CALIFORNIA STATE UNIVERSITY, NORTHRIDGE

MATHEMATICAL ANALYSIS AND NUMERICAL
COMPUTATION OF THE BRAIN RESPONSE TO
SINGLE-EVENT RELATED STIMULI

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Mathematics

by

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# Table of Contents

Signature page ii  
List of Tables v  
List of Figures vi  
Abstract ix  

## 1 Introduction 1  

## 2 The Mathematical Model: Direct and Inverse Formulation 4  
### 2.1 The Direct Problem: The Hemodynamic Model 5  
#### 2.1.1 Derivation of the Balloon Model 6  
#### 2.1.2 Derivation of the BOLD Signal 8  
#### 2.1.3 The Hemodynamic Model: Summary 10  
### 2.2 The Inverse Problem: Parameter Estimation 10  

## 3 Mathematical Study 12  
### 3.1 General Study of a First-Order, Nonlinear Ordinary Differential Equation 12  
### 3.2 Mathematical Study of the Hemodynamic Model 20  
#### 3.2.1 Properties of the Cerebral Blood Flow and the Flow Inducing Signal 20  
#### 3.2.2 Properties of the Cerebral Blood Volume 34  
#### 3.2.3 Properties of the Total Deoxyhemoglobin Content Level 37  
#### 3.2.4 Properties of the BOLD Signal 39  
### 3.3 Determination of the Jacobian Matrix of the Direct Mapping 41  

## 4 Solution Methodology 45  
### 4.1 The RNA-CKF Method 45  
#### 4.1.1 The Regularized Newton Algorithm 46  
#### 4.1.2 The Cubature Kalman Filter 47  
### 4.2 The Proposed Solution Methodology: A Multi-Step Strategy 50  
### 4.3 Numerical Implementation of the Proposed Algorithm 51  

## 5 Illustrative Numerical Results 53  
### 5.1 Performance Assessment with Synthetic Data 53  
#### 5.1.1 Results with an On-Off Input 53
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1.2 Results with a Gaussian Input</td>
<td>66</td>
</tr>
<tr>
<td>5.2 Performance Assessment with Real Data</td>
<td>78</td>
</tr>
<tr>
<td>5.2.1 Description of the Data</td>
<td>78</td>
</tr>
<tr>
<td>5.2.2 Numerical Results</td>
<td>78</td>
</tr>
<tr>
<td>6 Conclusion</td>
<td>81</td>
</tr>
<tr>
<td>References</td>
<td>84</td>
</tr>
</tbody>
</table>
List of Tables

5.1 Biophysical Parameters: Target vs. Initial Values, Case of an *On-Off* Stimulus ........................................ 53
5.2 Control Function Characteristics: Target vs. Initial Values, Case of an *On-Off* Stimulus .......................... 54
5.3 Biophysical Parameters: Target vs. Initial Values, Case of a Gaussian Stimulus ......................................... 66
5.4 Control Function Characteristics: Target vs. Initial Values, Case of a Gaussian Stimulus .............................. 67
5.5 Biophysical Parameters: Initial Guess vs. Computed Values, Finger-tapping Data ........................................ 79
5.6 Control Function Characteristics: Initial Guess vs. Computed Values, Finger-tapping Data .......................... 79
List of Figures

3.1 Illustrative behavior of $t \rightarrow y(t)$ in the neighborhood of $t = t_0$, where $y(t_0) = M$, $M$ being a positive number satisfying (3.13) ............................................ 15

3.2 Graphs of the functions $\varphi_1$ and $\varphi_2$, given by (3.29) and (3.30), respectively. ............................................ 17

4.1 Parameter Values: Target (black) vs. Computed with RNA-CKF (red). .................. 50

4.2 $\frac{\partial u}{\partial \bar{t}}$ with $\bar{t} = 7$, $a = 30$. ............................................................. 52

4.3 Numerical approximation of the Dirac delta function by the Gaussian function (12) at $t^* = 0$, $\Delta t = 0.4s$, and 21 values measured. ....................................................... 52

5.1 Synthetic BOLD signal corresponding to the On-Off control input. ...................... 54

5.2 Target BOLD signal (solid-black) and noisy BOLD signal measurements(dots-blue). Case of an On-Off stimulus. ................................................................. 55

