters have varying values across a population of many individuals. This type of variability is inherent when the parameter estimation problem is centered around observations from multiple individuals, where the parameters in question are assumed to vary among different individuals. An important example is the TCE concentration data discussed in Chapter 2, which were collected using several Long-Evans rats, so that each data point in time corresponds to a different rat.

It is reasonable to expect that different individuals of a population would possess different values for biological and chemical parameters. These parameters would then take on varying values across the population, so that each parameter would be associated with a probability distribution that would mathematically describe this variation. Using data from multiple individuals, we can estimate these probability
distributions.

In the remainder of this chapter we present theoretical results related to *inter-individual* variability in parameter estimation problems, and we address the implementation of estimation problems that incorporate inter-individual variability in Chapter 6.

### 4.3.1 Uncertainty in the general estimation problem

Consider the general parameter estimation problem

$$
\min_{q \in Q} J(q, z) = \sum_{i=1}^{N_t} |Oy(t_i, \cdot \cdot \cdot q) - z_i|^2
$$

discussed in Section 4.2, where $z_i$ are observations and $y(t_i, \cdot \cdot \cdot q)$ are solutions of the system (4.60), (4.61). As in [5], we incorporate uncertainty into the inverse problem by associating a probability distribution with the parameter set $q \in Q$. Specifically, we define the set $\mathcal{P}(Q)$ of probability distributions on the admissible parameter space $Q$ and seek a probability distribution function $P^* \in \mathcal{P}(Q)$ that minimizes

$$
J(P) = \sum_{i=1}^{N_t} |\mathcal{E}[Oy(t_i, \cdot \cdot \cdot q)|P] - \hat{z}_i|^2
$$

over $\mathcal{P}(Q)$, where $\hat{z}_i$, $i = 1, \ldots, N_t$ are observations corresponding to the expected value

$$
\mathcal{E}[Oy(t_i, \cdot \cdot \cdot q)|P] = \int_Q Oy(t_i, \cdot \cdot \cdot q) dP(q)
$$

for some $P \in \mathcal{P}(Q)$.

Banks and Bihari [5] have addressed theoretical issues related to this type of estimation problem. Using the Prohorov metric [17] defined on $\mathcal{P}(Q)$, they studied the convergence properties of sequences of probability distributions in $\mathcal{P}(Q)$. These results were then applied to a sequence of minimizers for finite dimensional approximations to the estimation problem for (4.84). Here we summarize their findings and apply them to the TCE model.
As in [17], the Prohorov metric is defined on the space of probability measures \( \mathcal{P}(Q) \) on the Borel subsets of \( Q \), where \( Q \) is a complete metric space with metric \( d \). The Prohorov metric \( \rho : \mathcal{P}(Q) \times \mathcal{P}(Q) \rightarrow \mathbb{R}^+ \) is defined by

\[
\rho(P_1, P_2) = \inf \{ \varepsilon > 0 : P_1[F] \leq P_2[F^\varepsilon] + \varepsilon; \ F \text{ closed}; \ F \subset Q \},
\]

where

\[
F^\varepsilon = \{ q \in Q : d(\bar{q}, q) < \varepsilon; \ \bar{q} \in F \}.
\]

It is well known that \( \rho \) is a metric on the space \( \mathcal{P}(Q) \), and that this metric space \((\mathcal{P}(Q), \rho)\) is complete. Moreover, \((\mathcal{P}(Q), \rho)\) is compact for all compact sets \( Q \).

Another well-known result [17] establishes equivalent conditions for convergence of probability distributions in the Prohorov metric. If \((Q, d)\) is a complete metric space, then the following convergence statements for \( P_k, P \in \mathcal{P}(Q) \) are equivalent:

(i) \( \rho(P_k, P) \to 0 \).

(ii) \( \int_Q f(q) dP_k(q) \to \int_Q f(q) dP(q) \) for all bounded and uniformly continuous functions \( f : Q \to \mathbb{R} \).

(iii) \( P_k[A] \to P[A] \) for all Borel sets \( A \subset Q \) with \( P[\partial A] = 0 \), where \( \partial A \) is the boundary of \( A \).

As discussed in [5], it follows that if the mapping \( q \to O_y(t_i, \cdot; q) \) is continuous, then the convergence \( \rho(P_k, P) \to 0 \) is equivalent to

\[
\mathcal{E}[O_y(t_i, \cdot; q)|P_k] \to \mathcal{E}[O_y(t_i, \cdot; q)|P],
\]

and hence the map

\[
P \to J(P) = \sum_{i=1}^{N_t} |\mathcal{E}[O_y(t_i, \cdot; q)|P] - \hat{z}_i|^2
\]

is continuous in the \( \rho \) topology. Moreover, if the space \( Q \) is compact we have that \((\mathcal{P}(Q), \rho)\) is a compact metric space, which along with the continuity of the map \( P \to J(P) \) guarantees the existence of a minimizer over \( \mathcal{P}(Q) \) for the estimation problem associated with (4.84).
In addition to establishing the existence of a solution for the above inverse problem, Banks and Bihari [5] developed results related to the stability of the problem

$$\min_{P \in \mathcal{P}(Q)} J(P, \hat{z}) = \sum_{i=1}^{N_1} |\mathcal{E}[O_y(t_i, \cdot; q)|P] - \hat{z}_i|^2.$$  \hspace{1cm} (4.85)

Using finite dimensional approximation techniques, they show in Theorem 4.1 that the solutions for (4.85) depend continuously on the data (see [5] for a complete discussion). This result is also useful in demonstrating the convergence of solutions for finite dimensional approximations to the original inverse problem.

### 4.3.2 Estimating truncated normal distributions for parameters

In this section we consider a special case of the general estimation problem for (4.84). Here we assume that each unknown parameter $q_i, i = 1, \ldots, N_q$ has a truncated normal distribution with mean $\mu_i$ and variance $\sigma_i^2$, where the support of the distribution is the compact interval $[\mu_i - 3\sigma_i, \mu_i + 3\sigma_i] \subset Q$. Thus $q \in Q$ has a truncated multi-normal distribution $\tilde{f}$ with mean vector $\mu = [\mu_1, \ldots, \mu_{N_q}]$. We further assume that the normal distributions are independent, so that the covariance matrix $C$ is a diagonal matrix in $\mathbb{R}^{N_q \times N_q}$ with diagonal $\sigma^2 = [\sigma_1^2, \ldots, \sigma_{N_q}^2]$. The support of this distribution is given by

$$\text{supp} \tilde{f} = [\mu_1 - 3\sigma_1, \mu_1 + 3\sigma_1] \times \cdots \times [\mu_{N_q} - 3\sigma_{N_q}, \mu_{N_q} + 3\sigma_{N_q}] \subset Q, \hspace{1cm} (4.86)$$

where $\sigma = [\sigma_1, \ldots, \sigma_{N_q}]$.

In general, these means and variances are unknown and must be estimated using inverse problem techniques. Here we formulate a special case of the general problem for (4.84) by seeking to minimize

$$J(\mu, \sigma; \hat{z}) = \sum_{i=1}^{N_1} |\mathcal{E}[O_y(t_i, \cdot; q)|P(\mu, \sigma)] - \hat{z}_i|^2.$$  \hspace{1cm} (4.87)
over the set of admissible vectors $\mu, \sigma \in \mathbb{R}^{N_q}$, where $P(\mu, \sigma)$ has a truncated multi-normal distribution with mean vector $\mu$ and covariance matrix $C = \text{diag}(\sigma^2)$, and with support given by (4.86). As before, $\mathcal{O}$ is the observation operator and $y(t_i, \cdot; q)$ is a solution for (4.60), (4.61) with parameters $q$. The observations $\tilde{z}_i, i = 1, \ldots, N_t$ are measurements corresponding to the expected value $E[\mathcal{O}y(t_i, \cdot; q) | P(\mu, \sigma)] = \int_{Q} \mathcal{O}y(t_i, \cdot; q) \tilde{f}(q; \mu, \sigma) dq,$ where $\tilde{f}(\cdot; \mu, \sigma)$ is the truncated multi-normal probability density function given by

$$\tilde{f}(q; \mu, \sigma) = \begin{cases} \frac{\sqrt{|A|}}{(0.9974\sqrt{2\pi})^{N_q}} e^{-\frac{1}{2}(q-\mu)^T A (q-\mu)} & \text{if } q \in \text{supp} \tilde{f} \\ 0 & \text{otherwise,} \end{cases}$$ (4.88)

where $A = C^{-1} = (\text{diag}(\sigma^2))^{-1}$ and $\text{supp} \tilde{f}$ is given by (4.86).

In other words, we seek to minimize

$$J(P; \tilde{z}) = \sum_{i=1}^{N_t} |E[\mathcal{O}y(t_i, \cdot; q) | P] - \tilde{z}_i|^2$$

over the space of truncated multi-normal probability distributions on $Q \subset \mathbb{R}^{N_q}$.

In Section 4.2.2, we established the convergence of sequences of minimizers for the finite dimensional estimation problems (4.56) to the minimizer for the infinite dimensional estimation problem (4.55). Here we prove a similar result for the estimation problem for (4.87) by adapting Theorem 4.2.2.

We define the parameter vector $\tilde{q} = (\mu, \sigma) \in Q$, where $Q$ denotes the space of admissible mean and variance parameters. We then formulate the family of finite dimensional estimation problems where we seek $\tilde{q} = (\mu, \sigma) \in Q$ that minimizes

$$J^N(\mu, \sigma; \tilde{z}) = \sum_{i=1}^{N_t} |E[\mathcal{O}y^N(t_i, \cdot; q) | P(\mu, \sigma)] - \tilde{z}_i|^2,$$ (4.89)

where $y^N(t_i, \cdot; q) \in \mathcal{H}^N$ is the solution to the finite dimensional parameterized system

$$\langle y^N(t), \psi \rangle + \sigma(q)(y^N(t), \psi) + \langle g(q)(y^N(t)), \psi \rangle = \langle f(t; q), \psi \rangle \quad (4.90)$$

$$y^N(0) = P^N y_0$$ (4.91)
at time $t_i$ for all $\psi \in \mathcal{H}^N$. For each $N$, we denote the minimizer for (4.89) by $\hat{q}^N = (\hat{\mu}^N, \hat{\sigma}^N)$.

Under certain compactness assumptions and the assumptions of Theorem 4.2.3, we can show using arguments similar to those in the proof of Theorem 4.2.2 (see [14], p. 124) that this sequence of minimizers for the finite dimensional estimation problems (4.89) converges to a minimizer for the infinite dimensional problem (4.87).

**Theorem 4.3.1** Assume that $Q$ is a compact metric space, and let 
\[ \{\hat{q}^N\} = \{\{\hat{\mu}^N, \hat{\sigma}^N\}\} \] 
be a sequence of minimizers for (4.89) subject to (4.90), (4.91). Then under the assumptions of Theorem 4.2.3, we have $\hat{q}^N \rightarrow \hat{q}$ as $N \rightarrow \infty$, where $\hat{q} = (\hat{\mu}, \hat{\sigma})$ is a minimizer for the infinite dimensional problem (4.87) subject to (4.60), (4.61).

**Proof:** The results of Theorem 4.2.3 guarantee the convergence of the sequence $Oy^N(t;q) \rightarrow Oy(t;q)$ as $N \rightarrow \infty$, where $y^N$ satisfies (4.90), (4.91) and $y$ satisfies (4.60), (4.61). Moreover, the truncated multi-normal probability density function given by (4.88) is a continuous function with respect to $\mu$ and $\sigma$, where $A = C^{-1} = (\text{diag}(\sigma^2))^{-1}$. Note that the arguments for Theorem 4.2.3 lead to the bound
\[ |y^N(t_i; \cdot; q)| \leq \hat{C} \]
for all $N$. Furthermore, we have
\[ \left| \tilde{f}(q; \mu^N, \sigma^N) \right| \leq \frac{1}{(0.9974\sigma_m\sqrt{2\pi})^N_q} \]
for all $N$, where $\sigma_m$ is the minimum value of $\sigma = [\sigma_1, \ldots, \sigma_{N_q}]$ in the compact set $Q$. Since the set $Q$ is also compact by assumption, we may apply the Bounded Convergence Theorem to obtain
\[ \mathcal{E}[Oy^N(t_i, \cdot; q)|P(\mu^N, \sigma^N)] = \int_Q Oy^N(t_i, \cdot; q) \tilde{f}(q; \mu^N, \sigma^N) dq \]
\[ \rightarrow \mathcal{E}[Oy(t_i, \cdot; q)|P(\mu, \sigma)] \] (4.92)
as $N \rightarrow \infty$, where $(\mu^N, \sigma^N) \rightarrow (\mu, \sigma)$. 

Chapter 4. Well-posedness results

Now let \( \tilde{q}^N \) be a sequence of solutions minimizing (4.89) subject to (4.90), (4.91). Using the compactness of \( Q \), we select a subsequence, which we denote by \( \tilde{q}^N \), which converges to some \( \tilde{q} \in Q \). The optimality of the sequence \( \{\tilde{q}^N\} \) implies that for every \( \tilde{q} \in Q \) we have

\[
J^N(\tilde{q}^N; \hat{z}) \leq J^N(\tilde{q}; \hat{z}).
\]

Therefore we may take the limit as \( N \to \infty \) and apply (4.92) to obtain

\[
J(\tilde{q}; \hat{z}) \leq J(\tilde{q}; \hat{z})
\]

for every \( \tilde{q} \in Q \). It follows that \( \tilde{q} \) is a minimizer for (4.87) subject to (4.60), (4.61).

4.3.3 Uncertainty applied to the TCE model

As discussed in Section 4.2.3, the space \( Q \) defined for the TCE PBPK-hybrid model is a compact subset of Euclidean space, and hence the existence result discussed in the previous section is valid for our model system. Therefore we can address the inherent uncertainty in our model parameters across a population by formulating an inverse problem for probability distributions for each of the parameters. This creates a framework for working with experimental data from multiple individuals, such as the data collected by Evans et al. [32].

In Chapter 6 we will present results related to parameter estimation problems for the TCE model, including the probabilistic type of problem discussed in Section 4.3.1. Specifically, we will study the special case outlined in Section 4.3.2 by assuming that each of our TCE model parameters is independently distributed with a truncated normal distribution.

Here we seek to minimize

\[
J(\mu, \sigma) = \sum_{i=1}^{N_t} |\mathcal{E}[O_y(t_i, \cdot; q)|P(\mu, \sigma))] - \hat{z}_i|^2
\]

over the set of admissible vectors \( \mu, \sigma \in \mathbb{R}^{N_q} \), where \( P(\mu, \sigma) \) has a truncated multivariate normal distribution with mean vector \( \mu \) and covariance matrix \( \mathbf{C} = \text{diag}(\sigma^2) \), and with
compact support given by (4.86). Moreover, \( \mathcal{O} \) is either of the observation operators defined in (4.82) and (4.83), and \( y(t_i, \cdot; q) \) is a solution for (4.3) with parameters \( q \). As in the previous section, the observations \( \hat{z}_i, i = 1, \ldots, N_t \) are measurements corresponding to the expected value

\[
E[\mathcal{O} y(t_i, \cdot; q)|P(\mu, \sigma)] = \int_Q \mathcal{O} y(t_i, \cdot; q) \tilde{f}(q; \mu, \sigma) dq,
\]

where \( \tilde{f}(\cdot; \mu, \sigma) \) is the truncated multi-normal probability density function given by (4.88) with mean vector \( \mu \) and \( A^{-1} = C = (\text{diag}(\sigma^2)) \), and with compact support as in (4.86).

As discussed in Section 4.2.3, the conditions of Theorem 4.2.3 are satisfied for the TCE PBPK-hybrid model. Therefore we can also apply Theorem 4.3.1 to the TCE model. Results related to this type of inverse problem for our model will be presented in Chapter 6.
Chapter 5

Model simulations

In this chapter we present results related to the numerical approximation of the PBPK-hybrid TCE model. We use the finite element method to discretize the partial differential equations in the model and implement our algorithm in Matlab. Moreover, we demonstrate the convergence of our numerical approximations and illustrate the dependence of the model simulations on several of the adipose model parameters. The methods described in this chapter also will be combined with inverse problem techniques in Chapter 6 to carry out the estimation of model parameters.

5.1 Weak form

In this section we derive a weak or variational form for the PBPK-hybrid TCE model (3.3) – (3.25), which is utilized in our finite element approximations.

Recall that the strong form for the capillary region is given by

\[ V_B \frac{\partial C_B}{\partial t} = \frac{V_B}{r_1 \sin \phi} \frac{\partial}{\partial \phi} \left[ \sin \phi \left( \frac{D_B}{r_1} \frac{\partial C_B}{\partial \phi} - vC_B \right) \right] + \lambda_B \mu_B (f_I C_I(\theta_0) - f_B C_B) + \lambda_A \mu_B (f_A C_A(\theta_0) - f_B C_B) \]  (5.1)

for \( t \geq 0, \varepsilon_1 < \phi < \pi - \varepsilon_2 \), where we have approximated \( r_2 \approx r_1 \). At the boundaries
we have the conditions

\[
-\frac{D_B}{r_1} \frac{\partial C_B}{\partial \phi} (t, \phi) + vC_B(t, \phi) \bigg|_{\phi=\epsilon_1} = \frac{Q_c}{1000A_B}C_a(t) \quad (5.2)
\]

\[
-\frac{D_B}{r_1} \frac{\partial C_B}{\partial \phi} (t, \phi) + vC_B(t, \phi) \bigg|_{\phi=\pi-\epsilon_2} = \frac{Q_c}{1000A_B}C_v(t) \quad (5.3)
\]

for \( t \geq 0 \). In the interstitial region, we have

\[
V_I \frac{\partial C_I}{\partial t} = \frac{V_ID_I}{r_1^2} \left[ \frac{1}{\sin^2 \phi} \frac{\partial^2 C_I}{\partial \theta^2} + \frac{1}{\sin \phi} \frac{\partial}{\partial \phi} \left( \sin \phi \frac{\partial C_I}{\partial \phi} \right) \right] + \delta_{\theta_0}(\theta) \chi_B(\phi) \lambda I \mu_{BI} (f_IC_B - f_IC_I) + \mu_{IA} (f_A C_A - f_IC_I) \quad (5.4)
\]

for \( t \geq 0, 0 \leq \theta \leq 2\pi \) and \( 0 < \phi < \pi \), where \( \delta_{\theta_0}(\theta) \) is the Dirac delta distribution centered at \( \theta = \theta_0 \), and

\[
\chi_B(\phi) = \begin{cases} 
1 & \text{if } \phi \in (\epsilon_1, \pi - \epsilon_2) \\
0 & \text{otherwise.}
\end{cases}
\]

The boundary conditions are given by

\[
C_I(t, \theta, \phi) = C_I(t, \theta + 2\pi, \phi) \quad (5.5)
\]

for \( t \geq 0, 0 < \phi < \pi \),

\[
\frac{\partial C_I}{\partial \theta}(t, \theta, \phi) = \frac{\partial C_I}{\partial \theta}(t, \theta + 2\pi, \phi) \quad (5.6)
\]

for \( t \geq 0 \) and almost every \( 0 < \phi < \pi \), and

\[
C_I(t, \theta, 0) < \infty \quad (5.7)
\]

\[
C_I(t, \theta, \pi) < \infty \quad (5.8)
\]

for \( t \geq 0 \) and \( 0 \leq \theta \leq 2\pi \). Finally, in the adipocyte region we have

\[
V_A \frac{\partial C_A}{\partial t} = \frac{V_AD_A}{r_1^2} \left[ \frac{1}{\sin^2 \phi} \frac{\partial^2 C_A}{\partial \theta^2} + \frac{1}{\sin \phi} \frac{\partial}{\partial \phi} \left( \sin \phi \frac{\partial C_A}{\partial \phi} \right) \right] + \delta_{\theta_0}(\theta) \chi_B(\phi) \lambda A \mu_{BA} (f_B C_B - f_A C_A) + \mu_{IA} (f_IC_I - f_A C_A) \quad (5.9)
\]
Chapter 5. Model simulations

for \( t \geq 0, 0 \leq \theta \leq 2\pi \) and \( 0 < \phi < \pi \), where as before we approximate \( r_0 \approx r_1 \). The boundary conditions are similar to those for the interstitial space, and are given by

\[
C_A(t, \theta, \phi) = C_A(t, \theta + 2\pi, \phi) \quad (5.10)
\]

for \( t \geq 0, 0 < \phi < \pi \),

\[
\frac{\partial C_A}{\partial \theta}(t, \theta, \phi) = \frac{\partial C_A}{\partial \theta}(t, \theta + 2\pi, \phi) \quad (5.11)
\]

for \( t \geq 0 \) and for almost every \( 0 < \phi < \pi \), and

\[
C_A(t, \theta, 0) < \infty \quad (5.12)
\]

\[
C_A(t, \theta, \pi) < \infty. \quad (5.13)
\]

for \( t \geq 0 \) and \( 0 \leq \theta \leq 2\pi \).

We choose the following weak form for our system:

\[
\langle V_B \frac{\partial C_B}{\partial t}(t), \psi \rangle_B = -\langle \frac{V_B}{r_1} \left( \frac{D_B}{r_1} \frac{\partial C_B}{\partial \phi}(t) - v C_B(t) \right), \frac{\partial \psi}{\partial \phi} \rangle_B + \langle \lambda_I \mu_B I(f_I C_I(t, \theta_0) - f_B C_B(t), \psi \rangle_B
\]

\[
+ \langle \lambda_{IA} \mu_{BA}(f_A C_A(t, \theta_0) - f_B C_B(t)), \psi \rangle_B + \frac{V_B Q_e}{1000 A_B r_1} |C_a(t) \sin(\varepsilon_1) \psi(\varepsilon_1) - C_v(t) \sin(\pi - \varepsilon_2) \psi(\pi - \varepsilon_2)|
\]

\[
(5.14)
\]

\[
\langle V_I \frac{\partial C_I}{\partial t}(t), \xi \rangle_{IA} = -\langle \frac{V_I D_I}{r_1^2 \sin^2 \phi} \frac{\partial C_I}{\partial \theta}(t), \frac{\partial \xi}{\partial \theta} \rangle_{IA} - \langle \frac{V_I D_I}{r_1^2} \frac{\partial C_I}{\partial \phi}(t), \frac{\partial \xi}{\partial \phi} \rangle_{IA} + \langle \lambda_I \mu_B I(f_B C_B(t) - f_I C_I(t, \theta_0)), \xi(\theta_0) \rangle_B + \langle \mu_{IA}(f_A C_A(t) - f_I C_I(t)), \xi(\theta_0) \rangle_{IA} \quad (5.15)
\]

\[
\langle V_A \frac{\partial C_A}{\partial t}(t), \eta \rangle_{IA} = -\langle \frac{V_A D_A}{r_1^2} \frac{\partial C_A}{\partial \theta}(t), \frac{\partial \eta}{\partial \theta} \rangle_{IA} - \langle \frac{V_A D_A}{r_1^2} \frac{\partial C_A}{\partial \phi}(t), \frac{\partial \eta}{\partial \phi} \rangle_{IA} + \langle \lambda_{IA} \mu_{BA}(f_B C_B(t) - f_A C_A(t, \theta_0)), \eta(\theta_0) \rangle_B + \langle \mu_{IA}(f_I C_I(t) - f_A C_A(t)), \eta(\theta_0) \rangle_{IA} \quad (5.16)
\]

for \( \psi \in H^1(\Omega_B), \xi \in H^1_{\text{per}}(\Omega_{IA}) = \{ u \in H^1(\Omega_{IA}) : u(\theta, \phi) = u(\theta + 2\pi, \phi) \} \) and \( \eta \in H^1_{\text{per}}(\Omega_{IA}), \) where

\[
\bar{\Omega}_B = \{(r, \theta, \phi) : r = r_1, \theta = \theta_0, \varepsilon_1 \leq \phi \leq \pi - \varepsilon_2\}
\]

\[
\bar{\Omega}_{IA} = \{(r, \theta, \phi) : r = r_1, 0 \leq \theta \leq 2\pi, 0 \leq \phi \leq \pi\}.
\]
Moreover, the inner products are given by
\[
\langle u, v \rangle_B = \int_{\xi_1}^{\pi - \varepsilon_2} u(\phi) v(\phi) \sin \phi \, d\phi
\]
\[
\langle u, v \rangle_{IA} = \int_0^{2\pi} \int_0^\pi u(\theta, \phi) v(\theta, \phi) \sin \phi \, d\phi \, d\theta.
\]
We use the inner product \(\langle \cdot, \cdot \rangle_B\) on the space \(L^2(\Omega_B)\), and we use \(\langle \cdot, \cdot \rangle_{IA}\) on the space \(L^2(\Omega_{IA})\).

Here we use the notation \(C_I(t, \theta_0)\) to denote the trace operation \(T^{0}_{\theta_0}C_I(t)\) for \(C_I(t) \in H^1_{\text{per}}(\Omega_{IA})\) (see (4.1) for a precise definition). Similarly, we denote \(T^{0}_{\theta_0}C_A(t)\) by \(C_A(t, \theta_0)\) for \(C_A(t) \in H^1_{\text{per}}(\Omega_{IA})\), as well as \(\xi(\theta_0) = T^{0}_{\theta_0}\xi\) and \(\eta(\theta_0) = T^{0}_{\theta_0}\eta\) for \(\xi, \eta \in H^1_{IA}\).

An additional condition is placed on the weak form equations (5.15) and (5.16) for the interstitial space and adipocyte regions. In the strong form, we require the solutions \(C_I(t, \theta, 0)\) and \(C_I(t, \theta, \pi)\) to be finite for all \(t \geq 0\) and \(0 \leq \theta \leq 2\pi\), with a similar finiteness requirement for \(C_A\) (see (5.7), (5.8) and (5.12), (5.13)). For the weak form, we require all of the integrals in (5.15) and (5.16) to be finite.

To verify that the weak form (5.14) – (5.16) matches up with the strong form (5.1) – (5.13), we assume additional smoothness and integrate by parts in each equation. Note that for \(C_B(t) \in H^2(\Omega_B)\) and \(\psi \in H^1_B\) we have

\[-\left\langle \frac{V_B}{r_1} \left( \frac{D_B}{r_1} \frac{\partial C_B}{\partial \phi}(t) - vC_B(t) \right), \frac{\partial \psi}{\partial \phi} \right\rangle_B = \right.
\]
\[
\left. - \int_{\xi_1}^{\pi - \varepsilon_2} \frac{V_B}{r_1} \sin \phi \left( \frac{D_B}{r_1} \frac{\partial C_B}{\partial \phi}(t) - vC_B(t) \right) \frac{\partial \psi}{\partial \phi} \, d\phi \right.
\]
\[
\left. = \int_{\xi_1}^{\pi - \varepsilon_2} \frac{V_B}{r_1} \frac{\partial \psi}{\partial \phi} \left[ \sin \phi \left( \frac{D_B}{r_1} \frac{\partial C_B}{\partial \phi}(t) - vC_B(t) \right) \right] \bigg|_{\phi=\pi - \varepsilon_2}^{\phi=\xi_1} \right.
\]
\[
\left. = \frac{V_B}{r_1} \left[ \sin \phi \left( \frac{D_B}{r_1} \frac{\partial C_B}{\partial \phi}(t) - vC_B(t) \right) \right] \bigg|_{\phi=\xi_1}^{\phi=\pi - \varepsilon_2} \right.
\]
\[
\left. - \left\langle \frac{V_B}{r_1} \frac{\partial}{\partial \phi} \left[ \sin \phi \left( \frac{D_B}{r_1} \frac{\partial C_B}{\partial \phi}(t) - vC_B(t) \right) \right], \psi \right\rangle_B \right.
\]
\[
\left. - \frac{V_B}{r_1} \left[ \sin \phi \left( \frac{D_B}{r_1} \frac{\partial C_B}{\partial \phi}(t) - vC_B(t) \right) \right] \bigg|_{\phi=\xi_1}^{\phi=\pi - \varepsilon_2} \right.
\]
and therefore (5.14) is equivalent to
\[
\langle V_B \frac{\partial C_B}{\partial t}(t), \psi \rangle_B = \left\langle \frac{V_B}{r_1 \sin \phi} \frac{\partial}{\partial \phi} \left[ \sin \phi \left( \frac{D_B}{r_1} \frac{\partial C_B}{\partial \phi}(t) - v C_B(t) \right) \right], \psi \rangle_B \\
+ \langle \lambda_B \mu_B \left( f_I C_1(t, \theta_0) - f_B C_B(t) \right), \psi \rangle_B \\
+ \langle \lambda_A \mu_B \left( f_A C_A(t, \theta_0) - f_B C_B(t) \right), \psi \rangle_B \\
+ \frac{V_B}{r_1} \left[ \left( \frac{Q_c}{1000 A_B} C_a(t) + \left( \frac{D_B}{r_1} \frac{\partial C_B}{\partial \phi}(t) - v C_B(t) \right) \right) \right] \psi \sin \phi \bigg|_{\phi = \epsilon_1} \\
+ \left( \frac{Q_c C_e(t)}{1000 A_B} - \left( \frac{D_B}{r_1} \frac{\partial C_B}{\partial \phi}(t) - v C_B(t) \right) \right) \psi \sin \phi \bigg|_{\phi = \pi - \epsilon_2} \right\rangle (5.17)
\]
for all \( \psi \in H^1(\Omega_B) \).