5.3 Target parameters (black) vs. estimated parameters using Multi-Step method (red). Case of an On-Off stimulus, Experiment 1: Different noisy measurements, no noise on the initial state $\bar{x}_0$ and the system ($\nu_t = 0$). ........................................... 56

5.4 Target BOLD signal (solid-black) vs. reconstructed BOLD signal using Multi-Step method (dashed-red). Case of an On-Off stimulus, Experiment 1: Different noisy measurements, no noise on the initial state $\bar{x}_0$ and the system ($\nu_t = 0$). ................................................................. 57

5.5 Convergence history of the Multi-Step method (dashed-red). Case of an On-Off stimulus, Experiment 1: Different noisy measurements, no noise on the initial state $\bar{x}_0$ and the system ($\nu_t = 0$). A blue line between iterations means that $\bar{p}$ was updated; a red line indicates that $\bar{\theta}$ was updated. The horizontal line represents the level of noise on the synthetic BOLD signal. ................ 58

5.6 Target parameters (black) vs. estimated parameters using Multi-Step method (red). Case of an On-Off stimulus, Experiment 2: Different noisy measurements, 5% noise on $\bar{x}_0$, and no noise on the system ($\nu_t = 0$). .............................................. 60

5.7 Target BOLD signal (solid-black) vs. reconstructed BOLD signal using Multi-Step method (dashed-red). Case of an On-Off stimulus, Experiment 2: Different noisy measurements, 5% noise on $\bar{x}_0$, and no noise on the system ($\nu_t = 0$). ................................................................. 61
5.8 Convergence history of the Multi-Step method (dashed-red). Case of an
On-Off stimulus, Experiment 2: Different noisy measurements, 5% noise
on $\vec{x}_0$, and no noise on the system ($\nu_t = 0$). A blue line between iterations
means that $\vec{p}$ was updated; a red line indicates that $\vec{\theta}$ was updated. The
horizontal line represents the level of noise on the synthetic BOLD signal.

5.9 Target parameters (black) vs. estimated parameters using Multi-Step method
(red). Case of an On-Off stimulus with different noisy measurements, 5%
oise on $\vec{x}_0$, and 1% process noise.

5.10 Target BOLD signal (solid-black) vs. reconstructed BOLD signal using
Multi-Step method (dashed-red). Case of an On-Off stimulus with different
noisy measurements, 5% noise on $\vec{x}_0$, and 1% process noise.

5.11 Convergence history of the Multi-Step method (dashed-red). Case of an
On-Off stimulus with different noisy measurements, 5% noise on $\vec{x}_0$, and
1% process noise. A blue line between iterations means that $\vec{p}$ was updated;
a red line indicates that $\vec{\theta}$ was updated. The horizontal line represents the
level of noise on the synthetic BOLD signal.

5.12 Reconstructed BOLD signals: Target (solid-black), computed with multi-
step method after 4 iterations (dashed-red), and computed with RNA-CKF

5.13 Synthetic BOLD signal corresponding to the Gaussian control input.

5.14 Target BOLD signal (solid-black) and noisy BOLD signal measurements(dots-
blue). Case of a Gaussian stimulus.

5.15 Target BOLD signal (solid-black) vs. reconstructed BOLD signal using
Multi-Step method (dashed-red). Case of a Gaussian stimulus, Experiment
1: different noisy measurements, no noise on the initial state $\vec{x}_0$ and the
system ($\nu_t = 0$).

5.16 Target parameters (black) vs. estimated parameters using Multi-Step method
(red). Case of a Gaussian stimulus, Experiment 1: different noisy measure-
ments, no noise on the initial state $\vec{x}_0$ and the system ($\nu_t = 0$)

5.17 Convergence history of the Multi-Step method (dashed-red). Case of a
Gaussian stimulus, Experiment 1: different noisy measurements, no noise
on the initial state $\vec{x}_0$ and the system ($\nu_t = 0$) A blue line between iterations
means that $\vec{p}$ was updated; a red line indicates that $\vec{\theta}$ was updated. The
horizontal line represents the level of noise on the synthetic BOLD signal.
5.18 Target BOLD signal (solid-black) vs. reconstructed BOLD signal using Multi-Step method (dashed-red). Case of a Gaussian stimulus, Experiment 2: different noisy measurements, 5% noise on $\vec{x}_0$, and no noise on the system ($\nu_t = 0$).