Now we choose \( \psi \in H^1_0(\Omega_B) = \{ u \in H^1(\Omega_B) : u(\pi - \epsilon_2) = 0 \} \subset H^1(\Omega_B) \)
so that (5.17) reduces to
\[
\langle V_B \frac{\partial C_B}{\partial t}(t), \psi \rangle_B = \left\langle \frac{V_B}{r_1 \sin \phi} \frac{\partial}{\partial \phi} \left[ \sin \phi \left( \frac{D_B}{r_1} \frac{\partial C_B}{\partial \phi}(t) - v C_B(t) \right) \right], \psi \rangle_B \\
+ \langle \lambda_B \mu_B \left( f_I C_1(t, \theta_0) - f_B C_B(t) \right), \psi \rangle_B \\
+ \langle \lambda_A \mu_B \left( f_A C_A(t, \theta_0) - f_B C_B(t) \right), \psi \rangle_B.
\]

Since \( H^1_0(\Omega_B) \) is dense in \( L^2(\Omega_B) \), it follows that (5.1) holds in the \( L^2 \) sense.

If we choose \( \psi \in H^1_R(\Omega_B) = \{ u \in H^1(\Omega_B) : u(\pi - \epsilon_2) = 0 \} \), then (5.17) becomes
\[
\frac{V_B}{r_1} \left[ \frac{Q_c}{1000 A_B} C_a(t) - \left( \frac{D_B}{r_1} \frac{\partial C_B}{\partial \phi}(t) + v C_B(t) \right) \right] \psi \sin \phi \bigg|_{\phi = \epsilon_1} = 0
\]
and hence (5.2) is satisfied. Similarly, if we choose \( \psi \in H^1_1(\Omega_B) = \{ u \in H^1(\Omega_B) : u(\epsilon_1) = 0 \} \) in (5.17), it is seen that (5.3) is also satisfied. Therefore the weak form for the capillary region is equivalent to the strong form.

Next we consider the interstitial space, where we assume that \( C_1(t) \in H^2(\Omega_{IA}) \cap H^1_{IA} \). Using integration by parts, we obtain
\[
-\langle V_I D_I \frac{\partial C_I}{\partial \phi}(t), \frac{\partial \xi}{\partial \phi} \rangle_{IA} = -\frac{V_I D_I}{r_1^2} \int_0^{2\pi} \int_0^\pi \left( \sin \phi \frac{\partial C_I}{\partial \phi}(t) \right) \frac{\partial \xi}{\partial \phi} d\phi d\theta \\
= \frac{V_I D_I}{r_1^2} \int_0^{2\pi} \int_0^\pi \left( \sin \phi \frac{\partial C_I}{\partial \phi}(t) \right) \xi d\phi d\theta
\]
for \( \xi \in H_{IA}^1 \), and similarly

\[-\langle \frac{V_ID_I}{r_1^2} \frac{\partial C_I}{\partial \phi}(t), \frac{\partial \xi}{\partial \theta} \rangle_{IA} = \langle \frac{V_ID_I}{r_1^2} \frac{\partial^2 C_I}{\partial \phi \partial \theta}(t), \xi \rangle_{IA} - \int_0^\pi \frac{V_ID_I}{r_1^2} \frac{\partial C_I}{\partial \theta}(t) \xi \bigg|_{\phi=0}^\phi d\phi \]

\[-\int_0^\pi \frac{V_ID_I}{r_1^2} \frac{\partial C_I}{\partial \theta}(t) \xi(0, \phi) \left[ \frac{\partial C_I}{\partial \theta}(t, 2\pi, \phi) - \frac{\partial C_I}{\partial \theta}(t, 0, \phi) \right] d\phi \]

for \( \xi \in H_{IA}^1 \). Moreover,

\[\langle \lambda_I \mu_{BI}(fBC(t) - f_1 C_1(t, \theta_0)), \xi(\theta_0) \rangle_B = \int_0^\pi \chi_B(\phi) \lambda_I \mu_{BI}(fBC(t) - f_1 C_1(t, \theta_0)) \xi(\theta_0) d\phi \]

\[= \int_0^\pi \int_0^\theta \delta_{\theta_0}(\theta) \chi_B(\phi) \lambda_I \mu_{BI}(fBC(t) - f_1 C_1(t)) \xi d\phi d\theta \]

\[= \langle \delta_{\theta_0}(\theta) \chi_B(\phi) \lambda_I \mu_{BI}(fBC(t) - f_1 C_1(t)), \xi \rangle_{IA} \]

for \( \xi \in H_{IA}^1 \).

Therefore

\[\langle \frac{V_ID_I}{r_1^2} \frac{\partial C_I}{\partial t}(t), \xi \rangle_{IA} = -\langle \frac{V_ID_I}{r_1^2} \frac{\partial C_I}{\partial \phi}(t), \frac{\partial \xi}{\partial \theta} \rangle_{IA} - \langle \frac{V_ID_I}{r_1^2} \frac{\partial C_I}{\partial \phi}(t), \frac{\partial \xi}{\partial \phi} \rangle_{IA} \]

\[+ \langle \lambda_I \mu_{BI}(fBC(t) - f_1 C_1(t, \theta_0)), \xi(\theta_0) \rangle_B \]

\[+ \langle \mu_{IA}(fAC(t) - f_1 C_1(t)), \xi \rangle_{IA} \]

\[= \frac{V_ID_I}{r_1^2} \left[ \frac{1}{\sin^2 \phi} \frac{\partial^2 C_I}{\partial \theta^2}(t) + \frac{1}{\sin \phi} \frac{\partial}{\partial \phi} \left( \sin \phi \frac{\partial C_I}{\partial \phi}(t) \right) \right] \xi \rangle_{IA} \]

\[+ \langle \delta_{\theta_0}(\theta) \chi_B(\phi) \lambda_I \mu_{BI}(fBC(t) - f_1 C_1(t)), \xi \rangle_{IA} \]

\[+ \langle \mu_{IA}(fAC(t) - f_1 C_1(t)), \xi \rangle_{IA} \]

\[- \int_0^\pi \frac{V_ID_I}{r_1^2} \frac{\partial C_I}{\partial t}(t, 2\pi, \phi) - \frac{\partial C_I}{\partial t}(t, 0, \phi) \right] \xi \rangle_{IA} \] (5.18)
for $\xi \in H^1_{IA}$. If we choose $\xi \in H^1_0(\Omega_{IA}) \subset H^1_{IA}$, then (5.18) becomes

$$
\langle V_{I} \frac{\partial C_I}{\partial t}(t), \xi \rangle_{IA} = -\langle \frac{V_{I} D_{I}}{r_{I}^2 \sin^2 \phi} \frac{\partial C_I}{\partial \theta}(t), \frac{\partial \xi}{\partial \theta} \rangle_{IA} - \langle \frac{V_{I} D_{I}}{r_{I}^2} \frac{\partial \xi}{\partial \phi}(t), \frac{\partial C_I}{\partial \phi} \rangle_{IA}
$$

$$
+ \langle \lambda_{I} \mu_{B I}(f_{B} C_{B}(t) - f_{I} C_{I}(t, \theta_0)), \xi(\theta_0) \rangle_{B}
$$

$$
+ \langle \mu_{IA}(f_{IA} C_{IA}(t) - f_{I} C_{I}(t)), \xi \rangle_{IA}
$$

$$
= \langle \frac{V_{I} D_{I}}{r_{I}^2} \left[ \frac{1}{\sin^2 \phi} \frac{\partial^2 C_I}{\partial \theta^2}(t) + \frac{1}{\sin \phi} \frac{\partial}{\partial \phi} \left( \sin \phi \frac{\partial C_I}{\partial \phi}(t) \right) \right], \xi \rangle_{IA}
$$

$$
+ \langle \delta_{B I}(\theta) \chi_{B}(\phi) \lambda_{I} \mu_{B I}(f_{B} C_{B}(t) - f_{I} C_{I}(t)), \xi \rangle_{IA}
$$

$$
+ \langle \mu_{IA}(f_{IA} C_{IA}(t) - f_{I} C_{I}(t)), \xi \rangle_{IA}.
$$

Since $H^1_{per}(\Omega_{IA})$ is dense in $L^2(\Omega_{IA})$, it follows that (5.4) is satisfied in the $L^2$ sense.

Now if we choose $\xi \in H^1_{IA}$ with $\xi|_{\theta=0} \neq 0$, then (5.18) reduces to

$$
\int_0^\pi \frac{V_{I} D_{I}}{r_{I}^2 \sin \phi} \xi(0, \phi) \left[ \frac{\partial C_I}{\partial \theta}(t, 2\pi, \phi) - \frac{\partial C_I}{\partial \theta}(t, 0, \phi) \right] d\phi = 0.
$$

Therefore (5.6) is satisfied for almost every $\phi \in [0, \pi]$, and hence the weak form (5.15) for the interstitial space is equivalent to the strong form. Similar arguments can be used to establish that the weak form (5.16) for the adipocyte region is equivalent to the strong form.

### 5.2 Finite element formulation

#### 5.2.1 Discretization

The capillary equation is one-dimensional in space, and we choose uniform subintervals of $(\varepsilon_1, \pi - \varepsilon_2)$ for our discretization nodes in that region. Both the interstitial space and adipocyte equations are two-dimensional in space, and for those regions we choose squares for our discretization meshes.

Using squares in the interstitial and adipocyte regions will allow us to match up the grid points in the $\phi$ variable with the nodal points in the capillary in a simple and systematic way. Moreover, we can take advantage of the one-dimensional matrix
structure for the capillary region to build the matrices for the other two regions using tensors. This leads to a computationally simple and fast implementation in Matlab, (The Mathworks Inc., Natick, MA) which is the programming language we use for our computational work.

5.2.2 Basis functions

Recall that our solution spaces are $H^1(\Omega_B)$ for the capillary region and $H^1_{\text{per}}(\Omega_{IA})$ for the interstitial and adipocyte regions. Based on the smoothness of these spaces, we choose piecewise linear splines for our basis functions in both the $\phi$ and $\theta$ variables. That is, in the capillary region we use piecewise linear splines and for the other two regions we use piecewise bilinear functions.

Note that the solutions $C_I$ and $C_A$ for the interstitial and adipocyte regions respectively are $2\pi$-periodic with respect to $\theta$, as required by the boundary conditions (5.5), (5.6) and (5.10), (5.11). This suggests that Fourier elements may be chosen as basis functions in the $\theta$ variable. The $\delta$ function that appears in the PDEs (5.4) and (5.9) for the interstitial and adipocyte regions, however, suggests that piecewise linear splines may be more appropriate than the global Fourier elements. We tested this hypothesis by implementing and comparing piecewise linear splines with sine/cosine functions as basis functions in the $\theta$ variable. The solutions generated with the piecewise linear splines were better able to capture the localized behavior of the $\delta$ function around $\theta = \theta_0$ than the solutions generated with sine and cosine basis functions. Here we report on our results related to the piecewise linear basis functions.

For any positive integer $N$ and for some discretization $\phi_1, \ldots, \phi_{N+1}$, we define
basis functions $B_j^N(\phi)$ by

$$
B_j^N(\phi) = \begin{cases} 
\frac{\phi - \phi_{j-1}}{\phi_j - \phi_{j-1}} & \text{if } \phi_{j-1} \leq \phi \leq \phi_j \\
\frac{\phi_{j+1} - \phi}{\phi_{j+1} - \phi_j} & \text{if } \phi_j \leq \phi \leq \phi_{j+1} \\
0 & \text{otherwise}
\end{cases}
$$

(5.19)

for $j = 2, \ldots, N$ and

$$
B_1^N(\phi) = \begin{cases} 
\frac{\phi_2 - \phi}{\phi_2 - \phi_1} & \text{if } \phi_1 \leq \phi \leq \phi_2 \\
0 & \text{otherwise}
\end{cases}
$$

(5.20)

$$
B_{N+1}^N(\phi) = \begin{cases} 
\frac{\phi - \phi_N}{\phi_{N+1} - \phi_N} & \text{if } \phi_N \leq \phi \leq \phi_{N+1} \\
0 & \text{otherwise}
\end{cases}
$$

(5.21)

In each of the three regions of the adipose tissue compartment, we specify $N$ and $\phi_1, \ldots, \phi_N$ in order to generate a discretization that includes the capillary boundary points $\varepsilon_1$ and $\pi - \varepsilon_2$, and so that the discretization points in each of the three regions are aligned. Specifically, we set $\varepsilon_1 = \varepsilon_2 = \pi/8$ and $N_\phi = 8\kappa$ for some positive integer $\kappa \geq 1$, and we define

$$
N_B = N_\phi - 2\kappa \\
N_I = N_\phi \\
N_A = N_\phi.
$$

Moreover, we define the discretization in the capillary region by

$$
\phi_j^B = \varepsilon_1 + \frac{(\pi - \varepsilon_2 - \varepsilon_1)(j - 1)}{N_B}
$$

(5.22)

for $j = 1, \ldots, N_B + 1$. Therefore the basis functions in the capillary are given by (5.19)–(5.21) where we set $N = N_B$ and $\phi_j = \phi_j^B$ as in (5.22) for $j = 1, \ldots, N_B + 1$. 
In the interstitial and adipocyte regions respectively, we define the discretizations with respect to $\phi$ by
\[
\phi^I_j = \frac{\pi(j - 1)}{N_I}, \quad j = 1, \ldots, N_I + 1 \tag{5.23}
\]
\[
\phi^A_j = \frac{\pi(j - 1)}{N_A}, \quad j = 1, \ldots, N_A + 1. \tag{5.24}
\]

Our basis functions are then given by (5.19)–(5.21) with $N = N_I$ and $\phi_j = \phi^I_j$, $j = 1, \ldots, N_I + 1$ as in (5.23) for the interstitial space, and with $N = N_A$ and $\phi_j = \phi^A_j$, $j = 1, \ldots, N_A + 1$ as in (5.24) for the adipocyte region. Note that by design we have $\phi^B_j = \phi^I_j + \phi^A_j$ for $j = 1, \ldots, N_B + 1$.

In the interstitial region we also require basis functions with respect to $\theta$. For each positive integer $M$ we define $\theta_j = 2\pi(j - 1)/M$ for $j = 1, \ldots, M + 1$, and
\[
\gamma^M_j(\theta) = \begin{cases} 
\frac{\theta - \theta_j - 1}{\theta_j - \theta_j - 1} & \text{if } \theta_{j-1} \leq \theta \leq \theta_j \\
\frac{\theta_{j+1} - \theta}{\theta_{j+1} - \theta_j} & \text{if } \theta_j \leq \theta \leq \theta_{j+1} \\
0 & \text{otherwise}
\end{cases}
\]
for $j = 2, \ldots, M$ and
\[
\gamma^M_1(\theta) = \begin{cases} 
\frac{\theta_2 - \theta}{\theta_2 - \theta_1} & \text{if } \theta_1 \leq \theta \leq \theta_2 \\
0 & \text{otherwise}
\end{cases}
\]
\[
\gamma^M_{M+1}(\theta) = \begin{cases} 
\frac{\theta - \theta_M}{\theta_{M+1} - \theta_M} & \text{if } \theta_M \leq \theta \leq \theta_{M+1} \\
0 & \text{otherwise.}
\end{cases}
\]

In the interstitial region we set $M = M_I = 2N_\phi$ and in the adipocyte region we set $M = M_A = 2N_\phi$. See Figure 5.1 for a schematic of the discretizations for each of the three regions with $N_\phi = 16$ ($\kappa = 2$).
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Figure 5.1: Schematic of an example finite element discretization with $N_\phi = 16$ ($\kappa = 2$). The interstitial and adipocyte regions are each represented by the large rectangle and the capillary region is represented by the smaller rectangle.

Now let $V_B^N = \text{span}\{B_k^{N_B}\}_{k=1}^{N_B+1}$, and

$$V_{I}^{M,N} = \text{span}\{\gamma_j^{M_I} B_k^{N_I}\}$$
$$V_{A}^{M,N} = \text{span}\{\gamma_j^{M_A} B_k^{N_A}\}$$

for $j = 1, \ldots, M_I + 1$, $k = 1, \ldots, N_I + 1$ and for $j = 1, \ldots, M_A + 1$, $k = 1, \ldots, N_A + 1$ respectively. Note that $V_B^N \subset H^1(\Omega_B)$, $V_{I}^{M,N} \subset H^1_{\text{per}}(\Omega_{IA})$ and $V_{A}^{M,N} \subset H^1_{\text{per}}(\Omega_{IA})$.

We define the finite-dimensional state space $V^{M,N}$ by

$$V^{M,N} = V_B^N \times V_{I}^{M,N} \times V_{A}^{M,N} \times \mathbb{R}^6 \subset \mathcal{V}.$$ 

This space is the subspace of $\mathcal{V}$ that we use for our finite dimensional approximations.
5.2.3 Finite element approximations

We now define the following approximation functions:

\[ C^N_B(t, \phi) = \sum_{n=1}^{N_B+1} u_n(t) B_n^N(\phi) \]  
(5.25)

\[ C^{M,N}_I(t, \theta, \phi) = \sum_{n=1}^{N_I+1} \sum_{m=1}^{M_I+1} v_{mn}(t) \gamma_m^M(\theta) B_n^N(\phi) \]  
(5.26)

\[ C^{M,A}_A(t, \theta, \phi) = \sum_{n=1}^{N_A+1} \sum_{m=1}^{M_A+1} w_{mn}(t) \gamma_m^M(\theta) B_n^A(\phi). \]  
(5.27)

If we insert the approximation functions (5.25) – (5.27) into the weak form (5.14) – (5.16) with \( \psi(\phi) = B_k^{N_B}(\phi) \), \( \xi(\theta, \phi) = \gamma_j^M(\theta) B_k^{N_I}(\phi) \) and \( \eta(\theta, \phi) = \gamma_j^M(\theta) B_k^{N_A}(\phi) \), we obtain

\[ V_B \sum_{n=1}^{N_B+1} u_n(t) \langle B_n^{N_B}, B_k^{N_B} \rangle_B = -\frac{V_B D_B}{r_1^2} \sum_{n=1}^{N_B+1} u_n(t) \langle B_n^{N_B'}, B_k^{N_B'} \rangle_B \]

\[ + \frac{V_B v}{r_1} \sum_{n=1}^{N_B+1} u_n(t) \langle B_n^{N_B}, B_k^{N_B'} \rangle_B \]

\[ + \lambda_I \mu_B f_I \sum_{n=1}^{N_I+1} \sum_{m=1}^{M_I+1} v_{mn}(t) \gamma_m^M(\theta_0) \langle B_n^{N_I}, B_k^{N_B} \rangle_B \]

\[ + \lambda_A \mu_B f_A \sum_{n=1}^{N_A+1} \sum_{m=1}^{M_A+1} w_{mn}(t) \gamma_m^M(\theta_0) \langle B_n^{N_A}, B_k^{N_B} \rangle_B \]

\[ - (\lambda_I \mu_B + \lambda_A \mu_B) f_B \sum_{n=1}^{N_B+1} u_n(t) \langle B_n^{N_B}, B_k^{N_B} \rangle_B \]

\[ + \frac{Q_e V_B}{1000 \mu_B f_A} (C_a(t) \sin(\varepsilon_1) B_k^{N_B}(\varepsilon_1) \]

\[ - C_v(t) \sin(\pi - \varepsilon_2) B_k^{N_B}(\pi - \varepsilon_2)) \]  
(5.28)

\[ V_I \sum_{n=1}^{N_I+1} \sum_{m=1}^{M_I+1} \dot{v}_{mn}(t) \langle \gamma_m^{M_I} B_n^{N_I}, \gamma_j^{M_I'} B_k^{N_I} \rangle_I \]

\[ = -\frac{V_I D_I}{r_1^2} \sum_{n=1}^{N_I+1} \sum_{m=1}^{M_I+1} v_{mn}(t) \langle \frac{1}{\sin^2(\phi)} \gamma_m^{M_I'} B_n^{N_I}, \gamma_j^{M_I'} B_k^{N_I} \rangle_I \]
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\[ - \frac{V_ID_I}{r_I^2} \sum_{n=1}^{N_B+1} \sum_{m=1}^{M_I+1} \nu_{mn}(t) \langle \gamma_{m}^{M_I} B_{n}^{N_I}, \gamma_{j}^{M_I} B_{k}^{N_I} \rangle_{IA} + \lambda_I \mu^{B_I} f_B \sum_{n=1}^{N_B+1} u_n(t) \gamma_{j}^{M_I} (\theta_0) \langle B_{n}^{N_B}, B_{k}^{N_I} \rangle_B \]

\[ - \lambda_I \mu^{B_I} f_I \sum_{n=1}^{N_I+1} \sum_{m=1}^{M_I+1} \nu_{mn}(t) \gamma_{m}^{M_I} (\theta_0) \gamma_{j}^{M_I} (\theta_0) \langle B_{n}^{N_I}, B_{k}^{N_I} \rangle_B + \mu^{I_A} f_A \sum_{n=1}^{N_A+1} \sum_{m=1}^{M_A+1} \nu_{mn}(t) \gamma_{m}^{M_A} B_{n}^{N_A}, \gamma_{j}^{M_A} B_{k}^{N_A} \rangle_{IA} \]

\[ - \mu^{I_A} f_I \sum_{n=1}^{N_I+1} \sum_{m=1}^{M_I+1} \nu_{mn}(t) \gamma_{m}^{M_I} B_{n}^{N_I} \gamma_{j}^{M_I} B_{k}^{N_I} \rangle_{IA} \]

\[ V_A \sum_{n=1}^{N_A+1} \sum_{m=1}^{M_A+1} \tilde{\nu}_{mn}(t) \langle \gamma_{m}^{M_A} B_{n}^{N_A}, \gamma_{j}^{M_A} B_{k}^{N_A} \rangle_{IA} - \frac{V_A D_A}{r_I^2} \sum_{n=1}^{N_A+1} \sum_{m=1}^{M_A+1} \nu_{mn}(t) \langle \frac{1}{\sin^2 \phi} \gamma_{m}^{M_A} B_{n}^{N_A}, \gamma_{j}^{M_A} B_{k}^{N_A} \rangle_{IA} \]

\[ - \frac{V_A D_A}{r_I^2} \sum_{n=1}^{N_A+1} \sum_{m=1}^{M_A+1} \nu_{mn}(t) \langle \gamma_{m}^{M_A} B_{n}^{N_A}, \gamma_{j}^{M_A} B_{k}^{N_A} \rangle_{IA} + \lambda_A \mu^{B_A} f_B \sum_{n=1}^{N_B+1} u_n(t) \gamma_{j}^{M_A} (\theta_0) \langle B_{n}^{N_B}, B_{k}^{N_A} \rangle_B \]

\[ - \lambda_A \mu^{B_A} f_A \sum_{n=1}^{N_A+1} \sum_{m=1}^{M_A+1} \nu_{mn}(t) \gamma_{m}^{M_A} (\theta_0) \gamma_{j}^{M_A} (\theta_0) \langle B_{n}^{N_A}, B_{k}^{N_A} \rangle_B + \mu^{I_A} f_I \sum_{n=1}^{N_I+1} \sum_{m=1}^{M_I+1} \nu_{mn}(t) \gamma_{m}^{M_I} B_{n}^{N_I} \gamma_{j}^{M_I} B_{k}^{N_I} \rangle_{IA} \]

\[ - \mu^{I_A} f_A \sum_{n=1}^{N_A+1} \sum_{m=1}^{M_A+1} \nu_{mn}(t) \langle \gamma_{m}^{M_A} B_{n}^{N_A}, \gamma_{j}^{M_A} B_{k}^{N_A} \rangle_{IA} \]

It is easily seen that all of the integrals in the above inner products are finite, with the exception of the term

\[ \langle \frac{1}{\sin^2 \phi} \gamma_{m}^{M_I} B_{n}^{N_I}, \gamma_{j}^{M_I} B_{k}^{N_I} \rangle_{IA} \]
in the interstitial space equation, and a similar term
\[
\left\langle \frac{1}{\sin^2 \phi} \gamma_m^A B_n^A, \gamma_j^A B_k^A \right\rangle_{IA}
\]
(5.32)
in the adipocyte equation. For \( n = k = 1 \) and \( n = k = N_I + 1 = N_A + 1 \), the inner products (5.31) and (5.32) are unbounded since we have, for example,
\[
\left\langle \frac{1}{\sin^2 \phi} \gamma_m^A B_1^A, \gamma_j^A B_1^A \right\rangle_{IA} = \int_0^{2\pi} \gamma_m^A(\theta) \gamma_j^A(\theta) \, d\theta \int_0^{\phi_2} \frac{\phi^2 - \phi}{\phi_2^2 \sin \phi} \, d\phi = \infty.
\]
To remove the singularities at \( \phi = 0 \) and \( \phi = \pi \), we eliminate these endpoints in the conventional way by requiring
\[
v_{m,1}(t) \equiv v_{m,(N_I+1)}(t) \equiv 0,
\]
and similarly we require
\[
w_{m,1}(t) \equiv w_{m,(N_A+1)}(t) \equiv 0.
\]
We now must show that (5.31) is well defined for all other choices of \( n \) and \( k \). This is clearly true for any choice of \( 2 < n < N_I \) or \( 2 < k < N_I \), since the basis functions corresponding to these values of \( k \) and \( n \) are uniformly zero on the intervals \([0, \phi_2]\) and \([\phi_N, \pi]\).

Consider the case \( n = k = 2 \). If we can show that the integral
\[
\int_0^{\pi} \frac{u}{\sin^2 u} \, dv
\]
is bounded, then it will follow that the inner product (5.31) is finite for \( n = k = 2 \) since
\[
\left\langle \frac{1}{\sin^2 \phi} \gamma_m^A B_2^A, \gamma_j^A B_2^A \right\rangle_{IA} = \int_0^{2\pi} \gamma_m^A(\theta) \gamma_j^A(\theta) \, d\theta \int_0^{\phi_2} \frac{\phi^2 - \phi}{\phi_2^2 \sin \phi} \, d\phi
\]
\[
+ \int_0^{2\pi} \gamma_m^A(\theta) \gamma_j^A(\theta) \, d\theta \int_{\phi_2}^{\phi_3} \frac{(\phi_3 - \phi)^2}{(\phi_3 - \phi_2)^2 \sin \phi} \, d\phi
\]
and
\[
\int_0^{\phi_2} \frac{\phi^2}{\phi_2^2 \sin \phi} \, d\phi \leq \frac{1}{\phi_2^2} \int_0^{\phi_2} \frac{\phi}{\sin \phi} \, d\phi \leq \frac{1}{\phi_2^2} \int_0^{\frac{\pi}{2}} \frac{\phi}{\sin \phi} \, d\phi
\]
for \( \phi_2 \leq 1 \). This will also imply that (5.31) is finite for \( n = k = N_I \) since
\[
\left\langle \frac{1}{\sin^2 \phi} \gamma_m^A B_{N_I}^A, \gamma_j^A B_{N_I}^A \right\rangle_{IA} = \int_0^{2\pi} \gamma_m^A(\theta) \gamma_j^A(\theta) \, d\theta \left[ \int_{\phi_{N_I}}^{\pi} \frac{(\pi - \phi)^2}{(\pi - \phi_{N_I})^2 \sin \phi} \, d\phi \right]
\]
\[
+ \int_{\phi_{N_I}}^{\phi_{N_I-1}} \frac{(\phi - \phi_{N_I-1})^2}{(\phi_{N_I} - \phi_{N_I-1})^2 \sin \phi} \, d\phi
\]
and

\[ \int_{\phi_{N_f}}^{\pi} \frac{(\pi - \phi)^2}{(\pi - \phi_{N_f})^2 \sin \phi} \, d\phi = \int_{0}^{\phi^2} \frac{\phi^2}{(\pi - \phi_{N_f})^2 \sin \phi} \, d\phi. \]

Similarly, if (5.33) is bounded then (5.32) will also be finite for all \( n \) and \( k \) when we require \( w_{m,1}(t) \equiv w_{m,N_A+1}(t) \equiv 0. \)

To show that (5.33) is bounded, observe that

\[
\int_{\pi}^{\frac{\pi}{2}} \frac{v}{\sin v} \, dv = 2 \int_{0}^{\frac{\pi}{4}} \frac{2u}{\sin(2u)} \, du
\]

\[
= 2 \int_{0}^{\frac{\pi}{4}} \frac{u}{\frac{1}{2}(\sin(u - u) + \sin(u + u))} \, du
\]

\[
= 2 \int_{0}^{\frac{\pi}{4}} \frac{u}{\sin u \cos u} \, du
\]

\[
= 2 \int_{0}^{\frac{\pi}{4}} \frac{u \cos u}{\sin u \cos u} \, du
\]

\[
= 2 \int_{0}^{1} \frac{\tan^{-1} x}{x} \, dx
\]

\[
= 2 \sum_{k=0}^{\infty} \frac{(-1)^k}{(2k + 1)^2}
\]

\[
\leq 2.
\]

Thus we have shown that (5.28) – (5.30) are well defined when we set \( v_{m,1}(t) = v_{m,N_f+1}(t) = 0 \) and \( w_{m,1}(t) = w_{m,N_A+1}(t) = 0 \) for all \( m = 1, \ldots, M_f + 1 = M_A + 1 \) and \( t \geq 0. \) The system of equations (5.28) – (5.30) can be rewritten in the following matrix-vector form:

\[
V_B \mathcal{M}^{B,B} \hat{u}(t) = -\frac{V_B D_B}{r_1^2} A^B u(t) + \frac{V_B^r}{r_1} K^B u(t) + \lambda_{I\mu_{BI}} f_I \mathcal{M}^{B,\Omega}(G^I(t)\gamma) + \lambda_{A\mu_{BA}} f_A \mathcal{M}^{B,\Omega}(G^A(t)\gamma) - (\lambda_{I\mu_{BI}} + \lambda_{A\mu_{BA}}) f_B \mathcal{M}^{B,B} u(t)
\]

\[
+ \frac{V_B Q_c}{1000 A_{Br_1}} [C_a(t) \sin(\varepsilon_1) e_1 - C_v(t) \sin(\pi - \varepsilon_2) e_{N_b+1}]
\]

\[
= \left[ -\frac{V_B D_B}{r_1^2} A^B + \frac{V_B^r}{r_1} K^B - (\lambda_{I\mu_{BI}} + \lambda_{A\mu_{BA}}) f_B \mathcal{M}^{B,B} \right] u(t)
\]

\[
+ \lambda_{I\mu_{BI}} f_I \mathcal{M}^{B,\Omega}(G^I(t)\gamma) + \lambda_{A\mu_{BA}} f_A \mathcal{M}^{B,\Omega}(G^A(t)\gamma) + \lambda_{I\mu_{BI}} f_I \mathcal{M}^{B,\Omega}(G^I(t)\gamma) + \lambda_{A\mu_{BA}} f_A \mathcal{M}^{B,\Omega}(G^A(t)\gamma)
\]
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\[ + \frac{V_B Q_c}{1000 \lambda_{BR1}} [C_a(t) \sin(\varepsilon_1) e_1 - C_v(t) \sin(\pi - \varepsilon_2) e_{N_B + 1}] \quad (5.34) \]

\[ V_M^{\Omega,\Omega} \dot{v}(t) = - \frac{V_1 D_I}{r_I^2} A_0 v(t) - \frac{V_1 D_I}{r_I^2} \check{A}_0 v(t) + \lambda_I \mu_{BfB} \Gamma(\mathcal{M}^{\Omega,B} u(t)) \]
\[ - \lambda_I \mu_{BfI} \check{M}_0 v(t) + \mu_{IAfA} \mathcal{M}^{\Omega,\Omega} w(t) - \mu_{IAfA} \mathcal{M}^{\Omega,\Omega} v(t) \]
\[ = \lambda_I \mu_{BfB} \Gamma(\mathcal{M}^{\Omega,B} u(t)) \]
\[ + \left[ - \frac{V_1 D_I}{r_I^2} A_0 - \frac{V_1 D_I}{r_I^2} \check{A}_0 - \lambda_I \mu_{BfI} \check{M}_0 - \mu_{IAfA} \mathcal{M}^{\Omega,\Omega} \right] v(t) \]
\[ + \mu_{IAfA} \mathcal{M}^{\Omega,\Omega} w(t) \]
\[ V_A^{\Omega,\Omega} \dot{w}(t) = \left[ - \frac{V_A D_A}{r_I^2} (A_0 + \check{A}_0) - \lambda_A \mu_{BfA} \check{M}_0 - \mu_{IAfA} \mathcal{M}^{\Omega,\Omega} \right] w(t) \]
\[ + \lambda_A \mu_{BfA} \Gamma(\mathcal{M}^{\Omega,B} u(t)) + \mu_{IAfA} \mathcal{M}^{\Omega,\Omega} v(t) \quad (5.36) \]

where

\[ u(t) = [u_1(t), u_2(t), \ldots, u_{N_B + 1}(t)]^T \]
\[ v(t) = [v_{11}(t), v_{12}(t), \ldots, v_{1,N_I + 1}(t), v_{21}(t), v_{22}(t), \ldots, v_{M_I + 1,N_J + 1}(t)]^T \]
\[ w(t) = [w_{11}(t), w_{12}(t), \ldots, w_{1,N_A + 1}(t), w_{21}(t), w_{22}(t), \ldots, w_{M_A + 1,N_A + 1}(t)]^T \]

\[ (M^{B,B})_{ij} = \langle B_j^{N_B}, B_i^{N_B} \rangle_B, \quad i, j = 1, \ldots, N_B + 1 \]
\[ (A^B)_{ij} = \langle B_j^{N_B}, B_i^{N_B} \rangle_B, \quad i, j = 1, \ldots, N_B + 1 \]
\[ (K^B)_{ij} = \langle B_j^{N_B}, B_i^{N_B} \rangle_B, \quad i, j = 1, \ldots, N_B + 1 \]
\[ (M^{B,0})_{ij} = \langle B_j^{N_B}, B_i^{N_B} \rangle_B, \quad i = 1, \ldots, N_B + 1; \ j = 1, \ldots, N_I + 1 \]
\[ (G^I(t))_{ij} = v_{ji}(t), \quad i = 1, \ldots, N_I + 1; \ j = 1, \ldots, M_I + 1 \]
\[ (\gamma^0)_{j} = \gamma^0_{M_I}(\theta_0), \quad j = 1, \ldots, M_I + 1 \]
\[ (G^A(t))_{ij} = w_{ji}(t), \quad i = 1, \ldots, N_A + 1; \ j = 1, \ldots, M_A + 1 \]
\[ (e_1)_{j} = \begin{cases} 1 & \text{if } j = 1 \\ 0 & \text{if } j = 2, \ldots, N_B + 1 \end{cases} \]
\[ (e_{N_B + 1})_{j} = \begin{cases} 1 & \text{if } j = N_B + 1 \\ 0 & \text{if } j = 1, \ldots, N_B \end{cases} \]
\[ (M^{0,B})_{ij} = \langle B_j^{N_B}, B_i^{N_I} \rangle_B, \quad i = 1, \ldots, N_I + 1; \ j = 1, \ldots, N_B + 1 \]
and
\[
\mathcal{M}^{\Omega, \Omega} = \begin{bmatrix}
M_{11}^\Omega & M_{12}^\Omega & \ldots & M_{1,M_I+1}^\Omega \\
M_{21}^\Omega & M_{22}^\Omega & \ldots & M_{2,M_I+1}^\Omega \\
\vdots & \vdots & \ddots & \vdots \\
M_{M_I+1,1}^\Omega & M_{M_I+1,2}^\Omega & \ldots & M_{M_I+1,M_I+1}^\Omega 
\end{bmatrix},
\]
where
\[
(M_{jm}^\Omega)_{kn} = \langle \gamma_m^{M_I} B_n^{N_I}, \gamma_j^{M_I} B_k^{N_I} \rangle_{IA}, \quad j, m = 1, \ldots, M_I + 1; k, n = 1, \ldots, N_I + 1.
\]
Similarly,
\[
(A_{jm}^\Omega)_{kn} = \langle \frac{1}{\sin^2 \phi} \gamma_m^{M_I} B_n^{N_I}, \gamma_j^{M_I} B_k^{N_I} \rangle_{IA}, \quad j, m = 1, \ldots, M_I + 1;
\]
\[
k, n = 1, \ldots, N_I + 1
\]
(\text{except } k = n = 1, k = n = N_I + 1)
\[
(\tilde{A}_{jm}^\Omega)_{kn} = \langle \gamma_m^{M_I} B_n^{N_I'}, \gamma_j^{M_I} B_k^{N_I'} \rangle_{IA}, \quad j, m = 1, \ldots, M_I + 1;
\]
\[
k, n = 1, \ldots, N_I + 1
\]
\[
(\tilde{M}_{jm}^\Omega)_{kn} = \gamma_m^{M_I} (\theta_0) \gamma_j^{M_I} (\theta_0) \langle B_n^{N_I}, B_k^{N_I} \rangle_B, \quad j, m = 1, \ldots, M_I + 1;
\]
\[
k, n = 1, \ldots, N_I + 1.
\]
Moreover, we define
\[
\Gamma = [\Gamma_1, \Gamma_2, \ldots, \Gamma_{M_I+1}]^T
\]
where
\[
(\Gamma_j)_{kn} = \begin{cases} 
\gamma_j(\theta_0) & \text{if } k = n \\
0 & \text{otherwise}
\end{cases}
\]
for \(j = 1, \ldots, M_I + 1\) and \(k, n = 1, \ldots, N_I + 1\).

The above inner products can be calculated analytically. Recall the definition (5.22) for \(\phi_j^B\), \(j = 1, \ldots, N_B + 1\) and the definitions (5.23) and (5.24) for \(\phi_j^A\), \(j = 1, \ldots, N_A + 1\) respectively. Then
\[
\langle B_1^{N_B}, B_1^{N_B} \rangle_B = \left(1 - 2 \left( \frac{N_I}{\pi} \right)^2 \right) \cos(\phi_1^B) + 2 \frac{N_I}{\pi} \sin(\phi_1^B) + 2 \left( \frac{N_I}{\pi} \right)^2 \cos(\phi_2^B)
\]
\[
\langle B_j^{N_B}, B_j^{N_B} \rangle_B = 4 \frac{N_I}{\pi} \sin(\phi_j^B) + 2 \left( \frac{N_I}{\pi} \right)^2 \cos(\phi_{j+1}^B) - 2 \left( \frac{N_I}{\pi} \right)^2 \cos(\phi_{j-1}^B),
\]
for \(j = 2, \ldots, N_B\).
\begin{align*}
\langle B^{N_B}_{N_{B+1}}, B^{N_B}_{N_{B+1}} \rangle_B &= \left(1 - 2 \left(\frac{N_I}{\pi}\right)^2\right) \cos(\phi^B_{N_{B+1}}) + 2 \frac{N_I}{\pi} \sin(\phi^B_{N_{B+1}}) \\
&\quad - 2 \left(\frac{N_I}{\pi}\right)^2 \cos(\phi^B_{N_B}) \\
\langle B^{N_B}_j, B^{N_B}_{j-1} \rangle_B &= -\frac{N_I}{\pi} \sin(\phi^B_j) - \frac{N_I}{\pi} \sin(\phi^B_{j-1}) - 2 \left(\frac{N_I}{\pi}\right)^2 \cos(\phi^B_j) \\
&\quad + 2 \left(\frac{N_I}{\pi}\right)^2 \cos(\phi^B_{j-1}), \quad j = 2, \ldots, N_B + 1 \\
\langle B^{N_B}_j, B^{N_B}_{j+1} \rangle_B &= -\frac{N_I}{\pi} \sin(\phi^B_{j+1}) - \frac{N_I}{\pi} \sin(\phi^B_j) - 2 \left(\frac{N_I}{\pi}\right)^2 \cos(\phi^B_{j+1}) \\
&\quad + 2 \left(\frac{N_I}{\pi}\right)^2 \cos(\phi^B_j), \quad j = 1, \ldots, N_B \\
\langle B^{N_B}_1', B^{N_B}_1 \rangle_B &= \left(\frac{N_I}{\pi}\right)^2 \left(\cos(\phi^B_1) - \cos(\phi^B_2')\right) \\
\langle B^{N_B}_j', B^{N_B}_j \rangle_B &= \left(\frac{N_I}{\pi}\right)^2 \left(\cos(\phi^B_{j-1}) - \cos(\phi^B_{j+1})\right), \quad j = 2, \ldots, N_B \\
\langle B^{N_B}_{N_{B+1}}, B^{N_B}_{N_{B+1}}' \rangle_B &= \left(\frac{N_I}{\pi}\right)^2 \left(\cos(\phi^B_{N_B}) - \cos(\phi^B_{N_{B+1}})\right) \\
\langle B^{N_B}_j', B^{N_B}_{j-1} \rangle_B &= \left(\frac{N_I}{\pi}\right)^2 \left(\cos(\phi^B_j) - \cos(\phi^B_{j-1})\right), \quad j = 2, \ldots, N_B + 1 \\
\langle B^{N_B}_j', B^{N_B}_{j+1} \rangle_B &= \left(\frac{N_I}{\pi}\right)^2 \left(\cos(\phi^B_{j+1}) - \cos(\phi^B_j)\right), \quad j = 1, \ldots, N_B \\
\langle B^{N_B}_1, B^{N_B}_1' \rangle_B &= -\frac{N_I}{\pi} \cos(\phi^B_1) + \left(\frac{N_I}{\pi}\right)^2 \left(\sin(\phi^B_1') - \sin(\phi^B_1)\right) \\
\langle B^{N_B}_j, B^{N_B}_j' \rangle_B &= -2 \frac{N_I}{\pi} \cos(\phi^B_j) + \left(\frac{N_I}{\pi}\right)^2 \left(\sin(\phi^B_{j+1}) - \sin(\phi^B_{j-1})\right), \quad j = 2, \ldots, N_B + 1 \\
\langle B^{N_B}_{N_{B+1}}, B^{N_B}_{N_{B+1}}' \rangle_B &= -\frac{N_I}{\pi} \cos(\phi^B_{N_{B+1}}) + \left(\frac{N_I}{\pi}\right)^2 \left(\sin(\phi^B_{N_{B+1}}) - \sin(\phi^B_{N_B})\right) \\
\langle B^{N_B}_j', B^{N_B}_{j-1} \rangle_B &= \left(\frac{N_I}{\pi}\right)^2 \left(\sin(\phi^B_{j-1}) - \sin(\phi^B_j)\right) + \frac{N_I}{\pi} \cos(\phi^B_j),
\end{align*}
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Moreover, we have

\[ \langle B_j^{N_B}, B_{j+1}^{N_B} \rangle_B = \begin{cases} \left( \frac{N_I}{\pi} \right)^2 \left( \sin(\phi_j^B) - \sin(\phi_{j+1}^B) \right) + \frac{N_I}{\pi} \cos(\phi_j^B), & j = 2, \ldots, N_B + 1 \\ \end{cases} \]

\[ \langle B_{\kappa+1}^{N_I}, B_{\kappa+1}^{N_I} \rangle_B = \begin{cases} \left( 1 - 2 \left( \frac{N_I}{\pi} \right)^2 \right) \cos(\phi_{\kappa+1}^I) \\ + \frac{2N_I}{\pi} \sin(\phi_{\kappa+1}^I) + 2 \left( \frac{N_I}{\pi} \right)^2 \cos(\phi_{\kappa+2}^I) \end{cases} \]

\[ \langle B_j^{N_I}, B_j^{N_I} \rangle_B = \begin{cases} \left( 1 - 2 \left( \frac{N_I}{\pi} \right)^2 \right) \cos(\phi_{j+1}^I) \\ + 2 \left( \frac{N_I}{\pi} \right)^2 \cos(\phi_{j-1}^I), & j = r + 2, \ldots, N_I - \kappa \\ \end{cases} \]

\[ \langle B_{N_I - \kappa+1}^{N_I}, B_{N_I - \kappa+1}^{N_I} \rangle_B = \begin{cases} \left( 1 - 2 \left( \frac{N_I}{\pi} \right)^2 \right) \cos(\phi_{N_I - \kappa}^I) \\ - 2 \left( \frac{N_I}{\pi} \right)^2 \cos(\phi_{N_I - \kappa}^I) \end{cases} \]

\[ \langle B_j^{N_I}, B_{j-1}^{N_I} \rangle_B = \begin{cases} -\frac{N_I}{\pi} \sin(\phi_j^I) - \frac{N_I}{\pi} \sin(\phi_{j-1}^I) - 2 \left( \frac{N_I}{\pi} \right)^2 \cos(\phi_j^I) \\ + 2 \left( \frac{N_I}{\pi} \right)^2 \cos(\phi_{j-1}^I), & j = \kappa + 2, \ldots, N_I - \kappa + 1 \end{cases} \]

\[ \langle B_j^{N_I}, B_{j-1}^{N_I} \rangle_B = 0, & j = 2, \ldots, \kappa + 1; j = N_I - \kappa + 2, \ldots, N_I + 1 \]

\[ \langle B_j^{N_I}, B_{j+1}^{N_I} \rangle_B = -\frac{N_I}{\pi} \sin(\phi_{j+1}^I) - \frac{N_I}{\pi} \sin(\phi_j^I) - 2 \left( \frac{N_I}{\pi} \right)^2 \cos(\phi_{j+1}^I) \\ + 2 \left( \frac{N_I}{\pi} \right)^2 \cos(\phi_j^I), & j = \kappa + 1, \ldots, N_I - \kappa \]

\[ \langle B_j^{N_I}, B_{j+1}^{N_I} \rangle_B = 0, & j = 1, \ldots, \kappa; j = N_I - \kappa + 1, \ldots, N_I. \]

Moreover, we have \( \theta_j = 2\pi(j - 1)/M_I = \pi(j - 1)/N_\phi \) for \( j = 1, \ldots, M_I + 1 \), so that

\[ \int_0^{2\pi} \gamma_j^{M_I}(\theta)\gamma_k^{M_I}(\theta)d\theta = \begin{cases} \frac{\pi}{3N_\phi}, & j = k = 1 \ or \ j = k = M_I + 1 \\ \frac{2\pi}{3N_\phi}, & j = k, \ j = 1, \ldots, M_I + 1 \\ \frac{\pi}{6N_\phi}, & |j - k| = 1, \ j = 1, \ldots, M_I + 1 \\ 0, \ otherwise \end{cases} \]
\[
\int_0^{2\pi} c_j^{M_j}(\theta) c_k^{M_k}(\theta) d\theta = \begin{cases} 
\frac{2N_\phi}{\pi} & j = k = 1 \text{ or } j = k = M_t + 1 \\
\frac{N_\phi}{\pi} & j = k, \quad j = 1, \ldots, M_t + 1 \\
-\frac{N_\phi}{\pi} & |j - k| = 1, \quad j = 1, \ldots, M_t + 1 \\
0 & \text{otherwise.}
\end{cases}
\]

5.2.4 The semi-discrete problem

We combine the finite element formulation (5.34) – (5.36) with the differential equations from the PBPK whole-body model to obtain the semi-discrete problem for the TCE PBPK-hybrid model:

\[
V_B \mathcal{M}^{B,B} \ddot{u}(t) = \left[ -\frac{V_B D_B}{r_1^2} A^B + \frac{V_B v}{r_1} K^B - (\lambda I_b + \lambda A_{BA}) f_B \mathcal{M}^{B,B} \right] u(t) \\
+ \lambda I B f_I \mathcal{M}^{B,\Omega}(G(t)\gamma) + \lambda A_{BA} f_A \mathcal{M}^{B,\Omega}(G^A(t)\gamma) \\
+ \frac{V_B Q_c}{1000A_{B\Omega}} [C_a(t) \sin(\varepsilon_1) e_1 - C_v(t) \sin(\pi - \varepsilon_2) e_{N_A+1}]
\]

\[
V_I \mathcal{M}^{\Omega,I} \ddot{v}(t) = \lambda I B f_I \mathcal{M}^{\Omega,B} \Gamma(\mathcal{M}^{\Omega,B} u(t)) \\
+ \left[ -\frac{V_I D_I}{r_1^2} A^\Omega - \frac{V_I D_I}{r_1^2} \tilde{A}^\Omega - \lambda I B f_I \mathcal{M}^{\Omega,B} - \mu I f_I \mathcal{M}^{\Omega,\Omega} \right] v(t) \\
+ \mu I A f_A \mathcal{M}^{\Omega,\Omega} w(t)
\]

\[
V_A \mathcal{M}^{\Omega,I} \ddot{w}(t) = \left[ -\frac{V_A D_A}{r_1^2} (A^\Omega + \tilde{A}^\Omega) - \lambda A_{BA} f_A \mathcal{M}^{\Omega,\Omega} - \mu I A f_I \mathcal{M}^{\Omega,\Omega} \right] w(t) \\
+ \lambda A_{BA} f_A \mathcal{M}^{\Omega,B} \Gamma(\mathcal{M}^{\Omega,B} u(t)) + \mu I A f_I \mathcal{M}^{\Omega,\Omega} v(t)
\]

\[
V_v \frac{dC_v}{dt} = Q_m C_{vm} + Q_t C_{vt} + Q_f C_{vf} + Q_{br} C_{vbr} + Q_{cl} C_{vl} + Q_{ck} C_{vk} - Q_c C_v
\]

\[
V_{br} \frac{dC_{vbr}}{dt} = Q_{br}(C_a - C_{vbr})
\]

\[
V_k \frac{dC_k}{dt} = Q_k(C_a - C_{vk})
\]

\[
V_m \frac{dC_m}{dt} = Q_m(C_a - C_{vm})
\]

\[
V_t \frac{dC_t}{dt} = Q_t(C_a - C_{vt})
\]

\[
V_I \frac{dC_I}{dt} = Q_I(C_a - C_{vt}) - \frac{v_{max} C_{vt}}{k_M + C_{vt}}
\]
where
\[ C_a = \frac{Q_c C_v + Q_p C_c}{Q_c + \frac{Q_p}{\rho_b}}. \]

This can be rewritten in the form
\[
\mathcal{M}^{M,N} y^{M,N}(t) = \mathcal{A}^{M,N} y^{M,N}(t) + \mathcal{G}(y^{M,N}(t)) + \mathcal{F}(t)
\]
(5.37)
\[
y^{M,N}(0) = y_0^{M,N}
\]
(5.38)

where
\[
y^{M,N}(t) = [u(t), v(t), w(t), C_v(t), C_{br}(t), C_k(t), C_m(t), C_t(t), C_l(t)]^T \in \mathbb{R}^{N_{tot}},
\]
\[
N_{tot} = (N_B + 1) + 2(N_I + 1)(M_I + 1) + 6.
\]

The matrices \( \mathcal{M}^{M,N} \) and \( \mathcal{A}^{M,N} \) are given by
\[
\mathcal{M}^{M,N} = \left[\begin{array}{cccccccccc}
V_B \mathcal{M}^{B,B} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & V_I \mathcal{M}^{\Omega,\Omega} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & V_A \mathcal{M}^{\Omega,\Omega} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & V_v & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & V_{br} & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & V_k & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & V_m & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & V_l & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & V_l & 0 \\
\end{array}\right]
\]
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\[ A_{M,N} = \begin{bmatrix}
A_1 & A_2 & A_3 & A_4 & 0 & 0 & 0 & 0 & 0 \\
A_5 & A_6 & A_7 & 0 & 0 & 0 & 0 & 0 & 0 \\
A_8 & A_9 & A_{10} & 0 & 0 & 0 & 0 & 0 & 0 \\
\frac{Q_f}{P_f} e_{N_B+1} & 0 & 0 & -Q_c & Q_{br} & Q_k & Q_m & Q_l & Q_l \\
0 & 0 & 0 & \frac{Q_c Q_{br}}{Q_c + \frac{Q_{br}}{P_f}} & \frac{Q_k}{P_f} & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \frac{Q_c Q_m}{Q_c + \frac{Q_m}{P_f}} & 0 & -\frac{Q_m}{P_m} & 0 & 0 & 0 \\
0 & 0 & 0 & \frac{Q_c Q_l}{Q_c + \frac{Q_l}{P_f}} & 0 & 0 & 0 & -\frac{Q_l}{P_l} & 0 \\
0 & 0 & 0 & \frac{Q_c Q_k}{Q_c + \frac{Q_k}{P_k}} & 0 & 0 & 0 & 0 & -\frac{Q_k}{P_k}
\end{bmatrix},
\]

where

\[ A_1 = -\frac{V_B D_B}{r_1^2} A^B + \frac{V_B v}{r_1} K^B - (\lambda_I \mu_{BI} + \lambda_A \mu_{BA}) f_B \mathcal{M}^{B,B} \]

\[ A_2 = \lambda_I \mu_{BI} \bar{f}_I \mathcal{M}^{B,\bar{\Gamma}\bar{\gamma}} \]

\[ A_3 = \lambda_A \mu_{BA} \bar{f}_A \mathcal{M}^{B,\bar{\Gamma}\bar{\gamma}} \]

\[ A_4 = \frac{V_B Q_c}{1000 A_B r_1} \left( \sin(\varepsilon_1) \frac{Q_c}{Q_c + \frac{Q_{br}}{P_f}} e_1 - \sin(\pi - \varepsilon_2) e_{N_B+1} \right) \]

\[ A_5 = \lambda_I \mu_{BI} \bar{f}_B \bar{\Gamma} \mathcal{M}^{B,B} \]

\[ A_6 = -\frac{V_I D_I}{r_1^2} \left( \mathcal{A}^{\Omega} + \bar{\mathcal{A}}^{\bar{\Omega}} \right) - \lambda_I \mu_{BI} \bar{f}_I \bar{\mathcal{M}}^{\Omega} - \mu_I \bar{f}_I \mathcal{M}^{\Omega,\Omega} \]

\[ A_7 = \mu_I \bar{f}_A \mathcal{M}^{\Omega,\Omega} \]

\[ A_8 = \lambda_A \mu_{BA} \bar{f}_B \bar{\Gamma} \mathcal{M}^{B,B} \]

\[ A_9 = \mu_I \bar{f}_A \mathcal{M}^{\Omega,\Omega} \]

\[ A_{10} = -\frac{V_A D_A}{r_1^2} \left( \mathcal{A}^{\Omega} + \bar{\mathcal{A}}^{\bar{\Omega}} \right) - \lambda_A \mu_{BA} \bar{f}_A \bar{\mathcal{M}}^{\Omega} - \mu_I \bar{f}_A \mathcal{M}^{\Omega,\Omega} \]

and

\[ \bar{\gamma} = [\gamma^M_I(\theta_0) I_{N_I+1}, \gamma^M_{\bar{I}}(\theta_0) I_{N_I+1}, \ldots, \gamma^M_{I_{N_I+1}}(\theta_0) I_{N_I+1}] \]

where \( I_{N_I+1} \) is the \((N_I + 1) \times (N_I + 1)\) identity matrix.
The nonlinear function $G$ is given by

$$G(y_{M,N}(t)) = \left[ 0, 0, 0, 0, 0, 0, 0, \frac{v_{max}C_l(t)}{P_l(k_M + \frac{C_l(t)}{P_l})} \right]^T$$

and the forcing function $F(t)$ has the form

$$F(t) = \begin{bmatrix}
\frac{V_BQ_cQ_c}{1000A_Br_1(Q_c + \frac{Q_c}{P_c})} C_c(t)e_1 \\
0 \\
0 \\
0 \\
\frac{Q_{br}Q_c}{Q_c + \frac{Q_c}{P_c}} C_c(t) \\
\frac{Q_kQ_c}{Q_c + \frac{Q_c}{P_c}} C_c(t) \\
\frac{Q_mQ_c}{Q_c + \frac{Q_c}{P_c}} C_c(t) \\
\frac{Q_lQ_c}{Q_c + \frac{Q_c}{P_c}} C_c(t) \\
\frac{Q_lQ_c}{Q_c + \frac{Q_c}{P_c}} C_c(t)
\end{bmatrix}.$$

The initial condition $y_0^{M,N}$ is defined as the $L^2$ projection of $y_0$ onto $V^{M,N}$. That is,

$$y_0^{M,N} = [y_{01}, y_{02}, \ldots, y_{09}]^T$$

with

$$(y_{01})_j = \langle (y_0)_1, B_j^{NB} \rangle_B, \quad j = 1, \ldots, N_B + 1$$

$$(y_{02})_{kj} = \langle (y_0)_2, \gamma_k^{NI} B_j^{NI} \rangle_{IA}, \quad j = 1, \ldots, N_I + 1, \ k = 1, \ldots, M_I + 1$$

$$(y_{03})_{kj} = \langle (y_0)_3, \gamma_k^{NA} B_j^{NA} \rangle_{IA}, \quad j = 1, \ldots, N_A + 1, \ k = 1, \ldots, M_A + 1$$

$$y_{04} = C_v(0)$$

$$y_{05} = C_{br}(0)$$

$$y_{06} = C_k(0)$$

$$y_{07} = C_m(0)$$
\[ y_{08} = C_t(0) \]
\[ y_{09} = C_t(0), \]

where \( y_{02} \) and \( y_{03} \) are arranged as \((N_I + 1)(M_I + 1)\) and \((N_A + 1)(M_A + 1)\)-vectors, respectively.

### 5.3 Numerical methods

In this section we outline the procedure used to solve numerically the semi-discrete problem for the PBPK-hybrid model. As discussed in Chapter 4, the solutions to our semi-discrete problem theoretically will converge to the solution of the infinite-dimensional model equations (5.14) – (5.16), (3.16) – (3.25) as \( M, N \to \infty \).

As in Section 5.2.3, we set \( N_B = N_\phi - 2\kappa \) and \( N_I = N_A = N_\phi \), \( M_I = M_A = 2N_\phi \), where \( N_\phi = 8\kappa \) for some positive integer \( \kappa \geq 1 \). Moreover, we choose \( \theta_0 = \pi \) and \( \varepsilon_1 = \varepsilon_2 = \pi/8 \). Recall that the choice \( N_\phi = 8\kappa \) allows us to include the boundary points \( \varepsilon_1 \) and \( \pi - \varepsilon_2 \) of the capillary domain as points in our discretization of \( \phi \) from 0 to \( \pi \). Furthermore, by setting \( N_B = N_\phi - 2\kappa = N_I - 2\kappa = N_A - 2\kappa \), the discretizations in each of the three regions will be aligned.

The integrals in the matrices \( M^{M,N} \) and \( A^{M,N} \) were evaluated analytically, as described in Section 5.2.3. The form for the forcing function \( F(t) \) was chosen to simulate one hour of exposure to a constant concentration of TCE in the chamber air, followed by \( t_f - 1 \) hours with zero concentration of TCE, where \( t_f \) is the final time of the simulation. That is, we define \( C_c(t) \), the chamber air concentration of TCE, by

\[
C_c(t) = \begin{cases} 
0 & \text{if } t = 0 \\
K & \text{if } 0 < t \leq 1 \\
0 & \text{if } 1 < t \leq t_f
\end{cases}
\]  

(5.39)

where \( K = 200, 2000 \) or 4000 parts per million. Note that this leads to a discontinuous forcing function \( F \in L^2(0, t_f) \).
In these simulations we set the initial condition $y_0$ to be identically zero. This simulates an experiment where each of the animals is assumed to have no TCE in its system before being exposed to TCE during the experiment. The choice of $C_c(0) = 0$ in (5.39) is necessary to obtain zero initial conditions, since the concentration $C_a$ of TCE in the arterial blood, which is given by

$$C_a(t) = \frac{Q_c C_v(t) + Q_p C_c(t)}{Q_c + \frac{Q_p}{F_b}},$$

will be nonzero when $C_c(t)$ is nonzero. Moreover, the flux-balancing boundary condition at the entrance to the capillary region of the adipose tissue

$$-\frac{D_B}{r_1} \frac{\partial C_B}{\partial \phi}(t, \phi) + v C_B(t, \phi) \bigg|_{\phi = \varepsilon_1} = \frac{Q_c}{1000 A_B} C_a(t)$$

implies that the concentration $C_B$ of TCE in the capillary region also will be nonzero when $C_c(t)$ is nonzero.