5.19 Target parameters (black) vs. estimated parameters using Multi-Step method (red). Case of a Gaussian stimulus, Experiment 2: different noisy measurements, 5% noise on $\vec{x}_0$, and no noise on the system ($\nu_t = 0$).

5.20 Convergence history of the Multi-Step method (dashed-red). Case of a Gaussian stimulus, Experiment 2: different noisy measurements, 5% noise on $\vec{x}_0$, and no noise on the system ($\nu_t = 0$). A blue line between iterations means that $\vec{p}$ was updated; a red line indicates that $\vec{\theta}$ was updated. The horizontal line represents the level of noise on the synthetic BOLD signal.

5.21 Target BOLD signal (solid-black) vs. reconstructed BOLD signal using Multi-Step method (dashed-red). Case of a Gaussian stimulus, Experiment 3: different noisy measurements, 5% noise on $\vec{x}_0$, and 1% process noise.

5.22 Target parameters (black) vs. estimated parameters using Multi-Step method (red). Case of a Gaussian stimulus, Experiment 3: different noisy measurements, 5% noise on $\vec{x}_0$, and 1% process noise.

5.23 Convergence history of the Multi-Step method (dashed-red). Case of a Gaussian stimulus, Experiment 3: different noisy measurements, 5% noise on $\vec{x}_0$, and 1% process noise. A blue line between iterations means that $\vec{p}$ was updated; a red line indicates that $\vec{\theta}$ was updated. The horizontal line represents the level of noise on the synthetic BOLD signal.

5.24 Real BOLD signal: 25 measured points.

5.25 Convergence history using real data.

5.26 Real BOLD signal (solid-black) vs. computed BOLD signal after 6 steps (dashed-red).
ABSTRACT

MATHEMATICAL ANALYSIS AND NUMERICAL COMPUTATION OF THE BRAIN RESPONSE TO SINGLE-EVENT RELATED STIMULI

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The goal of this study is to analyze mathematically and numerically the hemodynamic mathematical model that describes changes in blood flow and blood oxygenation during brain activation. At the mathematical level, we have established results pertaining to the existence, uniqueness, and asymptotic behavior of the state vector as well as the blood-oxygen-level dependent (BOLD) signal. At the numerical level, the goal is to propose a numerical strategy for retrieving accurately and efficiently the biophysiological parameters as well as the external stimulus characteristics of the considered hemodynamic model. The proposed method employs the RNA-CKF method developed in [21], but in a prediction/correction framework. Furthermore, numerical experiments have been conducted using synthetic functional Magnetic Resonance Imaging (fMRI) measurements, tainted with varying noise, to highlight the performance characteristics of this computational methodology. Finally, the algorithm was implemented to calibrate the model using real data obtained from a finger-tapping fMRI experiment conducted at the Nationwide Children’s Hospital in Columbus, Ohio.
Chapter 1

Introduction

The brain is the command center of the human body. With billions of neurons connected by trillions of synapses, the brain is easily the most complex organ in the body. And yet, in spite of its importance, the brain is one of the least understood organs. Though advancements are being made perennially, there is still much to be uncovered in terms of how this enigmatic system operates. Better understanding of brain function could lead to better understanding and treatment of countless diseases that occur when the brain does not behave the way that it should. Indeed, given its potential outcomes, it is clear that solving the brain mystery is a task of undeniable importance.