### 5.3.1 Implementation

The computer code was written and implemented in Matlab (The Mathworks Inc., Natick, MA), using Versions 6.0.0.88 (Release 12) and 5.3. Computations were conducted on Sun Ultra 5 and Ultra 10 workstations, a Windows ME-based personal computer with a 1.5 GHz Pentium 4 processor, and a Windows 98-based personal computer with a 400 MHz Pentium II processor.

We solved the semi-discrete problem (5.37), (5.38) using the Matlab ordinary differential equation solver `ode15s`. This variable order, variable time step solver is designed to solve both stiff and non-stiff systems efficiently, and is based on numerical differentiation formulas [59]. The stiffness of our system of equations (5.37), (5.38) varies as a function of the model parameters, which suggests that `ode15s` is an appropriate solver for this model and the associated parameter estimation problems.

We set the relative and absolute error tolerances for `ode15s` to $10^{-3}$. Moreover, we supplied the solver with the analytic Jacobian, resulting in reduced computational time, especially for parameter sets which led to a stiff system.
5.3.2 Convergence of the numerical scheme

In Chapter 4 we established the theoretical convergence of solutions for the system of finite dimensional Galerkin approximations to the solution for our infinite dimensional model system of equations. This convergence can be demonstrated in practice by solving the semi-discrete problem with fixed parameters for increasing values of $N$ and $M$.

As previously outlined in this section, we set $N = N_\phi = 8\kappa$ and $M = M_I = M_A = 2N_\phi$, where $\kappa$ is a positive integer. To test the convergence of our numerical scheme, we ran simulations for $t_f = 5$ hours with $\kappa$ ranging from one to five, resulting in the values $N_\phi = 8, 16, 24, 32, 40$. For values of $\kappa$ greater than 5 (i.e., $N_\phi > 40$ and $N_{tot} > 6679$), Matlab ran out of memory and was unable to complete the computation.

Figures 5.2–5.5 illustrate the convergence of the numerical scheme in each of the adipose subcompartments. Figure 5.2 depicts the concentrations of TCE at the exit to the capillary region and entrance to the venous blood ($\phi = \pi - \varepsilon_2$), while unbound TCE concentrations at the point $\mu = \mu_0 = \pi = \pi/2$ on the “equator” of the interstitial space are shown in Figure 5.3. Both of these plots suggest convergence of the approximate solutions, with concentrations at the exit to the capillary appearing to be nearly independent of the grid size.

See Figure 5.4 for unbound TCE concentrations at the point $\theta = \theta_0$, $\phi = \pi/2$ in the adipocyte region, and Figure 5.5 for unbound concentrations at the point $\theta = \theta_0$, $\phi = \pi/8 = \varepsilon_1$ in the adipocyte region. Each of these plots also suggests convergence of the numerical scheme, although the solutions appear to differ more significantly for varying values of $N$ than in the other two regions.

As seen in Figure 5.5, the concentrations in the adipocyte region at $\theta = \theta_0$, $\phi = \varepsilon_1$ appear to be converging most slowly. This point in the adipocyte region is located at the interface with the capillary where the capillary joins with the arterial blood system, and is also located near the pole $\phi = 0$. Recall from Section 5.2.3 that the
boundary conditions

\[ C_A(t, \theta, 0) < \infty, \quad C_A(t, \theta, \pi) < \infty \]

require that the coefficients \( w_{m,1}(t) \equiv w_{m,M_A+1}(t) \equiv 0 \) for all \( m = 1, \ldots, N_A + 1 \) and \( t \geq 0 \). This effectively imposes zero boundary conditions at each of the poles in the adipocyte region, and similar boundary conditions apply in the interstitial space.

The continuity of the basis functions dictates that these zero boundary conditions have a major influence on the shape of concentration curves near the poles, especially for small values of \( N \). In general, when \( N = 8\kappa \), there are \( \kappa - 1 \) grid points between the pole \( \phi = 0 \) and the point \( \theta = \theta_0, \phi = \varepsilon_1 \). Therefore, as \( \kappa \) and \( N \) increase, the solutions at the point \( \phi = \varepsilon_1 \) become less “dependent” on the values at the pole and at the grid points immediately adjacent to the pole. This results in the increasing levels of TCE concentrations at the point \((\theta_0, \varepsilon_1)\) as \( N \) becomes large.
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Figure 5.3: Model simulations in the interstitial region of the adipose tissue for $N = 8, 16, 24, 32, 40$.

Figure 5.4: Model simulations in time at the point $\theta = \theta_0 = \pi$, $\phi = \pi/2$ in the adipocyte region of the adipose tissue for $N = 8, 16, 24, 32, 40$. 
Figure 5.5: Model simulations in time at the point $\theta = \theta_0 = \pi$, $\phi = \varepsilon_1 = \pi/8$ in the adipocyte region of the adipose tissue for $N = 8, 16, 24, 32, 40$.

5.4 Simulations

5.4.1 Model parameters

In this section we present model simulations for the TCE PBPK-hybrid model. Appendix A contains a list of values for the adipose model parameters. Many of these parameters are specific to the adipose dispersion model, and would be difficult to measure experimentally. For these parameters we chose estimates based on several factors, including similar parameters in the well-mixed models, consistency across the parameter values, and simulated concentration profiles.

The volumes of the three subcompartments were obtained by subdividing the volume $V_f$ of the well-mixed fat compartment from Chapter 2. Note that based on the assumptions for the dispersion model, the domains for the three regions span from $r_2$ to $r_2 + 2\alpha$ in the capillary, from $r_1$ to $r_3$ in the interstitial space, and from $r_0$ to $r_1$ in the adipocyte. Therefore our model is defined on only a portion of the
entire interstitial space \((r > r_1)\) and a portion of the entire adipocyte \((0 \leq r \leq r_1)\). Accordingly, we estimate the volumes for these regions by \(V_B = 0.25V_f = 0.0084\) liters, \(V_I = 0.35V_f = 0.0118\) liters, and \(V_A = 0.4V_f = 0.0135\) liters.

The unbound fractions \(f_B\), \(f_I\) and \(f_A\) were approximated using values from the well-mixed models in Chapter 2. We assume that there is no binding of TCE in the blood [32], so that \(f_B = 1\). Moreover, the interstitial fluid is similar in content to the blood plasma but has additional lipids and proteins [41], so we estimate the unbound fraction there as \(f_I = 0.6667\). Finally, we use the estimate \(f_A = 1/P_f = 0.0381\) for the adipocyte, where \(P_f\) is the partition coefficient for the adipose tissue used in the perfusion-limited model in Chapter 2 [32].

The remaining adipose model parameters (see Appendix A) were less straightforward to estimate. Several of these parameters, including the axial dispersion coefficient \(D_B\) and the fractions of transport \(\lambda_I\), \(\lambda_A\), would be difficult to measure experimentally. Using experimental data, these parameters may be estimated with inverse problem techniques.

For the simulations presented here, we chose estimates for these parameters so that the values would be consistent (e.g., the radius \(r_1\) of the adipocyte should be much larger than the cross-sectional area \(A_B\) of the capillary), and so that the resulting model simulations yielded concentration profiles that seemed to approximate the expected behavior of TCE inside adipose tissue. That is, we chose parameters so that the concentrations of TCE in the adipose tissue were characterized by a sharp increase during the exposure period, followed by a slow but steady decrease after exposure has ceased.

### 5.4.2 Predicted adipose tissue concentrations

Model simulations were generated for \(t_f = 5\) hours with a forcing function chosen to simulate 2000 ppm TCE in the chamber air for one hour, followed by four hours of no exposure. See Appendix A for a complete list of model parameter values used for these simulations. We set \(N_\phi = 32\) for our finite element discretization, leading to an
overall system of $N_{tot} = 4064$ differential equations.

Simulations of capillary TCE concentrations at the points $\phi = \pi/8$, $\pi/4$, $\pi/2$, $3\pi/4$ and $7\pi/8$ are given in Figure 5.6. These concentration profiles are similar in shape to the concentrations of TCE in the venous blood, shown in Figure 5.7. In each of these two figures, the concentrations increase sharply during exposure to TCE and then decrease at an exponential rate following exposure. The similarity of behavior in the capillary region and the venous blood compartment is a consequence of the flux boundary condition (3.5), and is also consistent with the idea that the dynamics of TCE in the venous blood would be similar (but not necessarily identical) to the dynamics in the capillary.

Figure 5.8 depicts unbound TCE concentrations in the interstitial region of the adipose tissue at points along the “equator,” where $\phi = \pi/2$ and $\theta = 0$, $\pi/4$, $\pi/2$, $3\pi/4$ and $\pi$. These concentrations are similar to those in the venous blood compartment and the capillary region, with less-pronounced peaks. Note that the concentration profile with the largest magnitude is at the point $\theta = \pi = \theta_0$, which is closest in
Figure 5.7: Model simulations: TCE concentrations in time in the venous blood compartment.

location to the capillary region. Moreover, the concentration profile with the smallest magnitude corresponds to the point $\theta = 0$, which is the furthest point on the “equator” from the capillary region. Note the delay between the maximal value at the point $\theta = \pi$ and the maximal value at $\theta = 0$, which occurs because the TCE must diffuse from the region nearest the capillary around to areas in the interstitial space that are further away from the capillary.

Time snapshots of TCE concentrations on the spherical domain of the interstitial space with $t_f = 3$ can be seen in Figures 5.9 – 5.10. Each individual plot has a color scheme that is scaled between the minimum and maximum values for that point in time, with red representing the highest concentrations and blue representing the lowest. The colorbar to the right of each plot indicates the concentration levels that correspond to the color scheme.

The location in the interstitial space nearest the capillary ($\theta = \theta_0 = \pi$) can be seen clearly as the area with the highest concentrations. As time progresses past the hour of TCE exposure, the diffusion term in the model becomes more predominant and
Figure 5.8: Model simulations: Unbound TCE concentrations in time in the interstitial region of the adipose tissue at the points $\phi = \pi/2$ and $\theta = 0$, $\pi/4$, $\pi/2$, $3\pi/4$ and $\pi$.

the concentrations begin to level out with respect to $\phi$ and $\theta$, although the highest concentrations remain near the capillary interface.

Figures 5.11 – 5.12 depict time snapshots of concentrations in the adipocyte region. Note that the dynamics are similar to those seen in Figures 5.9 – 5.10 for the interstitial space, although the diffusion term seems to be less dominant in the adipocyte region compared to the interstitial space. This is likely an effect of the lower unbound fraction (or equivalently, the higher partition coefficient) in the adipocyte region, and a smaller diffusion coefficient $D_A = 0.001$ (compared to $D_I = 0.01$).

See Figure 5.13 for a simulation of TCE concentrations in the adipocyte region at the points $\phi = \pi/2$ and $\theta = 0$, $\pi/4$, $\pi/2$, $3\pi/4$ and $\pi$. The rate of decay of concentrations in the adipocyte region is slower than the decay rate in the other two adipose regions, which is a reflection of the lower unbound fraction in the adipocyte region. Note that these concentration profiles look similar to those for the diffusion-limited model in Figure 2.4.
Figure 5.9: Time snapshots from $t = 0$ to 1 hour of TCE concentrations in the interstitial space.
Figure 5.10: Time snapshots from $t = 1$ to 3 hours of TCE concentrations in the interstitial space.
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An important difference between the diffusion-limited model simulations and the dispersion model simulations is that all of the concentration profiles in Figure 5.13 were generated with fixed permeability parameters \( \mu_{BA} = 0.03 \), \( \mu_{BI} = 0.02 \), and \( \mu_{IA} = 0.025 \) liters/hour, \( \lambda_I = 0.6 \), \( \lambda_A = 0.4 \) and observations taken at varying locations, while those shown in Figure 2.4 were generated with varying values of the permeability coefficient \( \mu \). By design, the dispersion model accounts for spatial variation in concentrations within each region of the adipose tissue, and can be used to predict various concentration profiles within the fat.

A simulation for the mean concentration of TCE in the adipocyte region is given in Figure 5.14. The mean concentration was calculated by taking the average unbound concentration over the discretization points for the finite element approximations:

\[
\mathcal{E}[C_A^{M_I,N_\varphi}(t_i,\cdot,\cdot)] = \frac{1}{(N_\varphi + 1)(M_I + 1)} \sum_{j=1}^{M_I+1} \sum_{k=1}^{N_\varphi+1} f_A C_A^{M_I,N_\varphi}(t_i,\theta_j,\phi_k) \tag{5.40}
\]

where in this case we have \( N_\varphi = 32 \) and \( M_I = 64 \), and \( \theta_j \), \( \phi_k \) are given by

\[
\theta_j = \frac{2\pi}{M_I}(j - 1), \quad j = 1, \ldots, M_I + 1
\]

\[
\phi_k = \frac{\pi}{N_\varphi}(k - 1), \quad k = 1, \ldots, N_\varphi + 1.
\]

This type of simulation is useful in comparing model predictions with experimental data that are collected from homogenized tissue samples. The data gathered by Evans et al. [32], for example, include unbound TCE concentrations in homogenized samples of liver, brain and fat tissues. Calculating the mean TCE concentration in the adipocyte region allows a comparison of the dispersion model predictions with these experimental data. We will utilize this type of simulation in Chapter 6, where we carry out a study of parameter estimation problems for our model.

Note that the predicted concentration profile in Figure 5.14 is similar to the expected behavior of TCE in adipose tissue, with a slow rate of decay following the exposure period. Indeed, the predicted mean TCE adipocyte concentration appears to be more closely matched to this expected transport behavior than the prediction
generated by the perfusion-limited adipose tissue compartment. Moreover, the dispersion model is most likely more appropriate for TCE in adipose tissue than the diffusion-limited model. This is because the assumptions used to derive the dispersion model are based specifically on TCE and the physiology of adipose tissue, while the assumptions for the diffusion-limited model may not be valid for TCE, which transports easily across biological membranes.

5.4.3 Varying the flux between the capillary and the blood compartments to scale adipose concentrations

As discussed in Section 2.2, the diffusion-limited compartmental model allows for various shapes of concentration profiles in the intracellular compartment as the permeability coefficient $\mu$ is varied, but the peak concentration values also vary with $\mu$. Therefore, the diffusion-limited model has limited flexibility in capturing both the shape and the peak value of a concentration curve inside the fat tissue.

The dispersion model has a greater level of flexibility than the diffusion-limited model due to the increased number of model parameters. By varying the adipose model parameters $F$ and $A_B$, the reverse Fahraeus-Lindquist parameter and the cross-sectional area of the capillary respectively, we can control the peak concentration values inside the adipose tissue regions. This is accomplished by modifying the flux between the adipose capillary and the arterial blood compartment, as well as the flux between the adipose capillary and the venous blood compartment. The concentration profiles in Figure 5.15 were generated with $F = 0.16$ and $A_B = 10^{-4}$, and Figure 5.16 depicts concentrations for $F = 0.08$ and $A_B = 5 \times 10^{-5}$. Note that for a given value of $\theta$, the concentration curves are similar in shape but vary in their peak values.
Figure 5.11: Time snapshots from $t = 0$ to 1 hour of TCE concentrations in the adipocyte region.
Figure 5.12: Time snapshots from $t = 1$ to 3 hours of TCE concentrations in the adipocyte region.
Figure 5.13: Model simulations: Unbound TCE concentrations in time in the adipocyte region of the adipose tissue at the points $\phi = \pi/2$ and $\theta = 0, \pi/4, \pi/2, 3\pi/4$ and $\pi$.

Figure 5.14: Model simulations: Mean unbound TCE concentration in time in the adipocyte region of the adipose tissue.
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Figure 5.15: Model simulations: Concentrations in time of unbound TCE inside the adipocyte region of the adipose tissue at $\phi = \pi/2$ and $\theta = 0, \pi/4, \pi/2, 3\pi/4$ and $\pi$, with $\mathcal{F} = 0.16$, $A_B = 10^{-4}$, $\lambda_I = 0.5$ and $\lambda_A = 0.5$.

Figure 5.16: Model simulations: Concentrations in time of unbound TCE inside the adipocyte region of the adipose tissue at $\phi = \pi/2$ and $\theta = 0, \pi/4, \pi/2, 3\pi/4$ and $\pi$, with $\mathcal{F} = 0.08$, $A_B = 5 \times 10^{-5}$, $\lambda_I = 0.5$ and $\lambda_A = 0.5$. 
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Figure 5.17: Model simulations: Concentrations in time of unbound TCE inside the adipocyte region of the adipose tissue along $\phi = \pi/2$ with $F = 0.16$, $A_B = 10^{-4}$, and Left: $\lambda_I = 1$, $\lambda_A = 0$; Right: $\lambda_I = 0.6$, $\lambda_A = 0.4$.

5.4.4 Dependence on the proportions of direct and indirect transport between the capillary and adipocyte

Concentration profiles also can be altered significantly by changing the proportions $\lambda_A$ and $\lambda_I$ of direct and indirect transport between the capillary and the adipocyte. Figures 5.17 and 5.18 depict simulations of unbound TCE adipocyte concentrations along $\phi = \pi/2$ for varying values of $\lambda_A$, $\lambda_I$. In Figure 5.17, the indirect transport is predominant over the direct transport ($\lambda_A = 0$, $\lambda_I = 1$ and $\lambda_A = 0.4$, $\lambda_I = 0.6$), while the direct transport predominates in Figure 5.18 ($\lambda_A = 0.6$, $\lambda_I = 0.4$ and $\lambda_A = 0.65$, $\lambda_I = 0.35$). As $\lambda_A$ increases and $\lambda_I$ decreases, the levels of TCE increase and the shapes of the curves change dramatically. These example simulations demonstrate the importance of accounting for either or both of these types of transport, since the simulated dynamics of TCE in the fat tissue vary greatly with the changes in proportions of direct and indirect transport.
Figure 5.18: Model simulations: Concentrations in time of unbound TCE inside the adipocyte region of the adipose tissue along $\phi = \pi/2$ with $F = 0.16$, $A_B = 10^{-4}$, and Left: $\lambda_I = 0.4$, $\lambda_A = 0.6$; Right: $\lambda_I = 0.35$, $\lambda_A = 0.65$.

### 5.4.5 Dependence on model parameters

In this section we present model simulations for varying adipose parameter values, illustrating the sensitivity of the model to each of the parameters. The eight parameters that we study here are the adipose model parameters for which no reasonable estimate could be found in the literature or deduced from the well-mixed compartmental models.

Figure 5.19 depicts spatial predictions of TCE concentrations in the capillary region at time $t = 3$ hours for varying values of the axial dispersion coefficient $D_B$. As discussed in [53], as the dispersion coefficient $D_B$ approaches zero, the convective flow becomes predominant over the dispersion, yielding a response similar to plug flow. As $D_B$ becomes large, the model predictions more resemble the response of a well-mixed model. This is demonstrated in Figure 5.19, where the TCE concentrations have the most spatial variation for $D_B = 0.5$, while the profile for $D_B = 2$ is nearly constant with respect to the spatial variable $\phi$. See Figure 5.20 for the effect of varying values of $D_B$ on mean TCE adipocyte concentrations.

The equations of transport for the interstitial and adipocyte regions are similar
Figure 5.19: Spatial TCE concentrations in the capillary region at $t = 3$ hours with $D_B = 0.5$, 1, and 2.

Figure 5.20: Mean unbound TCE concentrations in time in the adipocyte region for $D_B = 0.1$, 0.5, 1, 2 and 3.
in structure, leading to a similar dependence on the two diffusivity coefficients $D_I$ and $D_A$. See Figure 5.21 for mean TCE adipocyte concentrations for $D_I = 0.001, 0.005, 0.01, 0.02, 0.03$, and Figure 5.22 for mean TCE adipocyte concentrations with $D_A = 0.0001, 0.0005, 0.001, 0.002$ and 0.003. As the values of $D_I$ and $D_A$ increase, the response curves have smaller magnitudes and the rate of decay increases following exposure.

See Figures 5.23 – 5.25 for predictions of mean TCE adipocyte concentrations with varying values of the permeability coefficients $\mu_{BA}$, $\mu_{BI}$ and $\mu_{IA}$ respectively. Moreover, Figures 5.26 and 5.27 depict simulations for varying values of the radius $r_1$ of the adipocyte and the cross-sectional area $A_B$ of the capillary. In Chapter 6 we will continue our study of these parameters and their effect on the TCE model by carrying out several parameter estimation problems.
Figure 5.22: Mean unbound TCE concentrations in time in the adipocyte region for $D_A = 0.0001, 0.0005, 0.001, 0.002$ and $0.003$.

Figure 5.23: Mean unbound TCE concentrations in time in the adipocyte region for $\mu_{BA} = 0.003, 0.015, 0.03, 0.06$ and $0.09$. 
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Figure 5.24: Mean unbound TCE concentrations in time in the adipocyte region for $\mu_{BI} = 0.002, 0.01, 0.02, 0.04$ and 0.06.

Figure 5.25: Mean unbound TCE concentrations in time in the adipocyte region for $\mu_{IA} = 0.0025, 0.0125, 0.025, 0.05$ and 0.075.
Figure 5.26: Mean unbound TCE concentrations in time in the adipocyte region for \( r_1 = 0.008, 0.04, 0.08, 0.16 \) and 0.24.

Figure 5.27: Mean unbound TCE concentrations in time in the adipocyte region for \( A_B = 5 \times 10^{-6}, 2.5 \times 10^{-5}, 5 \times 10^{-5}, 1 \times 10^{-4} \) and \( 1.5 \times 10^{-4} \).
Chapter 6

Parameter estimation

In this chapter we present results for several types of parameter estimation problems applied to the TCE PBPK-hybrid model. These problems include the standard type of deterministic estimation problem as discussed in Section 4.2, as well as the estimation problems based on probability and uncertainty presented in Section 4.3.

Here we develop and test several estimation problems with simulated data that qualitatively and quantitatively match the experimental data in [32], and we demonstrate which strategies and observations are most successful at capturing and predicting the dynamics of TCE in adipose tissue. This in-depth study of the parameter estimation process with simulated data is important for understanding the capability of these estimation techniques, and is a necessary first step to complete before working with actual experimental data.

6.1 The standard deterministic estimation problem

First we study the standard deterministic estimation problem, where we assume that each parameter is a fixed constant. The estimation problems we carry out here involve both observations from a single individual and observations from multiple individuals. The latter type of observation is often more feasible and is more commonly used than
the former type for the experiments that are appropriate for our model, and the experimental data gathered by Evans et al. [32] fall into the latter category.

We formulate the estimation problem for parameters \( q \) in an admissible parameter space \( Q \). Here we seek to minimize

\[
J(q, z) = \sum_{i=1}^{N_t} |O y(t_i, \cdot; q) - z_i|^2
\]

over \( q \in Q \), subject to

\[
\langle \dot{y}(t), \psi \rangle_{\mathbb{V}^*, \mathbb{V}} + \sigma(q)(y(t), \psi) + \langle g(q)(y(t)), \psi \rangle_{\mathbb{H}} = \langle f(t; q), \psi \rangle_{\mathbb{V}^*, \mathbb{V}},
\]

where

\[
y(t) = [C_B(t), C_I(t), C_A(t), C_v(t), C_{br}(t), C_k(t), C_m(t), C_l(t)]^T
\]

and \( \sigma(q) \), \( g(q) \) and \( f(t; q) \) are defined as in Section 4.1.1. In this case, we define the observations \( z_i, i = 1, \ldots, N_t \) and the observation operator \( O \) so that they correspond to the types of experimental observations used in the experiments conducted by Evans et al. [32]. The data that they collected include measurements of TCE concentrations in venous blood, as well as in homogenized samples of fat, liver and brain tissue. Therefore we define the observation operators

\[
O^v y(t_i, \cdot; q) = C_v(t_i; q)
\]

\[
O^{br} y(t_i, \cdot; q) = C_{br}(t_i; q)
\]

\[
O^l y(t_i, \cdot; q) = C_{vl}(t_i; q)
\]

\[
O^f y(t_i, \cdot; q) = \bar{C}_A^{M,N}(t_i; q)
\]

\[
= \frac{1}{(N_\phi + 1)(M_I + 1)} \sum_{j=1}^{M_I+1} \sum_{k=1}^{N_\phi+1} f_A^{M_I,N_\phi}(t_i, \theta_j, \phi_k; q)
\]

where

\[
\theta_j = 2\pi(j - 1)/M_I, \quad j = 1, \ldots, M_I + 1
\]

\[
\phi_k = \pi(k - 1)/N_\phi, \quad k = 1, \ldots, N_\phi + 1.
\]
Similarly, we define the simulated observations
\begin{align*}
z_i^v &= C_v(t_i; q^*) \quad (6.7) \\
z_i^{br} &= C_{vbr}(t_i; q^*) \quad (6.8) \\
z_i^l &= C_{vl}(t_i; q^*) \quad (6.9) \\
z_i^f &= C_M^{I;N_o}(t_i; q^*) \quad (6.10)
\end{align*}
for \(i = 1, \ldots, N_t\) and for some \(q^* \in Q\). The observations (6.10) are mean concentrations of TCE in the adipocyte region of the adipose tissue (see Section 5.4.2 for a detailed discussion).

Note that the four observations in (6.7) – (6.10) are defined to simulate measurements from a single individual. The experimental data [32], however, include measurements of TCE concentrations in several different rats. Indeed, within each of the four tissues, each data point in this collection of data represents a different individual. We define observations that correspond to these data with inter-individual variability by assuming that the parameters vary across the population, so that each \(q_j\) has a normal distribution with mean \(\mu_j\) and standard deviation \(\sigma_j = \omega \mu_j / 3\), where \(\omega > 0\). This results in a normal distribution with values in the interval \([(1 - \omega)\mu_j, (1 + \omega)\mu_j]\) for each parameter \(q_j\) with 99.87% certainty. Therefore the parameter vector \(q = [q_1, \ldots, q_{N_q}]\) has a multi-normal distribution with mean \(\mu = [\mu_1, \ldots, \mu_{N_q}]\) and a diagonal covariance matrix \(C(\omega)\) with diagonal \(\sigma^2 = [\sigma^2_1, \ldots, \sigma^2_{N_q}]\). Our observations are then given by
\begin{align*}
\tilde{z}_i^v &= C_v(t_i; q^*(i, \omega)) \quad (6.11) \\
\tilde{z}_i^{br} &= C_{vbr}(t_i; q^*(i, \omega)) \quad (6.12) \\
\tilde{z}_i^l &= C_{vl}(t_i; q^*(i, \omega)) \quad (6.13) \\
\tilde{z}_i^f &= \tilde{C}_M^{I;N_o}(t_i; q^*(i, \omega)) \quad (6.14)
\end{align*}
where \(q^*(i, \omega)\) is sampled from \(N(\mu, C(\omega))\) for each \(i = 1, \ldots, N_t\). This results in a collection of simulated observations at \(N_t\) time points, where each measurement in time is taken from a different individual.
In a laboratory setting, one would expect that experimental measurements would contain a certain level of noise, which could be a result of one or more factors such as instrument precision, environmental effects and human error. We incorporate this type of noise into our simulated data by adding relative random noise to our observations. Here we consider data with uniformly distributed random noise and data with normally distributed random noise. Specifically, for a given observation set \( z = [z_1, \ldots, z_N] \) we define

\[
\begin{align*}
    z_i^U &= (1 + \eta_i^U(\alpha))z_i \quad (6.15) \\
    z_i^N &= (1 + \eta_i^N(\alpha))z_i \quad (6.16)
\end{align*}
\]

for \( i = 1, \ldots, N \), where \( \eta_i^U(\alpha) \) is uniformly distributed on the interval \([\alpha, \alpha]\), and \( \eta_i^N(\alpha) \) is normally distributed with mean zero and standard deviation \( \alpha/3 \), so that \( \eta_i^N(\alpha) \) takes on values in the interval \([\alpha, \alpha]\) with 99.87% confidence. Both of these distributions result in data with \( \alpha \times 100\% \) relative noise.

The parameter space we consider in this section is eight-dimensional, and the parameters to be estimated are given by

\[ q = [D_B, D_I, D_A, \mu_{IA}, \mu_{BA}, \mu_{BI}, r_1, A_B]. \]

In Section 5.4.5, we studied the dependence of model simulations on each of these parameters, which we were not able to estimate using values from the literature or from the well-mixed models. Here we further study the dependence of the model on this parameter set by implementing several types of estimation problems.

### 6.1.1 A study of two and three-dimensional estimation problems

Before working directly with the full eight-dimensional problem, first we study estimation problems for pairs and triples of parameters in \( Q \). These smaller-dimension inverse problems will help establish the sensitivity of the model to these parameters,
and will also demonstrate how the estimation problem may be affected by coupling between parameters. Moreover, if we discover that these smaller inverse problems are extremely ill-conditioned and produce poor results, we will have little hope of successfully solving the full eight-dimensional inverse problem, which is likely to be less well-conditioned and to experience even stronger coupling effects than the smaller problems.

We implemented the estimation problem for (6.1) subject to (6.2) for the following parameter sets: $(D_B, \mu_{IA})$, $(D_I, \mu_{BA})$, $(D_A, \mu_{BI})$, $(r_1, A_B)$, $(D_B, D_I)$, $(D_B, D_A)$, $(D_I, D_A)$, $(\mu_{BA}, \mu_{BI})$, $(\mu_{IA}, \mu_{BI})$, $(\mu_{IA}, \mu_{BA})$, $(D_B, D_I, D_A)$ and $(\mu_{IA}, \mu_{BA}, \mu_{BI})$.

In each of these problems, we used observations that simulate TCE concentrations in homogenized adipose tissue samples from one individual. That is, we used $z = z^f$ as in (6.10) with $q^* \in Q$. Accordingly, we used the observation operator $O^f$ given by (6.6), where $t_i = 5(i - 1)/30$, $i = 1, \ldots, N_t = 31$. We tested these inverse problems using observations with no noise, as well as observations with uniformly distributed relative noise and observations with normally distributed relative noise (as in (6.15) and (6.16), respectively). The values of $\alpha$ we used include $\alpha = 0.01$, $0.05$ and $0.1$, corresponding to $1\%$, $5\%$ and $10\%$ random relative noise respectively.

The optimization was implemented in Matlab using *fminsearch*, which utilizes the simplex-based Nelder-Mead algorithm. This direct search method was chosen over a gradient-based method for its flexibility in optimizing over non-smooth objective functions. The objective functions we consider here are theoretically smooth with respect to each of the parameters, but in practice these objective functions are non-smooth. This may result from both approximation error in the finite element approximations and from numerical error in the computation of solutions. Moreover, a direct search algorithm does not require the gradient of the objective function with respect to each of the parameters. Evaluating such a gradient would require computing finite difference gradient approximations or solving an additional system of sensitivity equations, either of which would add significantly to the computational effort needed to solve the estimation problem.
This particular version of the Nelder-Mead algorithm uses two termination criteria: the maximum difference between any two objective function values for the simplex of parameter estimates, and the maximum “diameter” of the simplex itself (i.e., the maximum value of the norm of the difference between any two parameter sets in the simplex). We set the former tolerance to the default value of $10^{-4}$ and the latter tolerance to $10^{-5}$ for this and all subsequent calculations in this chapter. Moreover, for each estimation problem we ran \texttt{fminsearch} as many times as necessary so that the objective function for the initial iterate was equal to the value for the optimized solution, where the initial iterate was set to be the solution from the previous run of the routine.

We used a variety of initial iterates for the first run of \texttt{fminsearch}, including values from 0% to 150% away from the data-generating parameters $q^*$. For each of these estimation problems, the parameters $q^*$ are set to the values given in Appendix A, and the parameters that are not part of a given estimation problem are held constant at the values in Appendix A.

Results for each of the estimation problems listed above are included in Tables 6.1 – 6.12. In these and all subsequent tables, we use the abbreviated notation $\alpha e - \beta$ to represent $\alpha \times 10^{-\beta}$.

The first three estimation problems involve pairs of parameters where one parameter is a dispersion or diffusion coefficient and the second parameter is a permeability coefficient. Here we chose the pairings $(D_B, \mu_{IA})$, $(D_I, \mu_{BA})$ and $(D_A, \mu_{BI})$ so that there would as little coupling as possible between the two parameters in each pair. Note that the dispersion coefficient $D_B$ appears only in the equation for the capillary region, while the permeability coefficient $\mu_{IA}$ appears only in the equations for the interstitial and adipocyte regions. The other two parameter sets $(D_I, \mu_{BA})$ and $(D_A, \mu_{BI})$ are similarly paired. As seen in Tables 6.1 – 6.3, the optimization algorithm was able to estimate a reasonable approximation to $q^*$, even with noise levels up to 10% in magnitude. The results for the pair $(r_1, A_B)$ given in Table 6.4 are similar.

Tables 6.5 – 6.10 list results for the estimation problems involving various pairings
of parameters for the cases with 0% and 10% normally distributed relative noise. As before, the resulting optimized parameters were reasonably close to the data-generating parameters $q^*$, suggesting that the estimation problem for any two pairs of the eight parameters is well-conditioned.

The final two estimation problems we present in this section are for the triples $(D_B, D_I, D_A)$ and $(\mu_{BA}, \mu_{BI}, \mu_{IA})$ with both 0% and 10% normally distributed relative noise. The resulting optimized parameters are given in Tables 6.11 and 6.12 respectively. Note that these optimized parameters are not in general as close to the data-generating parameters $q^*$ as in the estimation problems involving pairs of parameters. This suggests that there may be additional coupling effects that occur in the 3-dimensional estimation problem.
Chapter 6. Parameter estimation

Table 6.1: Parameter estimation results for data generated by \( q^* = (\mathcal{D}_B^*, \mu^*_{IA}) = (1, 0.025) \) with various levels of noise (\( \mathcal{N} \) and \( \mathcal{U} \) correspond to normally and uniformly distributed noise, respectively) and initial iterates \( q_0 = (\mathcal{D}_{B0}, \mu_{IA0}) \). The optimized parameters are denoted by \( \tilde{q} = (\tilde{D}_B, \tilde{\mu}_{IA}) \).

<table>
<thead>
<tr>
<th>Noise</th>
<th>( \mathcal{D}_{B0} )</th>
<th>( \mu_{IA0} )</th>
<th>( D_B )</th>
<th>( \mu_{IA} )</th>
<th>( J(q_0, z) )</th>
<th>( J(\tilde{q}, z) )</th>
<th>( J(q^*, z) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>1.5</td>
<td>0.0375</td>
<td>1.0000</td>
<td>0.02500</td>
<td>148.36</td>
<td>4.853e-10</td>
<td>0</td>
</tr>
<tr>
<td>0%</td>
<td>0.5</td>
<td>0.0125</td>
<td>1.0000</td>
<td>0.02500</td>
<td>926.24</td>
<td>3.297e-12</td>
<td>0</td>
</tr>
<tr>
<td>5% ( \mathcal{N} )</td>
<td>1.5</td>
<td>0.0375</td>
<td>0.9937</td>
<td>0.02407</td>
<td>151.45</td>
<td>9.578e-1</td>
<td>9.738e-1</td>
</tr>
<tr>
<td>5% ( \mathcal{N} )</td>
<td>0.5</td>
<td>0.0125</td>
<td>0.9926</td>
<td>0.02408</td>
<td>920.76</td>
<td>9.559e-1</td>
<td>9.738e-1</td>
</tr>
<tr>
<td>10% ( \mathcal{N} )</td>
<td>1.5</td>
<td>0.0375</td>
<td>1.0106</td>
<td>0.02832</td>
<td>154.46</td>
<td>2.0947</td>
<td>2.2124</td>
</tr>
<tr>
<td>10% ( \mathcal{N} )</td>
<td>0.5</td>
<td>0.0125</td>
<td>1.0106</td>
<td>0.02832</td>
<td>922.42</td>
<td>2.0947</td>
<td>2.2124</td>
</tr>
<tr>
<td>5% ( \mathcal{U} )</td>
<td>1.5</td>
<td>0.0375</td>
<td>0.9881</td>
<td>0.02307</td>
<td>152.84</td>
<td>2.0642</td>
<td>2.1103</td>
</tr>
<tr>
<td>5% ( \mathcal{U} )</td>
<td>0.5</td>
<td>0.0125</td>
<td>0.9881</td>
<td>0.02307</td>
<td>921.84</td>
<td>2.0642</td>
<td>2.1103</td>
</tr>
<tr>
<td>10% ( \mathcal{U} )</td>
<td>1.5</td>
<td>0.0375</td>
<td>1.0219</td>
<td>0.03683</td>
<td>172.29</td>
<td>4.2904</td>
<td>5.7009</td>
</tr>
<tr>
<td>10% ( \mathcal{U} )</td>
<td>0.5</td>
<td>0.0125</td>
<td>1.0219</td>
<td>0.03683</td>
<td>892.61</td>
<td>4.2904</td>
<td>5.7009</td>
</tr>
</tbody>
</table>

Table 6.2: Parameter estimation results for data generated by \( q^* = (\mathcal{D}_I^*, \mu^*_{BA}) = (0.01, 0.03) \) with various levels of noise (\( \mathcal{N} \) and \( \mathcal{U} \) correspond to normally and uniformly distributed noise, respectively) and initial iterates \( q_0 = (\mathcal{D}_{I0}, \mu_{BA0}) \). The optimized parameters are denoted by \( \tilde{q} = (\tilde{D}_I, \tilde{\mu}_{BA}) \).

<table>
<thead>
<tr>
<th>Noise</th>
<th>( \mathcal{D}_{I0} )</th>
<th>( \mu_{BA0} )</th>
<th>( D_I )</th>
<th>( \mu_{BA} )</th>
<th>( J(q_0, z) )</th>
<th>( J(\tilde{q}, z) )</th>
<th>( J(q^*, z) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>0.015</td>
<td>0.045</td>
<td>1.000e-2</td>
<td>3.000e-2</td>
<td>2141.1</td>
<td>1.483e-10</td>
<td>0</td>
</tr>
<tr>
<td>0%</td>
<td>0.005</td>
<td>0.015</td>
<td>1.000e-2</td>
<td>3.000e-2</td>
<td>458.9</td>
<td>1.844e-8</td>
<td>0</td>
</tr>
<tr>
<td>5% ( \mathcal{N} )</td>
<td>0.015</td>
<td>0.045</td>
<td>9.452e-2</td>
<td>2.980e-2</td>
<td>2155.8</td>
<td>4.887e-1</td>
<td>5.076e-1</td>
</tr>
<tr>
<td>5% ( \mathcal{N} )</td>
<td>0.005</td>
<td>0.015</td>
<td>9.452e-3</td>
<td>2.980e-2</td>
<td>454.65</td>
<td>4.887e-1</td>
<td>5.076e-1</td>
</tr>
<tr>
<td>10% ( \mathcal{N} )</td>
<td>0.015</td>
<td>0.045</td>
<td>1.197e-2</td>
<td>3.065e-2</td>
<td>2132.9</td>
<td>2.0856</td>
<td>2.2124</td>
</tr>
<tr>
<td>10% ( \mathcal{N} )</td>
<td>0.005</td>
<td>0.015</td>
<td>1.197e-2</td>
<td>3.065e-2</td>
<td>4701.5</td>
<td>2.0856</td>
<td>2.2124</td>
</tr>
<tr>
<td>5% ( \mathcal{U} )</td>
<td>0.015</td>
<td>0.045</td>
<td>1.409e-2</td>
<td>3.099e-2</td>
<td>2170.0</td>
<td>1.8780</td>
<td>2.2825</td>
</tr>
<tr>
<td>5% ( \mathcal{U} )</td>
<td>0.005</td>
<td>0.015</td>
<td>1.408e-2</td>
<td>3.099e-2</td>
<td>455.05</td>
<td>1.8780</td>
<td>2.2825</td>
</tr>
<tr>
<td>10% ( \mathcal{U} )</td>
<td>0.015</td>
<td>0.045</td>
<td>8.347e-3</td>
<td>2.959e-2</td>
<td>2133.4</td>
<td>5.3881</td>
<td>5.4877</td>
</tr>
<tr>
<td>10% ( \mathcal{U} )</td>
<td>0.005</td>
<td>0.015</td>
<td>8.347e-3</td>
<td>2.959e-2</td>
<td>471.37</td>
<td>5.3881</td>
<td>5.4877</td>
</tr>
</tbody>
</table>
Table 6.3: Parameter estimation results for data generated by $q^* = (D_A^*, \mu^*_{BI}) = (0.001, 0.02)$ with various levels of noise ($N$ and $U$ correspond to normally and uniformly distributed noise, respectively) and initial iterates $q_0 = (D_{A0}, \mu_{BI0})$. The optimized parameters are denoted by $\bar{q} = (D_A, \bar{\mu}_{BI})$.

<table>
<thead>
<tr>
<th>Noise</th>
<th>$D_{A0}$</th>
<th>$\mu_{BI0}$</th>
<th>$D_A$</th>
<th>$\bar{\mu}_{BI}$</th>
<th>$J(q_0, z)$</th>
<th>$J(\bar{q}, z)$</th>
<th>$J(q^*, z)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>1.5e-3</td>
<td>3e-2</td>
<td>1.001e-3</td>
<td>2.000e-2</td>
<td>38.500</td>
<td>3.528e-6</td>
<td>0</td>
</tr>
<tr>
<td>0%</td>
<td>5e-4</td>
<td>1e-2</td>
<td>1.000e-3</td>
<td>2.000e-2</td>
<td>114.62</td>
<td>1.102e-7</td>
<td>0</td>
</tr>
<tr>
<td>5%</td>
<td>1.5e-3</td>
<td>3e-2</td>
<td>9.415e-4</td>
<td>2.080e-2</td>
<td>37.956</td>
<td>4.921e-1</td>
<td>5.076e-1</td>
</tr>
<tr>
<td>5%</td>
<td>5e-4</td>
<td>1e-2</td>
<td>9.413e-4</td>
<td>2.080e-2</td>
<td>116.79</td>
<td>4.921e-1</td>
<td>5.075e-1</td>
</tr>
<tr>
<td>10%</td>
<td>1.5e-3</td>
<td>3e-2</td>
<td>8.815e-4</td>
<td>2.168e-2</td>
<td>38.427</td>
<td>1.9676</td>
<td>2.0302</td>
</tr>
<tr>
<td>10%</td>
<td>5e-4</td>
<td>1e-2</td>
<td>9.027e-4</td>
<td>2.134e-2</td>
<td>11.997</td>
<td>1.9676</td>
<td>2.0302</td>
</tr>
<tr>
<td>5%</td>
<td>1.5e-3</td>
<td>3e-2</td>
<td>8.035e-4</td>
<td>2.200e-2</td>
<td>41.401</td>
<td>1.2678</td>
<td>1.3719</td>
</tr>
<tr>
<td>5%</td>
<td>5e-4</td>
<td>1e-2</td>
<td>8.008e-4</td>
<td>2.204e-2</td>
<td>113.28</td>
<td>1.2678</td>
<td>1.3719</td>
</tr>
<tr>
<td>10%</td>
<td>1.5e-3</td>
<td>3e-2</td>
<td>2.131e-3</td>
<td>1.195e-2</td>
<td>39.686</td>
<td>6.5177</td>
<td>9.1301</td>
</tr>
<tr>
<td>10%</td>
<td>1e-3</td>
<td>2e-2</td>
<td>2.132e-3</td>
<td>1.195e-2</td>
<td>138.94</td>
<td>6.5177</td>
<td>9.1301</td>
</tr>
</tbody>
</table>

Table 6.4: Parameter estimation results for data generated by $q^* = (r_1^*, A_B^*) = (0.08, 5 \times 10^{-5})$ with various levels of noise ($N$ and $U$ correspond to normally and uniformly distributed noise, respectively) and initial iterates $q_0 = (r_{10}, A_{B0})$. The optimized parameters are denoted by $\bar{q} = (\bar{r}_1, A_B)$.

<table>
<thead>
<tr>
<th>Noise</th>
<th>$r_{10}$</th>
<th>$A_{B0}$</th>
<th>$\bar{r}_1$</th>
<th>$A_B$</th>
<th>$J(q_0, z)$</th>
<th>$J(\bar{q}, z)$</th>
<th>$J(q^*, z)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>1.2e-1</td>
<td>7.5e-5</td>
<td>8.000e-2</td>
<td>5.000e-5</td>
<td>254.30</td>
<td>4.415e-7</td>
<td>0</td>
</tr>
<tr>
<td>0%</td>
<td>4e-2</td>
<td>2.5e-5</td>
<td>8.000e-2</td>
<td>5.000e-5</td>
<td>580.27</td>
<td>9.317e-7</td>
<td>0</td>
</tr>
<tr>
<td>5%</td>
<td>1.2e-1</td>
<td>7.5e-5</td>
<td>7.961e-2</td>
<td>4.948e-5</td>
<td>257.46</td>
<td>5.241e-1</td>
<td>5.531e-1</td>
</tr>
<tr>
<td>5%</td>
<td>4e-2</td>
<td>2.5e-5</td>
<td>7.961e-2</td>
<td>4.949e-5</td>
<td>582.78</td>
<td>5.241e-1</td>
<td>5.531e-1</td>
</tr>
<tr>
<td>10%</td>
<td>1.2e-1</td>
<td>7.5e-5</td>
<td>7.920e-2</td>
<td>4.893e-5</td>
<td>261.74</td>
<td>2.0981</td>
<td>2.2124</td>
</tr>
<tr>
<td>10%</td>
<td>4e-2</td>
<td>2.5e-5</td>
<td>7.927e-2</td>
<td>4.890e-5</td>
<td>372.83</td>
<td>2.0987</td>
<td>2.2124</td>
</tr>
<tr>
<td>5%</td>
<td>1.2e-1</td>
<td>7.5e-5</td>
<td>8.035e-2</td>
<td>5.021e-5</td>
<td>249.21</td>
<td>1.3549</td>
<td>1.3719</td>
</tr>
<tr>
<td>5%</td>
<td>4e-2</td>
<td>2.5e-5</td>
<td>8.035e-2</td>
<td>5.021e-5</td>
<td>586.83</td>
<td>1.3548</td>
<td>1.3719</td>
</tr>
<tr>
<td>10%</td>
<td>1.2e-1</td>
<td>7.5e-5</td>
<td>7.934e-2</td>
<td>4.967e-5</td>
<td>272.25</td>
<td>5.1741</td>
<td>5.2796</td>
</tr>
<tr>
<td>10%</td>
<td>4e-2</td>
<td>2.5e-5</td>
<td>7.934e-2</td>
<td>4.967e-5</td>
<td>570.51</td>
<td>5.1742</td>
<td>5.2796</td>
</tr>
</tbody>
</table>
Chapter 6. Parameter estimation

Table 6.5: Parameter estimation results for data generated by $q^* = (D_B^*, D_I^*) = (1, 0.01)$ with normally distributed noise and initial iterates $q_0 = (D_{B0}, D_{I0})$. The optimized parameters are denoted by $\tilde{q} = (D_B, D_I)$.

<table>
<thead>
<tr>
<th>Noise level</th>
<th>$D_{B0}$</th>
<th>$D_{I0}$</th>
<th>$D_B$</th>
<th>$D_I$</th>
<th>$J(q_0, z)$</th>
<th>$J(\tilde{q}, z)$</th>
<th>$J(q^*, z)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>1.5</td>
<td>0.015</td>
<td>1.0000</td>
<td>1.000e-2</td>
<td>233.29</td>
<td>1.395e-8</td>
<td>0</td>
</tr>
<tr>
<td>0%</td>
<td>0.5</td>
<td>0.005</td>
<td>1.0000</td>
<td>1.000e-2</td>
<td>2045.4</td>
<td>2.607e-9</td>
<td>0</td>
</tr>
<tr>
<td>10%</td>
<td>1.5</td>
<td>0.015</td>
<td>9.474e-1</td>
<td>1.373e-2</td>
<td>233.41</td>
<td>1.7576</td>
<td>1.8636</td>
</tr>
<tr>
<td>10%</td>
<td>0.5</td>
<td>0.005</td>
<td>9.474e-1</td>
<td>1.372e-2</td>
<td>2057.5</td>
<td>1.7576</td>
<td>1.8636</td>
</tr>
</tbody>
</table>

Table 6.6: Parameter estimation results for data generated by $q^* = (D_B^*, D_A^*) = (1, 0.001)$ with normally distributed noise and initial iterates $q_0 = (D_{B0}, D_{A0})$. The optimized parameters are denoted by $\tilde{q} = (D_B, D_A)$.

<table>
<thead>
<tr>
<th>Noise level</th>
<th>$D_{B0}$</th>
<th>$D_{A0}$</th>
<th>$D_B$</th>
<th>$D_A$</th>
<th>$J(q_0, z)$</th>
<th>$J(\tilde{q}, z)$</th>
<th>$J(q^*, z)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>1.5</td>
<td>0.0015</td>
<td>1.0000</td>
<td>1.000e-3</td>
<td>230.76</td>
<td>4.605e-8</td>
<td>0</td>
</tr>
<tr>
<td>0%</td>
<td>0.5</td>
<td>0.0005</td>
<td>1.0000</td>
<td>1.000e-3</td>
<td>1744.5</td>
<td>9.053e-8</td>
<td>0</td>
</tr>
<tr>
<td>10%</td>
<td>1.5</td>
<td>0.0015</td>
<td>9.910e-1</td>
<td>1.046e-3</td>
<td>233.96</td>
<td>1.2269</td>
<td>1.2366</td>
</tr>
<tr>
<td>10%</td>
<td>0.5</td>
<td>0.0005</td>
<td>9.910e-1</td>
<td>1.046e-3</td>
<td>1740.3</td>
<td>1.2269</td>
<td>1.2366</td>
</tr>
</tbody>
</table>

Table 6.7: Parameter estimation results for data generated by $q^* = (D_I^*, D_A^*) = (0.01, 0.001)$ with normally distributed noise and initial iterates $q_0 = (D_{I0}, D_{A0})$. The optimized parameters are denoted by $\tilde{q} = (D_I, D_A)$.

<table>
<thead>
<tr>
<th>Noise level</th>
<th>$D_{I0}$</th>
<th>$D_{A0}$</th>
<th>$D_I$</th>
<th>$D_A$</th>
<th>$J(q_0, z)$</th>
<th>$J(\tilde{q}, z)$</th>
<th>$J(q^*, z)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>0.015</td>
<td>0.0015</td>
<td>1.000e-2</td>
<td>9.999e-4</td>
<td>28.105</td>
<td>3.691e-8</td>
<td>0</td>
</tr>
<tr>
<td>0%</td>
<td>0.005</td>
<td>0.0005</td>
<td>9.690e-3</td>
<td>1.029e-3</td>
<td>48.216</td>
<td>3.400e-4</td>
<td>0</td>
</tr>
<tr>
<td>10%</td>
<td>0.015</td>
<td>0.0015</td>
<td>6.923e-3</td>
<td>1.389e-3</td>
<td>31.245</td>
<td>2.0784</td>
<td>2.2124</td>
</tr>
<tr>
<td>10%</td>
<td>0.005</td>
<td>0.0005</td>
<td>6.923e-3</td>
<td>1.389e-3</td>
<td>49.429</td>
<td>2.0784</td>
<td>2.2124</td>
</tr>
</tbody>
</table>
Chapter 6. Parameter estimation  

Table 6.8: Parameter estimation results for data generated by $q^* = (\mu_{BA}^*, \mu_{BI}^*) = (0.03, 0.02)$ with normally distributed noise and initial iterates $q_0 = (\mu_{BA0}, \mu_{BI0})$. The optimized parameters are denoted by $\bar{q} = (\mu_{BA}, \mu_{BI})$.

<table>
<thead>
<tr>
<th>Noise level</th>
<th>$\mu_{BA0}$</th>
<th>$\mu_{BI0}$</th>
<th>$\bar{\mu}_{BA}$</th>
<th>$\bar{\mu}_{BI}$</th>
<th>$J(q_0, z)$</th>
<th>$J(\bar{q}, z)$</th>
<th>$J(q^*, z)$</th>
</tr>
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<tbody>
<tr>
<td>0%</td>
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<td>$3.000e-2$</td>
<td>$2.000e-2$</td>
<td>1047.3</td>
<td>2.968e-8</td>
<td>0</td>
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<td>0.01</td>
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<td>601.42</td>
<td>1.606e-8</td>
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</tr>
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<td>$3.003e-2$</td>
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<td>1.2317</td>
<td>1.2366</td>
</tr>
<tr>
<td>10%</td>
<td>0.015</td>
<td>0.01</td>
<td>$2.999e-2$</td>
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<td>606.00</td>
<td>1.2307</td>
<td>1.2366</td>
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</table>

Table 6.9: Parameter estimation results for data generated by $q^* = (\mu_{BA}^*, \mu_{IA}^*) = (0.03, 0.025)$ with normally distributed noise and initial iterates $q_0 = (\mu_{BA0}, \mu_{IA0})$. The optimized parameters are denoted by $\bar{q} = (\mu_{BA}, \mu_{IA})$.

<table>
<thead>
<tr>
<th>Noise level</th>
<th>$\mu_{BA0}$</th>
<th>$\mu_{IA0}$</th>
<th>$\bar{\mu}_{BA}$</th>
<th>$\bar{\mu}_{IA}$</th>
<th>$J(q_0, z)$</th>
<th>$J(\bar{q}, z)$</th>
<th>$J(q^*, z)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>0.045</td>
<td>0.0375</td>
<td>$3.000e-2$</td>
<td>$2.500e-2$</td>
<td>3034.9</td>
<td>7.611e-9</td>
<td>0</td>
</tr>
<tr>
<td>0%</td>
<td>0.015</td>
<td>0.0125</td>
<td>$3.000e-2$</td>
<td>$2.500e-2$</td>
<td>695.08</td>
<td>1.028e-8</td>
<td>0</td>
</tr>
<tr>
<td>10%</td>
<td>0.045</td>
<td>0.0375</td>
<td>$2.984e-2$</td>
<td>$2.382e-2$</td>
<td>3096.2</td>
<td>1.7234</td>
<td>2.0367</td>
</tr>
<tr>
<td>10%</td>
<td>0.015</td>
<td>0.0125</td>
<td>$2.984e-2$</td>
<td>$2.382e-2$</td>
<td>6677.3</td>
<td>1.7234</td>
<td>2.0367</td>
</tr>
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</table>

Table 6.10: Parameter estimation results for data generated by $q^* = (\mu_{BI}^*, \mu_{IA}^*) = (0.02, 0.025)$ with normally distributed noise and initial iterates $q_0 = (\mu_{BI0}, \mu_{IA0})$. The optimized parameters are denoted by $\bar{q} = (\mu_{BI}, \mu_{IA})$.

<table>
<thead>
<tr>
<th>Noise level</th>
<th>$\mu_{BI0}$</th>
<th>$\mu_{IA0}$</th>
<th>$\bar{\mu}_{BI}$</th>
<th>$\bar{\mu}_{IA}$</th>
<th>$J(q_0, z)$</th>
<th>$J(\bar{q}, z)$</th>
<th>$J(q^*, z)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>0.03</td>
<td>0.0375</td>
<td>$2.000e-2$</td>
<td>$2.500e-2$</td>
<td>5.474</td>
<td>5.286e-8</td>
<td>0</td>
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<tr>
<td>0%</td>
<td>0.01</td>
<td>0.0125</td>
<td>$2.000e-2$</td>
<td>$2.500e-2$</td>
<td>25.212</td>
<td>1.397e-8</td>
<td>0</td>
</tr>
<tr>
<td>10%</td>
<td>0.03</td>
<td>0.0375</td>
<td>$1.923e-2$</td>
<td>$2.345e-2$</td>
<td>7.9746</td>
<td>1.4231</td>
<td>1.4698</td>
</tr>
<tr>
<td>10%</td>
<td>0.01</td>
<td>0.0125</td>
<td>$1.911e-2$</td>
<td>$2.349e-2$</td>
<td>25.091</td>
<td>1.4236</td>
<td>1.4698</td>
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</tbody>
</table>
Table 6.11: Parameter estimation results for data with $D_B^* = 1$, $D_I^* = 0.01$, $D_A^* = 0.001$, normally distributed noise.

<table>
<thead>
<tr>
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<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{B0}$</td>
<td>1.1</td>
<td>15</td>
</tr>
<tr>
<td>$D_{I0}$</td>
<td>0.9</td>
<td>15</td>
</tr>
<tr>
<td>$D_{A0}$</td>
<td>0.011</td>
<td>0.015</td>
</tr>
<tr>
<td>$D_B$</td>
<td>9.932e-1</td>
<td>8.230e-1</td>
</tr>
<tr>
<td>$D_I$</td>
<td>1.909e-2</td>
<td>6.151e-4</td>
</tr>
<tr>
<td>$D_A$</td>
<td>1.949e-4</td>
<td>4.117e-3</td>
</tr>
<tr>
<td>$J(q_0, z)$</td>
<td>21.940</td>
<td>280.77</td>
</tr>
<tr>
<td>$J(q, z)$</td>
<td>1.049e-3</td>
<td>1.3853</td>
</tr>
<tr>
<td>$J(q^*, z)$</td>
<td>0</td>
<td>1.4260</td>
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</tbody>
</table>

Table 6.12: Parameter estimation results for data with $\mu_{BA}^* = 0.03$, $\mu_{BI}^* = 0.02$, $\mu_{IA}^* = 0.025$, normally distributed noise.

<table>
<thead>
<tr>
<th>Noise level</th>
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<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_{BA0}$</td>
<td>0.033</td>
<td>0.045</td>
</tr>
<tr>
<td>$\mu_{BI0}$</td>
<td>0.222</td>
<td>0.03</td>
</tr>
<tr>
<td>$\mu_{IA0}$</td>
<td>0.0275</td>
<td>0.015</td>
</tr>
<tr>
<td>$\mu_{BA}$</td>
<td>3.163e-2</td>
<td>3.017e-2</td>
</tr>
<tr>
<td>$\mu_{BI}$</td>
<td>2.520e-2</td>
<td>2.016e-2</td>
</tr>
<tr>
<td>$\mu_{IA}$</td>
<td>2.127e-2</td>
<td>2.406e-2</td>
</tr>
<tr>
<td>$J(q_0, z)$</td>
<td>37.132</td>
<td>1213.0</td>
</tr>
<tr>
<td>$J(q, z)$</td>
<td>3.560e-6</td>
<td>1.2266</td>
</tr>
<tr>
<td>$J(q^*, z)$</td>
<td>0</td>
<td>1.2366</td>
</tr>
</tbody>
</table>
6.1.2 The parameter estimation problem for $q = (D_B, \mu_{IA})$

In this section we present expanded results for the inverse problem for $q = (D_B, \mu_{IA})$, where we use observations that simulate inter-individual variability. Here we test the ability of the deterministic parameter estimation strategy to estimate constant parameters from data that are collected from many individuals, where the parameters in question actually vary across the population.

The first inverse problem that we formulate here includes observations of both adipose and blood TCE concentrations at the following time points, as used in the experimental data [32]:

$$\tilde{t} = [0, 5/60, 20/60, 40/60, 1, 2] \text{ (hours)},$$

so that the final time $t_f$ is equal to two hours and the total number of time points is given by $N_t = 6$. We assume that the observations taken at each time point correspond to a different individual, as is the case with the actual experimental data. Note that this results in a total of six individuals (if we include $t = 0$) and a total of twelve data points, since we have observations of both fat and blood concentrations for each individual.