Though the magnitude of the mystery that is the human brain can be attributed in part to its complexity, the major hurdle to better understanding of brain function is the fact that the brain is encased in the skull, making it a difficult organ to examine and image. With this in mind, there have been great efforts made in recent history toward improving brain imaging technology. One of the most prominent methods used today is functional Magnetic Resonance Imaging (fMRI), with one of its key features being its noninvasiveness. Unlike its imaging predecessors, which produced static, two-dimensional images of a cross-section of the brain, fMRI yields a three-dimensional image of the entire brain at each time step, essentially creating a movie of the brain over the duration of the scan.

fMRI technology has greatly improved our ability to visualize the brain. This advancement has the potential to allow doctors to better understand, diagnose, and treat brain diseases by monitoring a patient’s brain activity. There is however an issue with the implementation of fMRI studies, the issue being that long-term monitoring is not feasible from a time or cost perspective. It is in an attempt to remedy this problem, that applied mathematics enters the equation. The idea is that, using only one fMRI scan from a patient, a suitable mathematical model could be calibrated in order to monitor and predict that patient’s brain activity. This mathematical model would be a time- and cost-efficient tool for long-term monitoring, that is, it would solve both of the problems associated with the use of fMRI technology alone.

To this end, we consider the mathematical model that describes hemodynamic responses that occur when the brain is subjected to a single external stimulus. This model is a dynamical system which includes a first-order differential system, known as the balloon
model [3]. This differential system is coupled with a nonlinear equation which represents the Blood Oxygenation Level Dependent (BOLD) Signal [17], a quantity whose values are obtained from functional Magnetic Resonance Imaging (fMRI) measurements. The brain response characterized by this model is sensitive to the biophysiological parameters of the system as well as to its control function representing the considered single external stimulus during brain activation. Accurate determination of the values of these parameters and the characteristics of the control function is crucial for successfully monitoring and possibly predicting brain activity, which in turn has the potential to provide diagnosis and treatment of brain diseases in early stages. Note that the problem of estimating the parameters of the hemodynamic model can be formulated mathematically as an inverse problem. This problem, however, is difficult to solve, both mathematically and numerically, due to its nonlinearity and ill-posedness. Extensive efforts have been made to address these difficulties (see, e.g., [3, 7, 12, 21, 22], among others). Among the most promising recent numerical procedures are the Cubature Kalman Filter (CKF) method [3], and the Tikhonov-regularized Newton Method equipped with the Cubature Kalman Filter (TNM-CKF) [21]. A major drawback of the CKF method [3] is its need for a priori knowledge about the values of the parameters. This is a very severe limitation since, in practice, such information is not readily accessible through measurements. On the other hand, and in spite of its efficiency and its superiority over the CKF method for determining the biophysiological parameters only, the TNM-CKF method seems to fail dramatically when applied to retrieve simultaneously both the biophysiological parameters and the control function characteristics, as illustrated in Section V. Given the preceding considerations, there is a clear scientific need of pressing importance for solving accurately and efficiently this inverse problem. We propose a new computational strategy to retrieve the biophysiological parameters of the model as well as the characteristics of its control function from the knowledge of some fMRI measurements. The main idea here is to employ the TNM-CKF method, but in an alternative manner. Specifically, we predict the values of one set of parameters and use TNM-CKF to correct these values. Then, using the updated values from the previous step as initial values, we restart the iterative process to correct the second set of parameters.

The remainder of this manuscript is organized as follows. In Chapter 2, we introduce and describe the mathematical concepts of forward and inverse problems. In Chapter 3, we introduce the mathematical model that describes changes in the brain in response to an exogeneous stimulus during brain activation. This model describes a forward problem. In addition, we formulate the inverse problem which consists of recovering the biophysiological parameters of the system as well as the characteristics of the considered stimulus. In
Chapter 4, we present obtained mathematical results about the solutions of the aforementioned forward problem. Chapter 5 consists of the formulation of the proposed solution methodology, as well as a description of the numerical techniques used in the proposed algorithm. Chapter 6 presents the results of two numerical studies to assess the performance of the proposed algorithm using synthetic data. The first experiment is performed with a Gaussian control input. In the second, we consider an On-Off control input. Finally, we present a summary and closing remarks in the Conclusion.
Chapter 2
The Mathematical Model: Direct and Inverse Formulation

Because of its desirable features, which include noninvasiveness, lack of radiation exposure, and good resolution, functional Magnetic Resonance Imaging (fMRI) has become the standard tool for brain mapping. fMRI technology exploits changes in the magnetic properties of the blood due to changes in deoxyhemoglobin content during brain activation. This effect, known as the blood oxygenation level-dependent (BOLD) contrast, is used to track associated changes in blood flow during activation [27, 28].