Our observations are then given by $\hat{z}_v^i$ and $\hat{z}_f^i$ for $i = 1, \ldots, N_t$, where $\hat{z}_v^i$ and $\hat{z}_f^i$ are defined as in (6.11) and (6.14) respectively with $\mu = q^* = (1, 0.03)$ and for $\omega = 0.25, 0.5$ and 1. Here we use the observation operators $\mathcal{O}_v$ and $\mathcal{O}_f$ as in (6.3) and (6.6), and we formulate a weighted objective function using these observations and operators:

$$J(q, \hat{z}) = \sum_{i=1}^{N_t} \frac{1}{\bar{z}_v} |\mathcal{O}_v y(t_i, \cdot; q) - \hat{z}_v^i|^2 + \frac{1}{\bar{z}_f} |\mathcal{O}_f y(t_i, \cdot; q) - \hat{z}_f^i|^2$$

$$= \sum_{i=1}^{N_t} \frac{1}{\bar{z}_v} |C_v(t_i; q) - \hat{z}_v^i|^2 + \frac{1}{\bar{z}_f} |\bar{C}_M(t_i; q) - \hat{z}_f^i|^2$$

subject to (6.2), where $t_i, i = 1, \ldots, N_t$ are the elements of $\tilde{t}$ as in (6.17). We use the
weights $\bar{z}^v$ and $\bar{z}^f$ defined by
\[
\bar{z}^v = \max_{j=1,\ldots,N_t} \hat{z}^v_j \\
\bar{z}^f = \max_{j=1,\ldots,N_t} \hat{z}^f_j
\]
to account for the large differences in magnitude between TCE concentrations in the venous blood and in the adipocyte region (compare Figures 5.7 and 5.14). This results in an objective function that places equal weight on the residual values in the venous blood compartment and the adipocyte region.

As discussed earlier in this section, we added random relative noise to the observations to simulate the effect of noise in experimental data. We tested the inverse problem with no noise, as well as with 10% normally distributed relative noise. We implemented these estimation problems in Matlab using \texttt{fminsearch} as detailed in Section 6.1.1.

Results for this problem with $\omega = 0.25, 0.5$ and 1 are given in Table 6.13. Note that in most cases, the optimized parameters are a reasonable approximation to the data-generating parameters $q^*$, even with relative noise added to the data. See Figure 6.1 for an example graph of the simulated data compared to the model predictions for $q^*$ and the optimized parameters $\bar{q}$. The simulations were computed for times ranging from zero to fifteen hours with $\bar{q}$ corresponding to the problem with $\omega = 0.25$ and no relative noise. Note that model predictions for $q^*$ and $\bar{q}$ are relatively similar.

Next we test the same inverse problem with an expanded observation set, adding observations from the liver and brain tissue to the previous simulated data. This leads to the objective function
\[
J(q, \hat{z}) = \sum_{i=1}^{N_t} \frac{1}{\bar{z}^v_i} \left| \mathcal{O}^v y(t_i, \cdot, \cdot; q) - \hat{z}^v_i \right|^2 + \frac{1}{\bar{z}^f_i} \left| \mathcal{O}^f y(t_i, \cdot, \cdot; q) - \hat{z}^f_i \right|^2 \\
+ \frac{1}{\bar{z}^{br}_i} \left| \mathcal{O}^{br} y(t_i, \cdot, \cdot; q) - \hat{z}^{br}_i \right|^2 + \frac{1}{\bar{z}^{bf}_i} \left| \mathcal{O}^{bf} y(t_i, \cdot, \cdot; q) - \hat{z}^{bf}_i \right|^2 \\
= \sum_{i=1}^{N_t} \frac{1}{\bar{z}^v_i} \left| C_v(t_i; q) - \hat{z}^v_i \right|^2 + \frac{1}{\bar{z}^f_i} \left| C_M^A(t_i; q) - \hat{z}^f_i \right|^2
\]
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\[ + \frac{1}{\tilde{z}_{br}} \left| C_{vbr}(t_i; q) - \tilde{z}_{br}^i \right|^2 + \frac{1}{\tilde{z}_l} \left| C_{vl}(t_i; q) - \tilde{z}_l^i \right|^2 \]  

(6.19)

subject to (6.2), where \( \hat{z} \) are observations given in (6.11) – (6.14) and with weights

\[
\begin{align*}
\tilde{z}^v &= \max_{j=1, \ldots, N_t} \tilde{z}_{vj}^v \\
\tilde{z}^{br} &= \max_{j=1, \ldots, N_t} \tilde{z}_{cj}^{br} \\
\tilde{z}^l &= \max_{j=1, \ldots, N_t} \tilde{z}_{jj}^l \\
\tilde{z}^f &= \max_{j=1, \ldots, N_t} \tilde{z}_{jj}^f.
\end{align*}
\]

(6.20) – (6.23)

As before, these weights account for differences in the magnitude of TCE concentrations across the four compartments used in these observations. We implemented this estimation problem with the same values \( \omega = 0.25, 0.5 \) and 1, and with the same initial iterates.

See Table 6.14 for results for this inverse problem, and Figure 6.2 for the resulting model predictions as before, where \( \omega = 0.25 \). The optimized parameters are similar to those obtained for the problem with just venous blood and fat observations, and the model prediction is also very similar to the prediction for \( q^* \). Note that the parameters \( D_B \) and \( \mu_{IA} \) appear only in the adipose compartmental model, which along with the results presented here suggest that observations from compartments such as the liver and the brain would likely have little impact in the estimation of these parameters.
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The optimized parameters are denoted by $q^*$ added to the observations, and the initial iterates are denoted by $\bar{q} = (\bar{D}_B, \bar{\mu}_{IA})$.

Table 6.13: Parameter estimation results for $q = (\mathcal{D}_B, \mu_{IA})$ with $t_f = 2, N_t = 6$. Simulated observations are given by $\hat{z}^o$ and $\hat{z}^f$ as in (6.11) and (6.14) with mean $q^* = (\mathcal{D}_B^*, \mu_{IA}^*) = (1, 0.03)$ and $\omega = 0.25, 0.5$ and 1. Normally distributed relative noise was added to the observations, and the initial iterates are denoted by $q_0 = (\mathcal{D}_{B0}, \mu_{IA0})$. The optimized parameters are denoted by $\bar{q} = (\bar{D}_B, \bar{\mu}_{IA})$.

<table>
<thead>
<tr>
<th>Noise level</th>
<th>$\omega$</th>
<th>$\mathcal{D}_{B0}$</th>
<th>$\mu_{IA0}$</th>
<th>$\mathcal{D}_B$</th>
<th>$\mu_{IA}$</th>
<th>$J(q_0)$</th>
<th>$J(\bar{q})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>0.25</td>
<td>1.0021</td>
<td>0.03</td>
<td>1.0021</td>
<td>3.041e-2</td>
<td>1.859e-3</td>
<td>8.360e-4</td>
</tr>
<tr>
<td>0%</td>
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<td>1.0021</td>
<td>0.045</td>
<td>1.0021</td>
<td>3.041e-2</td>
<td>1.022e-1</td>
<td>8.360e-4</td>
</tr>
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<td>0%</td>
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<td>1.0021</td>
<td>3.041e-2</td>
<td>2.746e-1</td>
<td>8.360e-4</td>
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<td>1.0021</td>
<td>0.03</td>
<td>9.948e-1</td>
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<td>5.123e-3</td>
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<tr>
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<td>0.25</td>
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<td>3.612e-2</td>
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<td>1.100e-3</td>
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<td>3.612e-2</td>
<td>2.490e-1</td>
<td>1.100e-3</td>
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<table>
<thead>
<tr>
<th>Noise level</th>
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<th>$\mathcal{D}_{B0}$</th>
<th>$\mu_{IA0}$</th>
<th>$\mathcal{D}_B$</th>
<th>$\mu_{IA}$</th>
<th>$J(q_0)$</th>
<th>$J(\bar{q})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>0.5</td>
<td>1.0021</td>
<td>0.03</td>
<td>9.605e-1</td>
<td>1.950e-2</td>
<td>8.650e-3</td>
<td>7.892e-3</td>
</tr>
<tr>
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<td>0.5</td>
<td>1.0021</td>
<td>0.045</td>
<td>9.605e-1</td>
<td>1.949e-2</td>
<td>1.107e-1</td>
<td>7.892e-3</td>
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<td>9.605e-1</td>
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<td>9.740e-1</td>
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<td>2.004e-2</td>
<td>1.002e-2</td>
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<td>0.045</td>
<td>9.740e-1</td>
<td>1.311e-2</td>
<td>8.344e-2</td>
<td>1.002e-2</td>
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<tr>
<td>10%</td>
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<td>1.0021</td>
<td>0.015</td>
<td>9.740e-1</td>
<td>1.311e-2</td>
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<td>1.002e-2</td>
</tr>
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</table>

<table>
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<th>$\mu_{IA0}$</th>
<th>$\mathcal{D}_B$</th>
<th>$\mu_{IA}$</th>
<th>$J(q_0)$</th>
<th>$J(\bar{q})$</th>
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Table 6.14: Parameter estimation results for $q = (\mathcal{D}_B, \mu_{IA})$ with $t_f = 2$, $N_t = 6$. Simulated observations are given by $\hat{z}^v$, $\hat{z}^{br}$, $\hat{z}^l$ and $\hat{z}^f$ as in (6.11) – (6.14) with mean $q^* = (\mathcal{D}_B^*, \mu_{IA}^*) = (1, 0.001)$ and $\omega = 0.25, 0.5$ and 1. Normally distributed relative noise was added to the observations, and the initial iterates are denoted by $q_0 = (\mathcal{D}_{B0}, \mu_{IA0})$. The optimized parameters are denoted by $\bar{q} = (\mathcal{D}_B, \bar{\mu}_{IA})$.

<table>
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<th>$\omega$</th>
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<th>$\mu_{IA0}$</th>
<th>$\mathcal{D}_B$</th>
<th>$\bar{\mu}_{IA}$</th>
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Figure 6.1: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$ and for the minimized solution $\bar{q}$ (denoted in the graph by $q$) of (6.18) with observations from venous blood and fat tissue, where $\omega = 0.25$, $t_f = 2$ hours, $N_t = 6$ and 0% noise.

Figure 6.2: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$ and for the minimized solution $\bar{q}$ (denoted in the graph by $q$) of (6.19) with observations of venous blood and fat, brain and liver tissue, $\omega = 0.25$, $t_f = 2$ hours, $N_t = 6$ and 0% noise.
6.1.3 The full eight-dimensional estimation problem

Now that we have completed a detailed study of smaller-dimensional parameter estimation problems, we progress to the full eight-dimensional problem. Here we present results for inverse problems that use observations simulating data from one individual, as well as problems with observations simulating multiple individuals. We study the effects of using concentration observations from various types of tissues (e.g., venous blood, fat, liver and brain), and we also study the estimation problem for varying final times $t_f$ and a varying total number of time points $N_t$. Based on these results, we formulate a strategy for designing experiments with a goal of generating the type and amount of data needed to successfully estimate the adipose model parameters.

6.1.3.a Observations from a single individual

First we implement the estimation problem using observations that simulate data from a single individual. In this case we generate observations of concentrations in venous blood and fat tissue at the six time points in (6.17). These observations all are assumed to be from one individual, so that each of these “data” points is generated from a single parameter set $q^* \in Q$, as in (6.7) and (6.10). We use the corresponding observation operators $O^v$ and $O^f$ given in (6.3) and (6.6) respectively, and we define the weights

$$z^v = \max_{j=1,\ldots,N_t} z_j^v$$
$$z^f = \max_{j=1,\ldots,N_t} z_j^f.$$
All model parameters excluding those we estimate are fixed at the values listed in Appendix A, and we use the parameter set $q^* \in Q$ given by

\begin{align*}
D_{B_i} &= 1 \\
D_{I_i}^* &= 0.01 \\
D_{A}^* &= 0.001 \\
\mu_{IA}^* &= 0.025 \\
\mu_{BA}^* &= 0.03 \\
\mu_{BI}^* &= 0.02 \\
r_1^* &= 0.08 \\
A_B^* &= 5 \times 10^{-5}.
\end{align*}

(6.24)

Our objective function is then given by

\begin{equation}
J(q, z) = \sum_{i=1}^{N_t} \frac{1}{z^v} \left| \mathcal{O}^v y(t_i, \cdot, \cdot; q) - z_i^v \right|^2 + \frac{1}{z^f} \left| \mathcal{O}^f y(t_i, \cdot, \cdot; q) - z_i^f \right|^2 = \sum_{i=1}^{N_t} \frac{1}{z^v} \left| C_v(t_i; q) - z_i^v \right|^2 + \frac{1}{z^f} \left| \bar{C}^{M,N}_A(t_i; q) - z_i^f \right|^2
\end{equation}

(6.25)

where $\bar{C}^{M,N}_A(t_i; q)$ is given in (6.6). As a first step, we implement this estimation problem with no noise added to the data. This will allow us to test the effectiveness of the algorithm and determine if the minimizers $q \in Q$ are “close” to the parameter set $q^*$ used to generate the observations.

Here we generate initial iterates for the optimization routine using uniformly distributed random numbers. Specifically, we define the vector $q_0(\nu) \in Q$ by

\begin{equation}
[q_0(\nu)]_i = (1 + \eta_i(\nu)) q_i^*
\end{equation}

(6.26)

for $i = 1, \ldots, N_q = 8$, where $\eta_i(\nu)$ is uniformly distributed on the interval $[-\nu, \nu]$. This results in an initial iterate that is up to $\nu \times 100\%$ away from the data-generating parameter set $q^*$. Here we report on results for $\nu = 0.25, 0.5$ and 1.

Table 6.15 lists results for the estimation problem corresponding to (6.25) for $\nu = 0.25, 0.5$ and 1. Note that for several individual parameters, the optimized
solution $\bar{q}_i$ is actually further away from $q^*_i$ than the initial iterate $[q_0(\nu)]_i$, although there is a significant reduction in the objective function $J$ for each value of $\nu$. This suggests that the objective function may have several local minima.

See Figure 6.3 for simulations of mean adipocyte TCE concentrations from zero to fifteen hours using the parameters $q^*$, $q_0(0.25)$ and the optimized solution $\bar{q}$ (with initial iterate $q_0(0.25)$) as given in Table 6.15. In this case, the parameters $\bar{q}$ yield a response that is very similar to the concentration curve for $q^*$, suggesting further that the estimation problem for (6.25) does not have a unique minimizer. Similar model predictions for the cases $\nu = 0.5$ and $\nu = 1$ are given in Figures 6.4 and 6.5, respectively. Note that these parameters $\bar{q}$ also generate simulations that are similar to those obtained with $q^*$, although neither of these responses are as closely matched with the concentration profile for $q^*$ as the response for the parameter set $\bar{q}$ obtained with the initial iterate $q_0(0.25)$.

Although the optimized parameters $\bar{q}$ listed in Table 6.15 provide model predictions that are reasonable approximations to the predictions for $q^*$, the actual parameter values themselves are not in general close to the values for $q^*$. The results discussed here suggest that there may be several local minima for this estimation problem, which may be a function of the small number of data points used as observations. Next we study the estimation problem associated with (6.25) for varying values of $t_f$ and $N_t$ to see how the size and nature of the observation set affects the performance of our estimation strategy.

First we test the inverse problem for (6.25) with $t_f = 2$ hours as before, but we choose $t_i = 2(i - 1)/30$ for $i = 1, \ldots, 31$, yielding $N_t = 31$ evenly spaced time points between zero and two hours. By comparing the results for this problem to the results in Table 6.15 with $t_f = 2$, $N_t = 6$, we can determine whether or not the optimized parameters are closer to $q^*$ when more time points within the original time interval $[0, 2]$ are included in the observations.

As before, we carried out the estimation problem using the same initial iterates $q_0(0.25)$, $q_0(0.5)$ and $q_0(1)$. See Table 6.16 for the resulting parameters $\bar{q}$ and their
Chapter 6. Parameter estimation

respective objective function values. Note that since $J$ is a function of both $q$ and the observations $z$, we cannot directly compare values of $J$ for this problem with those corresponding to $t_f = 2, N_t = 6$ since the observation sets are not the same. By comparing the parameter values (for each $\nu$) from each of the two problems, however, we see that a majority of the optimized parameters $\bar{q}_i$ ($i = 1, \ldots, N_q = 8$) from the problem with $t_f = 2, N_t = 31$ are closer to the values of $q_i^*$ than the optimized parameters $\bar{q}_i$ corresponding to $t_f = 2, N_t = 6$.

Figures 6.6, 6.7 and 6.8 depict model predictions for $q^*$, initial iterates $q_0(\nu)$ and the corresponding optimized parameters $\bar{q}$ with $\nu = 0.25, 0.5$ and 1, respectively. For $\nu = 0.25$ and 0.5, the predicted concentration curves for $\bar{q}$ appear to more closely match the prediction for $q^*$ than the corresponding parameters $\bar{q}$ for the problem with $t_f = 2, N_t = 6$. The predictions from the two problems with $\nu = 1$ look similar to each other on the scale used in the graphs. Based on these results, it appears that the addition of data points within the original time interval $[0, 2]$ yields parameters that are closer to $q^*$ and that generate predictions which more closely match the model response corresponding to $q^*$.

Next we test the inverse problem for (6.25) with observations that span over a longer time interval. At $t = 2$ hours, the chamber air TCE concentration has been set to zero parts per million for only one hour, which is a significantly shorter length of time than the half life of TCE in adipose tissue [30]. This suggests that observations taken over only the first two hours may not be enough to capture the dynamics of TCE inside the fat. To test this idea, we generate observations at the evenly spaced time points $t_i = 5(i - 1)/30, i = 1, \ldots, 31$, so that $t_f = 5$ hours and $N_t = 31$.

Results for this estimation problem are given in Table 6.17. Note that except for the case $\nu = 1$, most of the optimized parameters $\bar{q}_i$ are not closer to the values $q_i^*$ than the parameters $\bar{q}_i$ from the other two problems ($t_f = 2, N_t = 6$ and $t_f = 2, N_t = 31$). Indeed, for $\nu = 0.5$, the optimized parameter set obtained with $t_f = 2, N_t = 6$ has more values closer to $q^*$ than the $\bar{q}$ obtained with $t_f = 5, N_t = 31$.

As seen in Figures 6.9, 6.10 and 6.11 for $\nu = 0.25, 0.5$ and 1 respectively, however,
the response curves generated by the optimized parameters for $t_f = 5$, $N_t = 31$ are nearly identical to the concentration curve generated by $q^*$. Therefore, although the optimized parameters $\bar{q}$ are not as close to $q^*$ as the parameters from the problems with $t_f = 2$, the addition of observations beyond the first two hours appears to yield parameters that better predict the dynamics of TCE in adipose tissue (using $q^*$) than the parameters obtained with $t_f = 2$. This result further suggests that the objective function $J$ may have multiple local minima, but if one chooses the observation time points wisely, it may possible to obtain a minimizer that predicts dynamics similar to the dynamics generated with $q^*$.

We note here that the generated data we use in this section, which simulate observations from a single individual, are not typical of the actual experimental data that are collected. In general, it is difficult to measure concentrations in homogenized tissue from the same animal at different points in time. Many of the experiments related to toxicokinetics involve collecting tissue concentrations from multiple individuals, so that each time point represents a different animal as in [32]. An exception to this practice is the collection of blood samples from a single individual at various points in time, which is usually more practical experimentally than the collection of tissue samples at more than one time point.

The inverse problems that we have presented here for observations from a single individual are important for understanding the dependence of the model on the collection of eight parameters, and are a first step in studying the eight-dimensional estimation problem. In the next section we will design observation sets that better approximate the type of experimental data that is actually collected in the laboratory.
Table 6.15: Initial iterates $q_0(\nu)$ and optimized solutions $\bar{q}$ for (6.25) with adipose and venous blood observations from a single individual, where $t_f = 2$ hours and $N_t = 6$. The observations were simulated using $q^*$ given by (6.24).

<table>
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<tr>
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<th>$q^*$</th>
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<tr>
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<tr>
<td>$J(q)$</td>
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<td>3.622e-6</td>
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Figure 6.3: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(0.25)$ and for the minimized solution $\bar{q}$ (denoted in the graph by $q$) of (6.25) with $q_0(0.25)$ and $t_f = 2$ hours, $N_t = 6$.
Figure 6.4: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(0.5)$ and for the minimized solution $\bar{q}$ (denoted in the graph by $q$) of (6.25) with $q_0(0.5)$ and $t_f = 2$ hours, $N_t = 6$.

Figure 6.5: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(1)$ and for the minimized solution $\bar{q}$ (denoted in the graph by $q$) of (6.25) with $q_0(1)$ and $t_f = 2$ hours, $N_t = 6$. 
Table 6.16: Initial iterates $q_0(\nu)$ and optimized solutions $\bar{q}$ for (6.25) with adipose and venous blood observations from a single individual, where $t_f = 2$ hours and $N_t = 31$. The observations were simulated using $q^*$ given by (6.24).

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<td>$q_0$</td>
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<td>$J(q)$</td>
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Figure 6.6: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(0.25)$ and for the minimized solution $\bar{q}$ (denoted in the graph by $q$) of (6.25) with $q_0(0.25)$ and $t_f = 2$ hours, $N_t = 31$. 

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Figure 6.7: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for \( q^* \), \( q_0(0.5) \) and for the minimized solution \( \tilde{q} \) (denoted in the graph by \( q \)) of (6.25) with \( q_0(0.5) \) and \( t_f = 2 \) hours, \( N_t = 31 \).

Figure 6.8: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for \( q^* \), \( q_0(1) \) and for the minimized solution \( \tilde{q} \) (denoted in the graph by \( q \)) of (6.25) with \( q_0(1) \) and \( t_f = 2 \) hours, \( N_t = 31 \).
Table 6.17: Initial iterates $q_0(\nu)$ and optimized solutions $\bar{q}$ for (6.25) with adipose and venous blood observations from a single individual, where $t_f = 5$ hours and $N_t = 31$. The observations were simulated using $q^*$ given by (6.24).

<table>
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<td>0.9245</td>
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<td>0.0010</td>
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</tr>
<tr>
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<tr>
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<td>0.0215</td>
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<td>0.0996</td>
<td>0.0760</td>
</tr>
<tr>
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<td>5.456$e-5$</td>
</tr>
</tbody>
</table>

Figure 6.9: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(0.25)$ and for the minimized solution $\bar{q}$ (denoted in the graph by $q$) of (6.25) with $q_0(0.25)$ and $t_f = 5$ hours, $N_t = 31$. 

\[ \text{TCE conc. (mg/liter)} \]
Chapter 6. Parameter estimation

Figure 6.10: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(0.5)$ and for the minimized solution $\tilde{q}$ (denoted in the graph by $q$) of (6.25) with $q_0(0.5)$ and $t_f = 5$ hours, $N_t = 31$.

Figure 6.11: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(1)$ and for the minimized solution $\tilde{q}$ (denoted in the graph by $q$) of (6.25) with $q_0(1)$ and $t_f = 5$ hours, $N_t = 31$. 
6.1.3.b Observations from multiple individuals

In this section we implement parameter estimation problems with observations that simulate inter-individual variability, as we carried in Section 6.1.2 for the case with \( q = (D_B, \mu_A) \). Here we test the full 8-dimensional estimation problem using generated data that simulate the type of experimental data in [32]. Based on the results for this estimation problem, we design additional observation sets with a goal of finding parameters that are close to the data-generating parameters \( q^* \), and that yield response curves similar to those obtained with \( q^* \).

It is important to note here that although we assume inter-individual variability in the parameters and we generate observations that simulate this phenomenon, the inverse problems we implement here are still designed around estimating a single fixed value for each parameter. If the variability among individuals in the population is relatively small, one might expect that this type of estimation problem could successfully identify some type of “average” parameter set. For a population with large levels of variability between individuals, however, it is reasonable to suspect that these inverse problems would not be able to capture the true behavior of the parameters across the population. In that case, it may be more appropriate to design an estimation problem that specifically incorporates this variability and uncertainty, such as the type of problem we will implement and discuss in Section 6.2.

Here we present results for the estimation problem associated with the objective function

\[
J(q, \hat{z}) = \sum_{i=1}^{N_t} \frac{1}{\hat{z}^v_i} |\mathcal{O}^v y(t_i, \cdot; q) - \hat{z}_i^v|^2 + \frac{1}{\hat{z}^f} |\mathcal{O}^f y(t_i, \cdot; q) - \hat{z}_i^f|^2 \\
+ \frac{1}{\hat{z}^{br}_i} |\mathcal{O}^{br} y(t_i, \cdot; q) - \hat{z}^{br}_i|^2 + \frac{1}{\hat{z}^{br}_i} |\mathcal{O}^{f} y(t_i, \cdot; q) - \hat{z}^{f}_i|^2 \\
= \sum_{i=1}^{N_t} \frac{1}{\hat{z}^v_i} |C^v(t_i; q) - \hat{z}_i^v|^2 + \frac{1}{\hat{z}^f} |C^M(t_i; q) - \hat{z}_i^f|^2 \\
+ \frac{1}{\hat{z}^{br}_i} |C^{br}(t_i; q) - \hat{z}^{br}_i|^2 + \frac{1}{\hat{z}^{br}_i} |C^{f}(t_i; q) - \hat{z}^{f}_i|^2 \tag{6.27}
\]

subject to (6.2), where \( \hat{z} \) are observations given in (6.11) – (6.14), and with weights
First we test this estimation problem with observations that simulate data similar to the experimental data in [32]. Specifically, we choose \( t_f = 2 \) hours and \( N_t = 6 \), where the time points are defined as in (6.17). Recall that the observations \( z_i \) are generated using a normal distribution with mean \( \mu_i \) and standard deviation \( \omega \mu_i / 3 \); here we set \( \mu_i = q_i^* \) and \( \omega = 0.1, 0.25 \) and 0.5, where \( q^* \) is the parameter set given in (6.24). For each value of \( \omega \), we use the initial iterate \( q_0(0.25) \) as in the previous section. Note that for this choice of the mean and standard deviation, the parameters \( q_i^* \) are the average parameters for the population.

The resulting optimized parameter sets for this problem are given in Table 6.18. Note that there is a different value \( J(q_0(0.25), \hat{z}) \) for each \( \omega \) since the observation sets are different for each value of \( \omega \), resulting in different objective functions. It is seen that about half of the parameters \( \bar{q}_i \) listed in Table 6.18 are further away from \( q_i^* \) than those for the initial iterate \( [q_0(0.25)]_i \). Moreover, as seen in Figures 6.12, 6.13 and 6.14 (for \( \omega = 0.1, 0.25 \) and 0.5 respectively), the resulting predicted mean adipocyte concentration curves are not nearly as well-matched with the simulation generated by \( q^* \) as those generated with some of the optimized parameter sets from the previous section. For each of these values of \( \omega \), the concentration for the data point at \( t_f = 2 \) hours is significantly less than the concentration at \( t = 2 \) hours generated by \( q^* \), and this appears to have a major influence on the shape of the resulting predictions for the optimized parameter sets. Furthermore, these results also suggest that the sample size of \( N_t = 6 \) time points may be too small for this estimation strategy, which attempts to estimate a single fixed value for each parameter although the data include observations from multiple individuals, each with their own “intrinsic” parameter set.

Next we consider an observation set with additional time points over the same interval \([0, 2]\) hours. As before, we set \( N_t = 31 \) and generate \( N_t \) evenly spaced time points between \( t = 0 \) and \( t_f = 2 \). Using the resulting observations with \( \omega = 0.1, 0.25 \) and 0.5, we implement the inverse problem for (6.27) with the initial iterate \( q_0(0.25) \).

Results for these three estimation problems are listed in Table 6.19, and model
predictions from the optimized parameters are given in Figures 6.15, 6.16 and 6.17. As seen in Table 6.19, a majority of the optimized parameters $\tilde{q}_i$ for the problem with $\omega = 0.1$ are closer to the parameter set $q_i^*$ than those for both the initial iterate $q_0(0.25)$ and the optimized parameters $\tilde{q}$ corresponding to $\omega = 0.1$, $t_f = 2$ and $N_t = 6$ (see Table 6.18). Moreover, by comparing Figures 6.12 and 6.15, we see that for $\omega = 0.1$, the model prediction for $\tilde{q}$ with $N_t = 31$ is a closer match to the simulation generated by $q^*$ than the prediction for $\tilde{q}$ with $N_t = 6$.

For $\omega = 0.25$, less than half of the optimized parameters $\tilde{q}_i$ (for $t_f = 2$, $N_t = 31$) are closer to $q_i^*$ than either the parameters $[q_0(0.25)]_i$ or $\tilde{q}_i$ with $\omega = 0.25$, $t_f = 2$ and $N_t = 6$. As seen in Figures 6.13 and 6.16, the response curves for the optimized parameters corresponding to $N_t = 31$ do significantly better at predicting the curve for $q^*$ than the $\tilde{q}$ obtained with $N_t = 6$.

For the problem corresponding to $\omega = 0.5$, most of the parameters $\tilde{q}_i$ with $t_f = 2$ and $N_t = 6$ are a closer match to $q_i^*$ than the $\tilde{q}_i$ with $t_f = 2$ and $N_t = 31$. Moreover, the resulting model predictions for $\tilde{q}$ with $N_t = 6$ are significantly closer to the response for $q^*$ than the predictions for $\tilde{q}$ with $N_t = 31$ (compare Figures 6.14 and 6.17). Note that for this value of $\omega$, the simulated observations with $N_t = 31$ include concentrations that are significantly larger than the concentrations generated with $q^*$, and these data points seem to be a predominant factor in the resulting response of the optimized parameters. This further suggests that for this value of $\omega$, the variability across the population may be too large for this type of estimation problem with the relatively small sample sizes we use here. As discussed earlier in this section, the large amount of variability seen here may be better captured with an estimation strategy that accounts for and incorporates the variation in parameters across the population.

Now we implement the inverse problem for (6.27) with extended observations over the time interval $t = 0$ to $t = t_f = 5$ hours. We test simulated data sets with varying numbers of time points, including $N_t = 9, 17$ and $23$. We design each of these time vectors with the goal of capturing as much of the dynamics of TCE in the adipose tissue as possible with the smallest amount of data.
For the case $N_t = 9$, we include the six time points used in the experimental data [32] as well as additional time points at $t = 3, 4$ and 5 hours. This yields the time vector

$$\tilde{t} = [0, 5/60, 20/60, 40/60, 1, 2, 3, 4, 5] \text{ (hours)}.$$  \hfill (6.28)

Results for this inverse problem with $q_0(0.25)$ are given in Table 6.20, and model predictions for the optimized parameters corresponding to $\omega = 0.1, 0.25$ and 0.5 are depicted in Figures 6.18, 6.19 and 6.20 respectively. Note that a majority of the parameters $\tilde{q}_i$ are actually further away from $q^*_i$ than the initial iterate $q_0(0.25)$, and that the predicted response curves are not very closely matched with the concentration curve generated by $q^*$. From these graphs, it appears that the sample size $N_t = 9$ is too small for this estimation problem, especially for the case $\omega = 0.5$.

To further test this hypothesis, we increase the sample size of time points to $N_t = 17$ with the final time $t_f = 5$ hours as before. The time points that we add to the vector for $N_t = 9$ are clustered around two specific points in time: $t = 1$ hour and $t = 5$ hours. The time $t = 1$ hour is significant since it is the time at which the TCE chamber concentration changes from 2000 parts per million to zero. We can deduce a priori that the TCE concentrations will undergo a change in dynamics near this point in time, and we include several observation times there in order to better capture those dynamics.

Secondly, we add extra time points near the final time $t_f$ of the “observation period.” It is clear in Figures 6.19 and 6.20 for the problem with $t_f = 5$, $N_t = 9$ that the two data points nearest $t_f$ have a major influence on the optimized parameters $\tilde{q}$ and their resulting response curves. Therefore, by including more time points there we hope to better capture the dynamics near $t_f$ and beyond.

*Note that the above strategies for designing times at which to collect data are not dependent on prior knowledge of the precise dynamics of TCE inside adipose tissue.* Rather, they are based on the chamber air concentrations, which are specified by the experimentalist, and on the known half-life of TCE in fat tissue. Therefore one may use these strategies to design experiments with a goal of using parameter estimation...
techniques to identify parameters that best capture the dynamics of TCE.

We implemented the estimation problem (6.27) with $t_f = 5$, $N_t = 17$ and $q_0(0.25)$, where the observations are at the time points

$$
\tilde{t} = [0, 5, 20, 40, 60, 90, 105, 115, 120, 125, 135, 150, 180, 210, 240, 270, 300] \quad (6.29)
$$

minutes. Note that the time points for the observations associated with $t_f = 2$, $N_t = 6$ and $t_f = 5$, $N_t = 9$ are included in (6.29), and we generated the resulting observations so that the simulated data points are identical for the three observation sets at corresponding time points.

Results for this inverse problem are given in Table 6.21, with model predictions for the optimized parameter sets given in Figures 6.21, 6.22 and 6.23. Again, the resulting parameters $\bar{q}$ are not generally very close to the parameters $q^*$, but the model predictions appear to improve over the case $t_f = 5$, $N_t = 9$ for both $\omega = 0.25$ and $\omega = 0.5$. It is also clear that for $\omega = 0.5$, the wide variability in the data-generating parameters and their resulting data points makes it more difficult for the estimation problem to solve for parameters close to the “average” $q^*$. This further suggests that a parameter estimation strategy that incorporates the variability across the population may be more successful for large values of $\omega$ (including $\omega = 0.5$).

The final estimation problem that we study in this section has an observation set with $t_f = 5$ and $N_t = 23$. The generated observations are the same as those corresponding to $t_f = 5$, $N_t = 17$, with additional time points at $t = 110, 130, 275, 285, 290$ and 295 minutes. Therefore we have the time vector

$$
\tilde{t} = [0, 5, 20, 40, 60, 90, 105, 115, 120, 125, 135, 150, 180, 210, 240, 270, 275, 285, 290, 295, 300] \quad (minutes).
$$

Note that as before, we have included extra time points near the times $t = 1$ hour and $t_f = 5$ hours.

Results for this estimation problem with $q_0(0.25)$ are given in Table 6.22. The optimized parameters $\bar{q}$ are in general closer to the values of $q^*$ than the parameters
obtained with the other observation sets presented in this section. See Figures 6.24, 6.25 and 6.26 for resulting model predictions generated by $\bar{q}$ for this estimation problem. Note in Figure 6.25 that the predicted concentration curve corresponding to $\omega = 0.25$ is very close to the response generated by $q^*$, while the predictions for the other two values of $\omega$ (Figures 6.24 and 6.26) are not as closely matched.

Based on the results presented here for various values of $t_f$ and $N_t$ with this type of generated data, it appears that the estimation problem for (6.27) is not the best choice for problems that involve observations from multiple individuals, especially when there is a significant amount of variability in the parameters across the population. In the next section we implement an estimation strategy that is specifically designed to accommodate this kind of inter-individual variability.
Table 6.18: The initial iterate $q_0(0.25)$ and optimized parameters $\bar{q}$ for (6.27) corresponding to observations of multiple individuals with $\omega = 0.1$, 0.25 and 0.5, where $t_f = 2$, $N_t = 6$.

<table>
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<th>$q_0(0.25)$</th>
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Figure 6.12: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(0.25)$ and for the minimized solution $\bar{q}$ (denoted in the graph by $q$) of (6.27) with $q_0(0.25)$ and $t_f = 2$ hours, $N_t = 6$, $\omega = 0.1$. 
Figure 6.13: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(0.25)$ and for the minimized solution $\bar{q}$ (denoted in the graph by $\bar{q}$) of (6.27) with $q_0(0.25)$ and $t_f = 2$ hours, $N_t = 6$, $\omega = 0.25$.

Figure 6.14: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(0.25)$ and for the minimized solution $\bar{q}$ (denoted in the graph by $\bar{q}$) of (6.27) with $q_0(0.25)$ and $t_f = 2$ hours, $N_t = 6$, $\omega = 0.5$. 
Table 6.19: The initial iterate $q_0(0.25)$ and optimized parameters $\bar{q}$ for (6.27) corresponding to observations of multiple individuals with $\omega = 0.1$, 0.25 and 0.5, where $t_f = 2$, $N_t = 31$.

<table>
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<td>$q_0(0.25)$</td>
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Figure 6.15: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(0.25)$ and for the minimized solution $\bar{q}$ (denoted in the graph by $q$) of (6.27) with $q_0(0.25)$ and $t_f = 2$ hours, $N_t = 31$, $\omega = 0.1$. 
Figure 6.16: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*, q_0(0.25)$ and for the minimized solution $\bar{q}$ (denoted in the graph by $q$) of (6.27) with $q_0(0.25)$ and $t_f = 2$ hours, $N_t = 31$, $\omega = 0.25$.

Figure 6.17: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*, q_0(0.25)$ and for the minimized solution $\bar{q}$ (denoted in the graph by $q$) of (6.27) with $q_0(0.25)$ and $t_f = 2$ hours, $N_t = 31$, $\omega = 0.5$. 
**Table 6.20:** The initial iterate $q_0(0.25)$ and optimized parameters $\hat{q}$ (denoted in the graph by $\hat{q}$) for (6.27) corresponding to observations of multiple individuals with $\omega = 0.1$, 0.25 and 0.5, where $t_f = 5$, $N_t = 9$.

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**Figure 6.18:** Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(0.25)$ and for the minimized solution $\hat{q}$ (denoted in the graph by $\hat{q}$) of (6.27) with $q_0(0.25)$ and $t_f = 5$ hours, $N_t = 9$, $\omega = 0.1$. 
Figure 6.19: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(0.25)$ and for the minimized solution $\bar{q}$ (denoted in the graph by $q$) of (6.27) with $q_0(0.25)$ and $t_f = 5$ hours, $N_t = 9$, $\omega = 0.25$.

Figure 6.20: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(0.25)$ and for the minimized solution $\bar{q}$ (denoted in the graph by $q$) of (6.27) with $q_0(0.25)$ and $t_f = 5$ hours, $N_t = 9$, $\omega = 0.5$. 
Table 6.21: The initial iterate $q_0(0.25)$ and optimized parameters $\tilde{q}$ for (6.27) corresponding to observations of multiple individuals with $\omega = 0.1$, 0.25 and 0.5, where $t_f = 5$, $N_t = 17$.

<table>
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<tr>
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<th>$\omega = 0.5$</th>
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<tbody>
<tr>
<td></td>
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<tr>
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</tr>
<tr>
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</tr>
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</tr>
<tr>
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Figure 6.21: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(0.25)$ and for the minimized solution $\tilde{q}$ (denoted in the graph by $q$) of (6.27) with $q_0(0.25)$ and $t_f = 5$ hours, $N_t = 17$, $\omega = 0.1$. 
Figure 6.22: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(0.25)$ and for the minimized solution $\bar{q}$ (denoted in the graph by $q$) of (6.27) with $q_0(0.25)$ and $t_f = 5$ hours, $N_t = 17$, $\omega = 0.25$.

Figure 6.23: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(0.25)$ and for the minimized solution $\bar{q}$ (denoted in the graph by $q$) of (6.27) with $q_0(0.25)$ and $t_f = 5$ hours, $N_t = 17$, $\omega = 0.5$. 
Table 6.22: The initial iterate $q_0(0.25)$ and optimized parameters $\bar{q}$ for (6.27) corresponding to observations of multiple individuals with $\omega = 0.1, 0.25$ and $0.5$, where $t_f = 5$, $N_t = 23$.

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<td>$\bar{q}$</td>
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</tr>
<tr>
<td>$A_B$</td>
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<td>3.654e$-5$</td>
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<td>$J(q, \tilde{z})$</td>
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<td>3.0422</td>
<td>8.355e$-2$</td>
</tr>
</tbody>
</table>

Figure 6.24: Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for $q^*$, $q_0(0.25)$ and for the minimized solution $\bar{q}$ (denoted in the graph by $q$) of (6.27) with $q_0(0.25)$ and $t_f = 5$ hours, $N_t = 23$, $\omega = 0.1$. 
**Figure 6.25:** Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for \( q^* \), \( q_0(0.25) \) and for the minimized solution \( \bar{q} \) (denoted in the graph by \( q \)) of (6.27) with \( q_0(0.25) \) and \( t_f = 5 \) hours, \( N_t = 23 \), \( \omega = 0.25 \).

**Figure 6.26:** Simulated data and model predictions for 15 hours of mean TCE adipocyte concentrations for \( q^* \), \( q_0(0.25) \) and for the minimized solution \( \bar{q} \) (denoted in the graph by \( q \)) of (6.27) with \( q_0(0.25) \) and \( t_f = 5 \) hours, \( N_t = 23 \), \( \omega = 0.5 \).
6.2 An estimation problem based on probability and uncertainty

In this section we present results for parameter estimation problems that incorporate inter-individual variability. Specifically, we implement a probability-based estimation strategy that searches for probability distributions for parameters rather than fixed constants. This type of estimation problem is designed to account for data that include measurements of multiple individuals, as well as multiple measurements of a single individual, where there may be variability in the parameters themselves. Here we develop estimation techniques using the ideas presented in Section 4.3.2, where we assume that each of our parameters varies across the population with a truncated normal distribution. This is a special case of the more general type of problem discussed in Section 4.3.1, which involves estimating probability distributions with no \textit{a priori} assumptions on the nature of the distributions.

As discussed in Section 4.3.3, here we formulate an inverse problem for the TCE model that estimates a truncated multi-normal distribution for the parameter set \(q \in Q\). That is, we seek to minimize the objective function

\[
J(\mu, \sigma, \tilde{z}) = \sum_{i=1}^{N_t} |E[Oy(t_i, \cdot; q)|P(\mu, \sigma)]] - \tilde{z}_i|^2
\]  

(6.31)

over the set of admissible vectors \(\mu, \sigma \in \mathbb{R}^{N_q}\), where \(P(\mu, \sigma)\) has the truncated multi-normal distribution with mean vector \(\mu\) and covariance matrix \(\mathcal{C} = \text{diag}(\sigma^2)\) given by

\[
\tilde{f}(q; \mu, \sigma) = \begin{cases} 
\frac{\sqrt{|A|}}{(0.9974 \sqrt{2\pi})^{N_q}} e^{-\frac{1}{2}(q-\mu)A(q-\mu)^T} & \text{if } q \in \text{supp} \tilde{f} \\
0 & \text{otherwise},
\end{cases}
\]  

(6.32)

where \(A = \mathcal{C}^{-1}\) and

\[
\text{supp} \tilde{f} = [\mu_1 - 3\sigma_1, \mu_1 + 3\sigma_1] \times \cdots \times [\mu_{N_q} - 3\sigma_{N_q}, \mu_{N_q} + 3\sigma_{N_q}] \subset Q.
\]  

(6.33)

Moreover, \(O\) is the observation operator \(O\) defined in (6.6), and \(y(t_i, \cdot; q)\) is a solution for (6.2) with parameters \(q\).
In this section we use the parameter set \( q = D_B \), so that we estimate a one-dimensional truncated normal probability distribution and hence a single mean \( \mu \) and standard deviation \( \sigma \). This leads to a two-dimensional estimation problem for \( \tilde{q} = (\mu, \sigma) \in Q \). In general, the size of \( \tilde{q} \) is equal to twice the dimension \( N_q \) of \( Q \), and the expectation \( \mathcal{E}[O_y(t_i, \cdot; q) \mid P(\mu, \sigma)) \) will involve an integral that has dimension \( N_q \) since we have

\[
\mathcal{E}[O_y(t_i, \cdot; q) \mid P(\mu, \sigma)] = \int_Q O_y(t_i, \cdot; q) \tilde{f}(q; \mu, \sigma) dq. \tag{6.34}
\]

Here we consider the case \( N_q = 1 \) as a first step in studying the effectiveness of this type of estimation problem. For larger dimensions \( N_q \), the computational efforts related to approximating the expected value become more involved as a multi-dimensional quadrature algorithm is required. The one-dimensional problem is very straightforward to implement computationally, and is used here as a proof of concept for the estimation problem associated with (6.31).

In this section we report on results for this estimation problem using two different types of observations in adipose tissue. In the first case, we assume that our observations \( \tilde{z}_i, i = 1, \ldots, N_t \) are measurements corresponding to the expected value, i.e.,

\[
\tilde{z}_i \approx \mathcal{E}[O_y(t_i, \cdot; q) \mid P(\mu^*, \sigma^*))]
\]

for some \( \tilde{q}^* = (\mu^*, \sigma^*) \in Q \), where \( P(\mu^*, \sigma^*) \) has a truncated normal distribution with mean \( \mu^* \), standard deviation \( \sigma^* \), and with support \([\mu^* - 3\sigma^*, \mu^* + 3\sigma^*] \). This type of observation is appropriate for generating observations that simulate experimental data collected from multiple individuals where there is one measured observation for each time point. In this case, each time point corresponds to a different individual. Thus one could think of each of these data points as an observation of the expected value across the population of possible TCE concentrations at that given point in time.

The second type of observation we consider is similar in nature to the experimental data collected by Evans et al. [32]. Here there are multiple observations at each time
point, and the samples are collected in such a way that within each tissue, every data point corresponds to a different individual. Therefore this data set includes inter-individual variability, and there is more than one data point for each given point in time. One way to work with these data in an estimation problem is to take the mean value of all data points at a given point in time, yielding an approximation of the expected value. Thus we have the observations

\[ \bar{z}_i = \frac{1}{N_s(i)} \sum_{j=1}^{N_s(i)} \mathcal{O}_{y\left(t_i, \cdot, \cdot; q_{ij}\right)} \]  

for \( i = 1, \ldots, N_t \), where each \( q_{ij} \) corresponds to a different individual. In general, \( N_s(i) \) may vary with \( i \) depending on the number of observations measured at a given time \( t_i \).

Note that this type of observation is different from (6.35), and in fact is a finite-dimensional approximation for the expected value. The accuracy of the approximation is dependent on the number of samples \( N_s(i) \) at each time point \( t_i \), with larger values of \( N_s(i) \) theoretically yielding approximations that are more likely to be closer to the true expected value. In practice, these sample sizes are likely to be relatively small (\( N_s(i) < 10 \)) for this type of experiment, which may have a negative impact on the effectiveness of the estimation problem.

It is important to note, however, that the type of experimental data simulated in (6.35) may also pose difficulties in the parameter estimation process. If only one measurement is collected at each time point, significant “error” could be introduced into the estimation problem by assuming that this single measurement is an approximation of the true expected value across the population. Indeed, the larger the variability of the parameters among individuals, the more likely it is that a single measurement will be a poor approximation of the expected value.
6.2.1 Observations corresponding to the expected value

In this section we consider the inverse problem for (6.31) using observations $\tilde{z}_i$, $i = 1, \ldots, N_t$ corresponding to the expected value (6.35). We assume here that all observations are measurements of TCE concentrations in homogenized adipose tissue samples, so that the observation operator is given by (6.6). Moreover, there is exactly one observation for each given time point $t_i, i = 1, \ldots, N_t$.

There are two types of noise that may affect these observations $\tilde{z}$. First, there is the usual noise that arises when collecting experimental data, including effects from instrument precision, human error, etc. In addition, there is likely to be noise associated with the amount of error that occurs when one approximates the expected value $\mathcal{E}[Oy(t_i, \cdot; q)|P(\mu^*, \sigma^*)]$ by the single observation $\tilde{z}_i$.

In the estimation problems we report on here, we approximate both of these kinds of noise by adding relative random noise to the observations $\tilde{z}$, so that

$$\tilde{z}_i^U = (1 + \eta_i^U(\alpha))\tilde{z}_i$$
$$\tilde{z}_i^N = (1 + \eta_i^N(\alpha))\tilde{z}_i.$$  

As before, $\eta_i^U(\alpha)$ is uniformly distributed on the interval $[-\alpha, \alpha]$ and $\eta_i^N(\alpha)$ is normally distributed with mean zero and standard deviation $\alpha/3$, yielding values in the interval $[-\alpha, \alpha]$ with 99.87% confidence.

First we test this estimation problem using observations at the time points in (6.17) corresponding to $t_f = 2$ hours and $N_t = 6$, as in the experimental data [32]. We use the parameter set $\tilde{q}^* = (\mu^*, \sigma^*)$ with $\mu^* = 1$ and $\sigma^* = 0.0833$ to generate the observations $\tilde{z}$. This $\tilde{q}^*$ corresponds to a truncated normal distribution that has values in the interval

$$[\mu^* - 3\sigma^*, \mu^* + 3\sigma^*] = [0.75, 1.25].$$

We generated the initial iterate $\tilde{q}_0 = (\mu_0, \sigma_0)$ using uniformly distributed random relative noise added to $q^*$ as in (6.26) with $\nu = 0.25$. 

In our computations we approximated the expected value (6.34) using the Matlab function \texttt{trapz}, which utilizes trapezoidal integration. As before, we used the Nelder-Mead routine \texttt{fminsearch} for the optimization.

Results for the inverse problem are given in Table 6.23 for observations with various levels of noise. Figure 6.27 depicts the simulated data with 5% uniformly distributed noise, as well as the predicted expected values corresponding to the parameters \( \bar{q}, \tilde{q}_0 \) and \( \bar{q} \). Plots of the resulting truncated normal probability distributions and densities are given in Figures 6.28 and 6.29, respectively. Note that although both the expected value and probability distribution for \( \bar{q} \) are reasonable matches with the respective responses obtained with \( \bar{q}^* \), the density function for \( \bar{q} \) is significantly different in shape from the density for \( \bar{q}^* \).

It is important to note here that the theoretical results of Section 4.3.1 establish the convergence of both the expected values and the distributions, but do not guarantee any kind convergence for the probability densities. Therefore we expect the optimized parameters to yield expected values and distributions that are close approximations to the expected values and distributions for \( \bar{q}^* \), but in general the probability densities will not necessarily be similar to each other.

Next we test this parameter estimation problem with the final time \( t_f = 5 \) hours and varying values of \( N_t \) as in the previous section. Here we use \( N_t = 9, 17 \) and 23, yielding the observation time vectors in (6.28), (6.29) and (6.30) respectively. Results are given for these three problems in Tables 6.24, 6.25 and 6.26. In general, as \( N_t \) increases, the resulting optimized parameters \( \bar{q} \) yield a better approximation to \( \bar{q}^* \) in both expected value and distribution.

For \( N_t = 9 \), see Figures 6.30, 6.31 and 6.32 for plots of the resulting expected values, distributions and densities respectively for the case with 5% uniformly distributed relative noise. Corresponding plots for \( N_t = 17 \) and \( N_t = 23 \) follow in Figures 6.33 – 6.38. In Figure 6.37, note the close similarity between the distribution for \( \bar{q} \) with \( N_t = 23 \) and the distribution for \( \bar{q}^* \). This suggests the convergence of the optimized parameters in the sense of distributions, as guaranteed by the theoretical
results in Section 4.3.
Table 6.23: Optimized parameters \( \tilde{q} = (\tilde{\mu}, \tilde{\sigma}) \) for (6.31) with observations \( \tilde{z} \) corresponding to (6.34) with various levels of noise, where \( \tilde{q}^* = (1, 0.0833) \) and \( t_f = 2, N_t = 6 \). The initial iterate used was \( \tilde{q}_0(0.25) = (1.0534, 0.0827) \).

<table>
<thead>
<tr>
<th>Noise type and level</th>
<th>( \tilde{\mu} )</th>
<th>( \tilde{\sigma} )</th>
<th>( J(\tilde{q}, \tilde{z}) )</th>
<th>( J(\tilde{q}_0, \tilde{z}) )</th>
<th>( J(\tilde{q}^*, \tilde{z}) )</th>
</tr>
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<tbody>
<tr>
<td>0%</td>
<td>1.0015</td>
<td>9.4514e-2</td>
<td>2.8600e-7</td>
<td>1.3637e-1</td>
<td>0</td>
</tr>
<tr>
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<td>9.0852e-2</td>
<td>3.1724e-5</td>
<td>1.5706e-1</td>
<td>7.6184e-4</td>
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<td>0.9928</td>
<td>7.0722e-2</td>
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<td>1.7512e-1</td>
<td>4.1174e-3</td>
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Figure 6.27: Simulated data and model predictions for the expected value (over \( q \)) of mean TCE adipocyte concentrations for \( \tilde{q}^* = (1, 0.0833) \), \( \tilde{q}_0(0.25) \) and for the solution \( \tilde{q} \) of (6.31) with observations corresponding to (6.34) with 5\% uniformly distributed noise, and where \( q_0(0.25), t_f = 2 \) hours, \( N_t = 6 \). In the graph, \( \tilde{q}^*, \tilde{q} \) and \( \tilde{q}_0(0.25) \) are denoted by \( q^* \), \( q \) and \( q_0 \) respectively.
Chapter 6. Parameter estimation

Figure 6.28: Truncated normal probability distributions for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the solution $\tilde{q}$ of (6.31) with observations corresponding to (6.34) with 5% uniformly distributed noise, and where $q_0(0.25)$, $t_f = 2$ hours, $N_t = 6$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.

Figure 6.29: Truncated normal probability densities for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the solution $\tilde{q}$ of (6.31) with observations corresponding to (6.34) with 5% uniformly distributed noise, and where $q_0(0.25)$, $t_f = 2$ hours, $N_t = 6$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.
Table 6.24: Optimized parameters $\bar{q} = (\mu, \sigma)$ for (6.31) with observations $\tilde{z}$ corresponding to (6.34) with various levels of noise, where $\bar{q}^* = (1, 0.0833)$ and $t_f = 5$, $N_t = 9$. The initial iterate used was $\bar{q}_0(0.25) = (1.0534, 0.0827)$.

<table>
<thead>
<tr>
<th>Noise type and level</th>
<th>$\bar{\mu}$</th>
<th>$\bar{\sigma}$</th>
<th>$J(\bar{q}, \tilde{z})$</th>
<th>$J(q_0, \tilde{z})$</th>
<th>$J(\bar{q}^*, \tilde{z})$</th>
</tr>
</thead>
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<tr>
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<td>7.8146e-1</td>
<td>0</td>
</tr>
<tr>
<td>1% normal</td>
<td>0.9974</td>
<td>6.9204e-2</td>
<td>1.1936e-3</td>
<td>8.1157e-1</td>
<td>1.5474e-3</td>
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<tr>
<td>5% normal</td>
<td>1.0451</td>
<td>2.5169e-1</td>
<td>6.3441e-2</td>
<td>1.2278</td>
<td>1.2002e-1</td>
</tr>
<tr>
<td>10% normal</td>
<td>0.9920</td>
<td>2.6001e-2</td>
<td>1.1414e-1</td>
<td>9.5209e-1</td>
<td>1.1843e-1</td>
</tr>
<tr>
<td>1% uniform</td>
<td>1.0055</td>
<td>1.2652e-1</td>
<td>7.8716e-3</td>
<td>8.9058e-1</td>
<td>1.1505e-2</td>
</tr>
<tr>
<td>5% uniform</td>
<td>0.9809</td>
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<td>1.5490e-1</td>
<td>1.4532</td>
<td>2.2147e-1</td>
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<tr>
<td>10% uniform</td>
<td>1.0746</td>
<td>2.8179e-1</td>
<td>4.1869e-1</td>
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<td>4.5006e-1</td>
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Figure 6.30: Simulated data and model predictions for the expected value (over $q$) of mean TCE adipocyte concentrations for $\bar{q}^* = (1, 0.0833)$, $\bar{q}_0(0.25)$ and for the minimized solution $\bar{q}$ of (6.31) with observations corresponding to (6.34) with 5% uniformly distributed relative noise, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 9$. In the graph, $\bar{q}^*$, $\bar{q}$ and $\bar{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.
Figure 6.31: Truncated normal probability distributions for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the solution $\tilde{q}$ of (6.31) with observations corresponding to (6.34) with 5% uniformly distributed noise, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 9$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.

Figure 6.32: Truncated normal probability densities for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the solution $\tilde{q}$ of (6.31) with observations corresponding to (6.34) with 5% uniformly distributed noise, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 9$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.
Table 6.25: Optimized parameters $\tilde{q} = (\tilde{\mu}, \tilde{\sigma})$ for (6.31) with observations $\tilde{z}$ corresponding to (6.34) with various levels of noise, where $\tilde{q}^* = (1, 0.0833)$ and $t_f = 5$, $N_t = 17$. The initial iterate used was $\tilde{q}_0(0.25) = (1.0534, 0.0827)$.

<table>
<thead>
<tr>
<th>Noise type and level</th>
<th>$\tilde{\mu}$</th>
<th>$\tilde{\sigma}$</th>
<th>$J(\tilde{q}, \tilde{z})$</th>
<th>$J(q_0, \tilde{z})$</th>
<th>$J(q^*, \tilde{z})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>1.0005</td>
<td>8.5220e-2</td>
<td>3.7304e-7</td>
<td>1.9571</td>
<td>0</td>
</tr>
<tr>
<td>1% normal</td>
<td>0.9988</td>
<td>7.4266e-2</td>
<td>8.7438e-3</td>
<td>1.9863</td>
<td>8.8772e-3</td>
</tr>
<tr>
<td>5% normal</td>
<td>1.0421</td>
<td>2.2738e-1</td>
<td>2.3549e-1</td>
<td>2.0947</td>
<td>2.7788e-1</td>
</tr>
<tr>
<td>10% normal</td>
<td>1.0252</td>
<td>1.6493e-1</td>
<td>1.0561</td>
<td>2.5060</td>
<td>1.1023</td>
</tr>
<tr>
<td>1% uniform</td>
<td>1.0014</td>
<td>1.1013e-1</td>
<td>1.7227e-2</td>
<td>2.2371</td>
<td>2.6085e-2</td>
</tr>
<tr>
<td>5% uniform</td>
<td>1.0646</td>
<td>2.4513e-1</td>
<td>8.4754e-1</td>
<td>1.7678</td>
<td>1.1078</td>
</tr>
<tr>
<td>10% uniform</td>
<td>0.9955</td>
<td>5.6502e-2</td>
<td>4.4396</td>
<td>6.5805</td>
<td>4.4515</td>
</tr>
</tbody>
</table>

Figure 6.33: Simulated data and model predictions for the expected value (over $q$) of mean TCE adipocyte concentrations for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the minimized solution $\tilde{q}$ of (6.31) with observations corresponding to (6.34) with 5% uniformly distributed relative noise, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 17$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.
Figure 6.34: Truncated normal probability distributions for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the solution $\tilde{q}$ of (6.31) with observations corresponding to (6.34) with 5% uniformly distributed noise, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 17$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.

Figure 6.35: Truncated normal probability densities for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the solution $\tilde{q}$ of (6.31) with observations corresponding to (6.34) with 5% uniformly distributed noise, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 17$. 
Table 6.26: Optimized parameters $\tilde{q} = (\tilde{\mu}, \tilde{\sigma})$ for (6.31) with observations $\tilde{z}$ corresponding to (6.34) with various levels of noise, where $\tilde{q}^* = (1, 0.0833)$ and $t_f = 5$, $N_t = 23$. The initial iterate used was $\tilde{q}_0(0.25) = (1.0534, 0.0827)$.