The task of creating a mathematical model capable of accurately reproducing the BOLD signal phenomena is not an easy one. Indeed, disagreements have stemmed from issues including the nonlinearity of brain activity and a coupling or uncoupling of cerebral blood flow and oxygen metabolism [3]. As a result, two distinct approaches have emerged—General Linear Modeling (GLM) and Nonlinear Modeling (NLM)—in attempt to describe the hemodynamic response during brain activation. GLM involves statistical analysis, whereby a predefined kernel is used to assess the convolution of the neural activity. The kernel—known as the Hemodynamic Reaction Function (HRF)—has been defined using several different basis functions, including Poisson [8], Gaussian [29], Gamma [5, 9], and inverse Logit [24] functions. The problem with the linear approach is that it is blind to the physiological causes of the transient aspects of the BOLD signal. In addition, nonlinear activity in the BOLD signal has been observed on multiple occasions [3, 4, 10, 11].

These deficiencies in GLM gave rise to the nonlinear approach to modeling neural activity [3, 25], in which the venous compartment is modeled as a balloon that expands to account for the increased blood flow that occurs during local activation. The increase in blood flow results in a local decrease in deoxyhemoglobin concentration, and a corresponding increase in the BOLD signal [25]. This new characterization of the BOLD signal’s dependence on cerebral blood flow, volume, and deoxyhemoglobin content was made complete with the introduction of the flow-inducing signal [12], which serves as the link between neural activation and the associated changes in local cerebral blood dynamics.

In this chapter, we present the nonlinear mathematical model that describes local changes in hemodynamic properties of the brain in the presence of a stimulus as a dynamical system [12]. Then, we introduce the inverse problem that consists of retrieving the unknown parameters of the considered dynamical system from the knowledge of some fMRI mea-
surements.

2.1 The Direct Problem: The Hemodynamic Model

Throughout the rest of this manuscript, we adopt the following notations and hypotheses:

- $t$ is a nonnegative real number which represents time.
- $\Delta t$ is a positive real number representing the chosen time step.
- $t_n = n\Delta t$ represents the time at step $n$.
- $\vec{x}(t) = (x_1(t), x_2(t), x_3(t), x_4(t))^T \in \mathbb{R}^4$ is the state vector function whose components are:
  - $x_1(t)$, the normalized cerebral blood flow
  - $x_2(t)$, the flow inducing signal
  - $x_3(t)$, the normalized cerebral blood volume
  - $x_4(t)$, the normalized total deoxyhemoglobin content level
- $\vec{x}_0$ is the initial state vector. $\vec{x}_0 = \vec{x}(0) = (1, 0, 1, 1)^T$.
- $\vec{\theta} = (\theta_1, \theta_2, \theta_3, \theta_4, \theta_5, \theta_6, \theta_7)^T \in \mathbb{R}^7$ is the biophysical parameters vector whose components are:
  - $\theta_1$, the reciprocal of the stiffness exponent
  - $\theta_2$, the neural efficacy
  - $\theta_3$, the reciprocal of the rate of signal decay
  - $\theta_4$, the reciprocal of the rate of flow-dependent elimination
  - $\theta_5$, the reciprocal of the hemodynamic transit time
  - $\theta_6$, the resting net oxygen extraction
  - $\theta_7$, the resting blood volume
- $\nu_t$ represents the noise at time $t$ in the process equation. $\nu_t$ is a random Gaussian vector with zero mean and covariance $Q_t$, a 4x4 positive semidefinite matrix.
- $\omega_t$ represents the noise at time $t$ in the measurement equation. $\omega_t$ is a random Gaussian vector with zero mean and covariance $R_t$, a real-valued scalar.
• $u(t, \vec{p})$ is the external stimulus–or control function–at time $t$. In this study, we consider an On-Off stimulus, given by:

$$u(t) = \chi \left( \frac{t - \bar{t}}{a} \right),$$

(2.1)

and a Gaussian stimulus, given by:

$$u(t) = 2 \exp \left( -\frac{(t - \bar{t})^2}{2a^2} \right).$$

(2.2)

• $\vec{p} = (\bar{t}, a)^T$ is a vector characterizing the considered external stimulus, also called the control function.