<table>
<thead>
<tr>
<th>Noise type and level</th>
<th>$\tilde{\mu}$</th>
<th>$\tilde{\sigma}$</th>
<th>$J(\tilde{q}, \tilde{z})$</th>
<th>$J(q_0, \tilde{z})$</th>
<th>$J(q^*, \tilde{z})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>1.0005</td>
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<td>4.7229e−7</td>
<td>3.0631</td>
<td>0</td>
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<tr>
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<td>0.9998</td>
<td>8.5057e−2</td>
<td>1.1315e−2</td>
<td>3.1539</td>
<td>1.1832e−2</td>
</tr>
<tr>
<td>5% normal</td>
<td>1.0308</td>
<td>1.9027e−1</td>
<td>2.8916e−1</td>
<td>2.9739</td>
<td>3.2996e−1</td>
</tr>
<tr>
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<td>1.0326</td>
<td>1.9246e−1</td>
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<td>4.0433</td>
<td>1.5472</td>
</tr>
<tr>
<td>1% uniform</td>
<td>1.0032</td>
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<td>3.1199e−2</td>
<td>3.5988</td>
<td>5.2157e−2</td>
</tr>
<tr>
<td>5% uniform</td>
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<td>9.2729e−2</td>
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<td>1.7370</td>
</tr>
<tr>
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<td>3.1668e−2</td>
<td>5.2291</td>
<td>8.1746</td>
<td>5.2490</td>
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</table>

Figure 6.36: Simulated data and model predictions for the expected value (over $q$) of mean TCE adipocyte concentrations for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the minimized solution $\tilde{q}$ of (6.31) with observations corresponding to (6.34) with 5% uniformly distributed relative noise, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 23$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.
Figure 6.37: Truncated normal probability distributions for $\tilde{q}^* = (1, 0.0833)$, $q_0(0.25)$ and for the solution $\tilde{q}$ of (6.31) with observations corresponding to (6.34) with 5% uniformly distributed noise, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 23$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $q_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.

Figure 6.38: Truncated normal probability densities for $\tilde{q}^* = (1, 0.0833)$, $q_0(0.25)$ and for the solution $\tilde{q}$ of (6.31) with observations corresponding to (6.34) with 5% uniformly distributed noise, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 23$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $q_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.
6.2.2 Observations with multiple data points per time point

In this section we study the estimation problem for (6.31) with a simulated data set that assumes multiple observations at each time point. We further assume that these multiple observations yield an approximation to the expected value (with respect to \( q \)) of mean TCE concentrations in adipose tissue at that given time. Therefore we generate observations of the form

\[
\tilde{z}_i = \frac{1}{N_s(i)} \sum_{j=1}^{N_s(i)} \mathcal{O}^f y(t_i, \cdot, \cdot; q_{ij})
\]  

(6.37)

for \( i = 1, \ldots, N_t \), where each \( q_{ij} \) corresponds to a different individual. Note that in general, \( N_s(i) \) may vary with \( i \) depending on the number of observations measured at a given \( t_i \).

We implemented this inverse problem with the same values of \( t_f \) and \( N_t \) as before, i.e., for \( t_f = 2 \) hours, \( N_t = 6 \), and for \( t_f = 5 \) hours with \( N_t = 9, 17 \) and 23. Moreover, for each of these problems we tested several values of \( N_s \), including \( N_s = 5, 10, 20, 50 \) and 100. In each case, we used a constant \( N_s(i) = N_s \) for each \( i = 1, \ldots, N_t \). For each of the problems we used the observations (6.37) with no added noise. This allows us to test the change in performance of the optimization as we increase both \( N_s \) and \( N_t \).

Results for these estimation problems are given in Tables 6.27 – 6.30, where each table corresponds to a different pair \((t_f, N_t)\). We include here graphs of the estimated expected values and distributions for the case \( t_f = 5 \) hours, \( N_t = 9 \) with \( N_s = 5, 10, 20 \) and 100, which are given in Figures 6.39 – 6.46. In these and all subsequent figures depicting expected values, the simulated data \( \mathcal{O}^f y(t_i, \cdot, \cdot; q_{ij}), i = 1, \ldots, N_t, j = 1, \ldots, N_s \) used in (6.37) are represented by the small dots (\( \cdot \)), and the resulting means \( \tilde{z}_i, i = 1, \ldots, N_t \) given in (6.37) are represented by open circles (\( \circ \)). As before, the model predictions corresponding to \( \tilde{q}^*, \tilde{q} \) and \( \tilde{q}_0 \) are represented by solid, dashed and dotted lines, respectively.

Note the apparent convergence in Figures 6.39 – 6.46 in both the expected values and in the distributions as \( N_s \) increases. It appears that the inclusion of additional...
observations at each time point is resulting in a better approximation to the true expected value of the population, as one would expect.

Next we present results for a fixed value $N_s = 10$ with varying observation time vectors. See Figures 6.47 – 6.54 for resulting expected values and distributions for the problems with $t_f = 2$, $N_t = 6$ and $t_f = 5$, $N_t = 9, 17$ and 23.

Note that as $N_t$ increases, there is an apparent convergence in both the expected values and the distributions. Similar results for the expected values were obtained with other fixed values of $N_s$, although the convergence in distribution was not as evident.

We conclude that for the estimation problem associated with (6.31) using multiple observations at each time point as in (6.36), in general there is an improvement in the resulting optimized parameters when the number of observations $N_s$ taken at each time is increased, and also when there is an increase in the number of time points $N_t$ at which the observations are collected. Note that an increase in $N_s$ theoretically yields a better approximation to the expected value (6.34) over the population and hence the expected improvement in the optimized parameters. The improved performance as $N_t$ increases is likely a result of a richer observation set with respect to time, so that the dynamics are more fully represented in the data.
Table 6.27: Optimized parameters \( \tilde{q} = (\tilde{\mu}, \tilde{\sigma}) \) for (6.31) with observations \( \tilde{z} \) corresponding to (6.37) for various values of \( N_s \), where \( \bar{q}^* = (1, 0.0833) \) and \( t_f = 2, N_t = 6 \). The initial iterate used was \( \bar{q}_0(0.25) = (1.0534, 0.0827) \).

<table>
<thead>
<tr>
<th>( N_s )</th>
<th>( \mu )</th>
<th>( \sigma )</th>
<th>( J(\tilde{q}, \tilde{z}) )</th>
<th>( J(\bar{q}_0, \tilde{z}) )</th>
<th>( J(\bar{q}^*, \tilde{z}) )</th>
</tr>
</thead>
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<td>1.1001e-1</td>
<td>6.8058e-3</td>
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<td>6.8518e-2</td>
<td>2.9521e-2</td>
</tr>
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<td>9.2336e-3</td>
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<tr>
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<tr>
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<td>6.3423e-4</td>
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Table 6.28: Optimized parameters \( \tilde{q} = (\tilde{\mu}, \tilde{\sigma}) \) for (6.31) with observations \( \tilde{z} \) corresponding to (6.37) for various values of \( N_s \), where \( \bar{q}^* = (1, 0.0833) \) and \( t_f = 5, N_t = 9 \). The initial iterate used was \( \bar{q}_0(0.25) = (1.0534, 0.0827) \).

<table>
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<tr>
<th>( N_s )</th>
<th>( \mu )</th>
<th>( \sigma )</th>
<th>( J(\tilde{q}, \tilde{z}) )</th>
<th>( J(\bar{q}_0, \tilde{z}) )</th>
<th>( J(\bar{q}^*, \tilde{z}) )</th>
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</thead>
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</tr>
<tr>
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<td>1.5298e-2</td>
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</table>
Table 6.29: Optimized parameters $\tilde{q} = (\tilde{\mu}, \tilde{\sigma})$ for (6.31) with observations $\tilde{z}$ corresponding to (6.37) for various values of $N_s$, where $\tilde{q}^* = (1, 0.0833)$ and $t_f = 5$, $N_t = 17$. The initial iterate used was $\tilde{q}_0(0.25) = (1.0534, 0.0827)$.

<table>
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<th>$N_s$</th>
<th>$\tilde{\mu}$</th>
<th>$\tilde{\sigma}$</th>
<th>$J(\tilde{q}, \tilde{z})$</th>
<th>$J(\tilde{q}_0, \tilde{z})$</th>
<th>$J(\tilde{q}^*, \tilde{z})$</th>
</tr>
</thead>
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<td>$2.8317$</td>
<td>$3.9083e-1$</td>
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<tr>
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<td>$4.9767e-2$</td>
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</table>

Table 6.30: Optimized parameters $\tilde{q} = (\tilde{\mu}, \tilde{\sigma})$ for (6.31) with observations $\tilde{z}$ corresponding to (6.37) for various values of $N_s$, where $\tilde{q}^* = (1, 0.0833)$ and $t_f = 5$, $N_t = 23$. The initial iterate used was $\tilde{q}_0(0.25) = (1.0534, 0.0827)$.

<table>
<thead>
<tr>
<th>$N_s$</th>
<th>$\tilde{\mu}$</th>
<th>$\tilde{\sigma}$</th>
<th>$J(\tilde{q}, \tilde{z})$</th>
<th>$J(\tilde{q}_0, \tilde{z})$</th>
<th>$J(\tilde{q}^*, \tilde{z})$</th>
</tr>
</thead>
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<td>$3.9734e-1$</td>
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<td>$6.3950e-2$</td>
<td>$3.0201$</td>
<td>$6.7665e-2$</td>
</tr>
</tbody>
</table>
Figure 6.39: Expected values for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the minimized solution $\tilde{q}$ of (6.31) with observations corresponding to (6.36) $N_s = 5$, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 9$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.

Figure 6.40: Truncated normal probability distributions for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the solution $\tilde{q}$ of (6.31) with observations corresponding to (6.36) $N_s = 5$, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 9$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.
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Figure 6.41: Expected values for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the minimized solution $\tilde{q}$ of (6.31) with observations corresponding to (6.36) $N_s = 10$, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 9$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.

Figure 6.42: Truncated normal probability distributions for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the solution $\tilde{q}$ of (6.31) with observations corresponding to (6.36) $N_s = 10$, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 9$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.
Figure 6.43: Expected values for \( \tilde{q}^* = (1, 0.0833) \), \( \tilde{q}_0(0.25) \) and for the minimized solution \( \tilde{q} \) of (6.31) with observations corresponding to (6.36) \( N_s = 20 \), and where \( q_0(0.25) \), \( t_f = 5 \) hours, \( N_t = 9 \). In the graph, \( \tilde{q}^* \), \( \tilde{q} \) and \( \tilde{q}_0(0.25) \) are denoted by \( q^* \), \( q \) and \( q_0 \) respectively.

Figure 6.44: Truncated normal probability distributions for \( \tilde{q}^* = (1, 0.0833) \), \( \tilde{q}_0(0.25) \) and for the solution \( \tilde{q} \) of (6.31) with observations corresponding to (6.36) \( N_s = 20 \), and where \( q_0(0.25) \), \( t_f = 5 \) hours, \( N_t = 9 \). In the graph, \( \tilde{q}^* \), \( \tilde{q} \) and \( \tilde{q}_0(0.25) \) are denoted by \( q^* \), \( q \) and \( q_0 \) respectively.
Figure 6.45: Expected values for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the minimized solution $\tilde{q}$ of (6.31) with observations corresponding to (6.36) $N_s = 100$, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 9$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.

Figure 6.46: Truncated normal probability distributions for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the solution $\tilde{q}$ of (6.31) with observations corresponding to (6.36) $N_s = 100$, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 9$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.
Figure 6.47: Expected values for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the minimized solution $\tilde{q}$ of (6.31) with observations corresponding to (6.36) $N_s = 10$, and where $q_0(0.25)$, $t_f = 2$ hours, $N_t = 6$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.

Figure 6.48: Truncated normal probability distributions for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the solution $\tilde{q}$ of (6.31) with observations corresponding to (6.36) $N_s = 10$, and where $q_0(0.25)$, $t_f = 2$ hours, $N_t = 6$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.
Figure 6.49: Expected values for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the minimized solution $\tilde{q}$ of (6.31) with observations corresponding to (6.36) $N_s = 10$, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 9$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.

Figure 6.50: Truncated normal probability distributions for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the solution $\tilde{q}$ of (6.31) with observations corresponding to (6.36) $N_s = 10$, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 9$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.
Figure 6.51: Expected values for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the minimized solution $\tilde{q}$ of (6.31) with observations corresponding to (6.36) $N_s = 10$, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 17$.

Figure 6.52: Truncated normal probability distributions for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the solution $\tilde{q}$ of (6.31) with observations corresponding to (6.36) $N_s = 10$, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 17$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.
Figure 6.53: Expected values for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the minimized solution $\tilde{q}$ of (6.31) with observations corresponding to (6.36) $N_s = 10$, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 23$. In the graph, $\tilde{q}^*$, $\tilde{q}$ and $\tilde{q}_0(0.25)$ are denoted by $q^*$, $q$ and $q_0$ respectively.

Figure 6.54: Truncated normal probability distributions for $\tilde{q}^* = (1, 0.0833)$, $\tilde{q}_0(0.25)$ and for the solution $\tilde{q}$ of (6.31) with observations corresponding to (6.36) $N_s = 10$, and where $q_0(0.25)$, $t_f = 5$ hours, $N_t = 23$. 
6.3 Summary of results

In this chapter we have presented results for several types of inverse problems, including the deterministic problems discussed in Section 6.1 and the probabilistic problems detailed in Section 6.2. Here we have studied the effectiveness of these estimation procedures for various observations sets, including observations that simulate data from a single individual and observations that simulate inter-individual variability. Each of these inverse problems provided insight into the dependence of the model on the adipose parameters, and laid the groundwork for using actual experimental data to estimate these parameters.

The deterministic problems that we have studied here include two and three dimensional estimation problems with observations simulating data from single and multiple individuals. In Section 6.1.1, we implemented estimation problems for various pairs and triples of adipose model parameters using observation sets that simulated measurements from one individual. These results suggested that problems with dimension larger than two may experience coupling between the parameters to be estimated, but overall the resulting optimized parameters were reasonably accurate estimates of the data-generating parameters $q^*$. In Section 6.1.2, we conducted a further study of the parameters $q = (D_B, \mu_{IA})$, carrying out inverse problems with simulated data corresponding to observations of multiple individuals. The minimized solutions obtained for these problems were relatively successful at estimating parameters close to the data-generating parameter set $q^*$, although the results were less accurate in general as the simulated variability in the population was increased.

These smaller-dimension estimation problems paved the way for a complete study of the full eight-dimensional inverse problem, which we presented in Section 6.1.3. As before, we used simulated data that represented observations from a single individual, as well as observations simulating inter-individual variability. In Section 6.1.3.a we
presented results for the former type of observations, i.e., simulated data representing a single individual. We discovered that the eight-dimensional estimation problem yielded parameters that were not nearly as accurate as approximations for $q^*$ than the optimized parameters from the smaller estimation problems. Moreover, the results suggested that there may be several local minimizers for this problem, but that the optimization algorithm could obtain a minimizer that produces model responses similar to those for $q^*$.

In studying the effectiveness of the eight-dimensional problem with inter-individual variability simulated in the observations, we found that a substantial amount of variability in the population (with respect to the parameters) had a negative impact on the quality of the optimization results. These findings, presented in Section 6.1.3.b, added support to the idea of using an estimation problem based on probability which could directly account for such variability.

In Section 6.2 we tested this type of probability-based problem by estimating truncated normal distributions for the parameter $q = D_B$. Specifically, we assumed that $q$ has a truncated normal probability distribution, and we implemented inverse problems to estimate the mean and standard deviation. In Section 6.2.1, we presented results for these estimation problems with simulated observations corresponding to the expected value. As guaranteed by the theoretical results discussed in Section 4.3, these results appeared to demonstrate convergence in both the resulting expected values and probability distributions as we increased the number of time points $N_t$.

We tested the same estimation problem in Section 6.2.2 with simulated data sets that included multiple observations at each time point. These data were utilized in the inverse problem by comparing their mean at each time point with model simulations of the expected value at the same time points. As in the previous section, the results we obtained for this problem suggested the convergence of the expected values and distributions as we increased the number of time points $N_t$. Furthermore, we saw the same type of convergence behavior as we increased the number of simulated data points $N_s$ at each time point, which corresponded to improved approximations for the
“true” expected value over the population. Together, the results from Section 6.2.1 and Section 6.2.2 for the two-dimensional probability-based inverse problem have demonstrated the effectiveness of this type of estimation strategy, and have provided a basis for a further study of higher-dimensional estimation problems.

In summary, the estimation problems that we have studied in this chapter have provided insight on the dependence of the TCE PBPK-hybrid model on the adipose model parameters, and on the effectiveness of various types of estimation techniques with different kinds of observation sets. We have developed a strategy for determining \textit{a priori} an appropriate collection of time points at which to collect experimental measurements, based only on the amount of TCE exposure time in the chamber and on the known half-life of TCE. Finally, we have demonstrated that a probability-based estimation method, such as those discussed in Section 6.2, is a good type of estimation problem to use for parameters that may vary across the population, and for data that involve observations of multiple individuals.
Chapter 7

Conclusions and future work

7.1 Concluding remarks

In this dissertation we have discussed various modeling techniques for capturing the systemic transport of trichloroethylene, with a focus on the transport of TCE in the adipose tissue. Here we have presented three physiologically based pharmacokinetic models for the systemic transport of TCE, each with a different model for the adipose tissue compartment.

TCE is a member of a class of chemicals that is known to accumulate inside the adipose tissue, and its persistence there has a major impact on the overall disposition of TCE inside the body. Physiologically based pharmacokinetic modeling is the standard approach for describing the systemic transport of compounds such as TCE, and is based on a system of coupled compartmental equations that each model a specific tissue or organ.

In the second chapter we implemented the standard PBPK model to simulate inhaled TCE in Long-Evans rats, using a perfusion-limited compartment for the adipose tissue. We then adapted this model by changing the fat compartment to a diffusion-limited model. The perfusion-limited model assumes that the entire tissue is in rapid equilibrium and the diffusion-limited model assumes that the intracellular space and extracellular space of a tissue are individually in rapid equilibrium. These
“well-stirred” assumptions may not be adequate to capture the behavior of TCE inside the fat tissue.

Adipose is a significantly heterogeneous tissue, with widely varying physiological properties such as fat cell size, lipid distribution, blood flow rates and cell permeabilities. Each adipocyte is a relatively independent functional unit with its own blood supply, suggesting that a lipophilic compound such as TCE may have more complicated transport dynamics in the fat tissue. These dynamics are likely to be spatially varying, reflecting the spatial heterogeneities in the adipose tissue itself.

To account for these heterogeneities and more closely model the specific physiology of adipose tissue, in Chapter 3 we developed an axial dispersion type model to describe the transport of TCE inside the fat. This aggregate model uses a representative adipocyte-capillary structure to approximate the dynamics occurring in individual adipocytes throughout the tissue. The representative geometry and the model itself are based on the physiological features of adipose tissue and the expected behavior of lipophilic compounds in the body. We then coupled the adipose dispersion model with the PBPK whole-body model, yielding a PBPK-hybrid model for the systemic transport of TCE.

In Chapter 4 we addressed theoretical issues related to the PBPK-hybrid model, including the well-posedness of solutions and the parameter identification problem. Specifically, we established existence, uniqueness and continuous dependence results for an abstract class of nonlinear parabolic systems which includes the TCE PBPK-hybrid model. Moreover, we proved convergence results for the Galerkin finite element approximations that we implemented in Chapter 5, establishing the theoretical convergence of numerical solutions to the solution of the infinite-dimensional system of model equations. Finally, we formulated several general parameter estimation problems related to the abstract class of nonlinear parabolic systems and specifically to the TCE PBPK-hybrid model. We addressed theoretical issues for these estimation problems, which include problems of the deterministic type as in Section 4.2, as well as probability-based estimation problems as discussed in Section 4.3.
We developed numerical methods for the PBPK-hybrid model in Chapter 5, using the finite element method to implement the model computationally. Model simulations were generated for various parameter sets, demonstrating that concentration profiles depend greatly on the choice of model parameters and on the predominant type of transport between the capillary and adipocyte regions. Based on these results and comparisons with the two standard models, it appears that accounting for the specific physiology of adipose tissue is important in developing an accurate model for the transport of TCE in the adipose tissue and the body. Moreover, the results presented here suggest that this type of model might be well-suited to predict the experimental behavior of TCE inside adipose tissue using parameter estimation techniques.

In Chapter 6 we formulated several types of parameter estimation problems for the TCE PBPK-hybrid model, including both deterministic and probability-based inverse problems. In Section 6.1 we presented results for deterministic estimation problems with generated observation sets that simulate measurements of TCE concentrations from a single individual, as well as with observations that simulate inter-individual variability. The results obtained with the latter type of simulated data suggested that a probability-based estimation problem may be better suited to capture variability across a population. Such inter-individual variability is commonly found in experimental data related to toxicokinetics, including the TCE data collected by Evans et al. [32].

We implemented an example probability-based estimation problem in Section 6.2, in which we estimated a truncated normal distribution for the dispersion coefficient $D_B$. The results presented there demonstrated convergence in the expected value and in the distributions, as guaranteed by the theory developed in Chapter 4. Moreover, these results suggest that this type of estimation problem may be successful in identifying parameters that exhibit variability across the population.
Chapter 7. Conclusions and future work

7.2 Future work

7.2.1 A three-dimensional axial dispersion model for TCE in adipose tissue

The TCE axial dispersion model developed in Chapter 3 is based in part on the simplifying assumption of radial uniformity in each of the three regions of the adipose tissue. It is reasonable to assume that TCE would diffuse radially through both the interstitial space and the adipocyte, so that concentrations in these two regions would be dependent on the radial variable $r$. The dispersion model presented in this dissertation could be extended and adapted to include such radial diffusion, resulting in a full three-dimensional model. The theoretical results for the 3-d model would be similar to those for our 2-d model, although the computational efforts would be substantially more involved as the third dimension is added to the model and to the finite element approximations.

7.2.2 Modeling the kinetics of TCE metabolites

Each of the systemic PBPK models presented in this dissertation involves the transport of TCE only, with the assumption of an irreversible metabolism that is modeled with Michaelis-Menten kinetics. As we point out in Chapter 1, many of the toxic effects associated with TCE are suspected to be a result of several of its metabolites rather than TCE itself. This suggests the need for a PBPK model that includes both the parent compound TCE as well as its toxic metabolites.

As discussed in Chapter 2, several such models have been developed which make use of perfusion-limited compartmental models for the adipose tissue. Using the ideas presented in this dissertation, one could develop a PBPK model for TCE and its metabolites that utilizes an axial dispersion model for TCE in adipose tissue.
7.2.3 Identifying model parameters using experimental data

The parameter estimation results detailed in Chapter 6 were obtained exclusively using simulated observation sets. We completed a thorough study of several types of estimation techniques with simulated data, establishing the dependence of the model on the parameters and testing the effectiveness of each of the estimation techniques. The next step in this process is to use the most successful parameter estimation strategies with actual experimental data. In this particular case, such data would likely involve inter-individual variability, so that a probability-based estimation problem may be most appropriate. One could extend the ideas presented in Section 6.2 to estimate truncated normal distributions for multiple parameters using experimental data as observations.

7.2.4 Estimating general probability distributions for model parameters

In Section 6.2 we presented results for inverse problems that involved estimating truncated normal probability distributions for model parameters. In this case, a specific probability distribution is assumed \textit{a priori} to approximate the variability of each parameter across the population. One can estimate probability distributions for parameters without making such an assumption on the exact type of distribution by formulating a family of finite dimensional inverse problems using Dirac measures. Examples of this type of estimation problem and related theoretical, computational and experimental results can be found in [5] and [8]. When using actual experimental data, it may not be practical to determine \textit{a priori} the specific type of probability distribution that best approximates the variability of the parameters. In that case, a general probability distribution estimation problem may be most appropriate.
7.2.5 Comparing the TCE PBPK-hybrid model to other systemic TCE models

To our knowledge, there are no other existing models for TCE that incorporate spatial variability of TCE in the adipose tissue as suggested by the physiology of adipose tissue and the properties of TCE (see Chapter 3). Using statistical methods outlined in [6] and [7], one could compare the results of the parameter estimation problem for the TCE PBPK-hybrid model with parameter identification results for other systemic TCE models, including the two ODE-based models presented in Chapter 2. These statistical tests may help distinguish between an improvement in results caused by a simple increase in the number of degrees of freedom, and an improvement caused by using a model that is a better approximation to the true transport behavior of TCE.


Appendix A

Model parameters

Parameters for whole-body PBPK model with a perfusion-limited fat compartment. Source: [32].

<table>
<thead>
<tr>
<th>Model parameter</th>
<th>Abbr.</th>
<th>Estimated value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>$bw$</td>
<td>0.437</td>
</tr>
<tr>
<td>Blood volumes (liters)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>$V_v$</td>
<td>0.0393</td>
</tr>
<tr>
<td>Brain</td>
<td>$V_{br}$</td>
<td>0.0026</td>
</tr>
<tr>
<td>Fat</td>
<td>$V_f$</td>
<td>0.0336</td>
</tr>
<tr>
<td>Kidney</td>
<td>$V_k$</td>
<td>0.002</td>
</tr>
<tr>
<td>Liver</td>
<td>$V_l$</td>
<td>0.017</td>
</tr>
<tr>
<td>Muscle</td>
<td>$V_m$</td>
<td>0.3277</td>
</tr>
<tr>
<td>Remaining tissue</td>
<td>$V_t$</td>
<td>0.0146</td>
</tr>
<tr>
<td>Blood flow rates (liters/hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output</td>
<td>$Q_c$</td>
<td>7.6322</td>
</tr>
<tr>
<td>Brain</td>
<td>$Q_{br}$</td>
<td>0.1755</td>
</tr>
<tr>
<td>Fat</td>
<td>$Q_f$</td>
<td>0.6106</td>
</tr>
</tbody>
</table>
### Appendix A. Model parameters

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Symbol</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>$Q_k$</td>
<td>0.6182</td>
</tr>
<tr>
<td>Liver</td>
<td>$Q_l$</td>
<td>1.1448</td>
</tr>
<tr>
<td>Muscle</td>
<td>$Q_m$</td>
<td>2.4423</td>
</tr>
<tr>
<td>Remaining tissue</td>
<td>$Q_t$</td>
<td>2.6407</td>
</tr>
</tbody>
</table>

| Ventilation rate (liters/hr) | $Q_p$ | 7.6322 |

| Blood/air partition coefficient | $P_b$ | 21.9   |

<table>
<thead>
<tr>
<th>Tissue/blood partition coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
</tr>
<tr>
<td>Fat</td>
</tr>
<tr>
<td>Kidney</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Muscle</td>
</tr>
<tr>
<td>Remaining tissue</td>
</tr>
</tbody>
</table>

| Michaelis-Menten constant (mg/liters) | $k_M$ | 0.18  |
| Metabolic constant (mg/hour)         | $v_{max}$ | 2.8997 |
Appendix A. Model parameters

Parameters for diffusion-limited fat compartment.

<table>
<thead>
<tr>
<th>Model parameter</th>
<th>Abbr.</th>
<th>Estimated value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volumes (liters)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracellular space</td>
<td>$V_{fi}$</td>
<td>0.0269</td>
</tr>
<tr>
<td>Extracellular space</td>
<td>$V_{fe}$</td>
<td>0.0067</td>
</tr>
<tr>
<td>Permeability coefficient (liters/hr)</td>
<td>$\mu$</td>
<td>0.1</td>
</tr>
<tr>
<td>Blood flow rate to fat (liters/hr)</td>
<td>$Q_f$</td>
<td>0.6106</td>
</tr>
<tr>
<td>Blood/fat partition coefficient</td>
<td>$P_f$</td>
<td>26.26</td>
</tr>
</tbody>
</table>

Parameters for adipose dispersion model.

<table>
<thead>
<tr>
<th>Model parameter</th>
<th>Abbr.</th>
<th>Estimated value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volumes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capillary</td>
<td>$V_B$</td>
<td>0.0084</td>
</tr>
<tr>
<td>Interstitial space</td>
<td>$V_I$</td>
<td>0.0118</td>
</tr>
<tr>
<td>Adipocyte</td>
<td>$V_A$</td>
<td>0.0135</td>
</tr>
<tr>
<td>Unbound fraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capillary</td>
<td>$f_B$</td>
<td>1</td>
</tr>
<tr>
<td>Interstitial space</td>
<td>$f_I$</td>
<td>0.6667</td>
</tr>
<tr>
<td>Adipocyte</td>
<td>$f_A$</td>
<td>0.0381</td>
</tr>
</tbody>
</table>
### Appendix A. Model parameters

**Permeability coefficients (liters/hr)**

- Capillary – Interstitial space \( \mu_{BI} \) 0.02
- Capillary – Adipocyte \( \mu_{BA} \) 0.03
- Interstitial space – Adipocyte \( \mu_{IA} \) 0.025

**Fraction of transport between the capillary and the other two adipose regions**

- Capillary – Interstitial space \( \lambda_I \) 0.6
- Capillary – Adipocyte \( \lambda_A \) 0.4

**Dispersivity coefficient for capillary (m\(^2\)/hr)** \( D_B \) 1

**Diffusion coefficients (m\(^2\)/hr)**

- Interstitial space \( D_I \) 0.01
- Adipocyte \( D_A \) 0.001

**Cross-sectional area of capillary (m\(^2\))** \( A_B \) \( 5 \times 10^{-5} \)

**Radius of adipocyte (m)** \( r_1 \) 0.08

**Velocity of blood in capillary (m/hr)** \( v \) 0.9769

**Reverse Fahraeus-Lindquist parameter** \( F \) 0.08

**Location (in \( \theta \)) of capillary central axis** \( \theta_0 \) \( \pi \)

**Points of interface (in \( \phi \)) between capillary and blood compartments**

- Capillary – Arterial blood \( \varepsilon_1 \) \( \pi/8 \)
- Capillary – Venous blood \( \pi - \varepsilon_2 \) \( 7\pi/8 \)
List of References


[40] M. S. Greenberg, G. A. Burton, and J. W. Fisher, Physiologically based pharmacokinetic modeling of inhaled trichloroethylene and its oxidative