The model that describes brain activity consists of a process equation coupled with a measurement equation. The process equation describes the underlying physical changes that occur during brain activation and, as such, it is given as a system of differential equations. The measurement equation models the measured data, in this case, the BOLD signal output of an fMRI brain scan. The compact representation of such a state-space model is given by:

$$\begin{align*}
\dot{\vec{x}}(t) &= A(\vec{x}(t), u(t, \vec{p}), \vec{\theta}) + \nu_t \quad \text{(Process Equation)} \\
y(t) &= B(\vec{x}(t), \vec{\theta}) + \omega_t \quad \text{(Measurement Equation)},
\end{align*}$$

(2.3)

where $A$ is a nonlinear algebraic operator that describes the underlying physics of the system, $B$ is an algebraic operator that describes the measured data, that is, $B$ models the BOLD signal output. Operators $A$ and $B$ are described in full detail in the ensuing subsections.

2.1.1 Derivation of the Balloon Model

In the presence of an external stimulus, neurons are activated in some region or regions of the brain. During this neuronal activity, higher levels of oxygen and glucose are consumed than when the brain is at rest. To make up for the excess oxygen consumption, there is a local increase in blood flow. This increased flow causes the venous compartment to act as an expanding balloon, thereby causing an increase in blood volume and a decrease in the total deoxyhemoglobin content. The balloon model [3] describes the dynamics of, as well as the relationship between, blood flow, blood volume, and deoxyhemoglobin content.

The balloon model [3] is a simple model with two state variables–normalized volume,
\( x_3 \), and normalized deoxyhemoglobin content, \( x_4 \)–both of which are driven by the blood flow, \( F_{in} \), a function of time. The flow out, \( F_{out} \) is assumed to be a function of the blood volume, \( V \) [15, 25]. Then the rate of change of blood volume is the difference between \( F_{in} \) and \( F_{out} \), that is,

\[
\frac{dV}{dt} = F_{in}(t) - F_{out}(V(t)).
\]

(2.4)

In addition, for \( E \) the net extraction of \( O_2 \) from the blood and \( C_a \) the arterial \( O_2 \) concentration, the rate of change of total deoxyhemoglobin content, \( Q \), is

\[
\frac{dQ}{dt} = F_{in}(t)E C_a - F_{out}(V(t))Q(t)/V(t).
\]

(2.5)

By normalizing each of these values, i.e., dividing by their values at rest, (2.4) and (2.5) become

\[
\frac{dx_3}{dt} = \theta_5 (x_1(t) - f_{out}(x_3(t))),
\]

(2.6)

\[
\frac{dx_4}{dt} = \theta_5 \left( x_1(t) \frac{E(t)}{\theta_6} - f_{out}(x_3(t)) \frac{x_4(t)}{x_3(t)} \right),
\]

(2.7)

where \( \theta_5 = F_0/V_0 \) is the reciprocal of the mean transit time at rest, \( F_0 \) is the resting blood flow, and \( V_0 = \theta_7 \) is the resting blood volume.

At this point, the functions that remain to be specified are \( E(t) \) and \( f_{out}(x_3(t)) \). \( E(t) \) represents the fraction of oxygen extracted from the blood that is flowing into the venous compartment, and is therefore a function of \( x_1 \) for which a reasonable approximation [4] is

\[
E(t) = E(x_1(t)) = 1 - (1 - \theta_6)^{1/x_1(t)}.
\]

(2.8)

Next, we seek an expression for \( f_{out}(x_3(t)) \). According to the work of Grubb, et al. [15],

\[
f_{out}(x_3(t)) = x_3^{\theta_1}(t)
\]

(2.9)

where \( \theta_1 = 1/\alpha \) and \( \alpha \) is the stiffness exponent for the venous compartment. The work of Mandeville, et al. [25] and, consequently, (2.9) suggest that the flow out of the compartment depends both on the volume and the elasticity of the compartment, i.e., the venous compartment’s compliance and capacitance in the presence of a large inflow. To conclude the balloon model component, we substitute (2.8) and (2.9) into (2.6) and (2.7) to get

\[
\frac{dx_3}{dt} = \theta_5 (x_1(t) - x_3^{\theta_1}(t)),
\]

(2.10)
\[
\frac{dx_1}{dt} = \theta_5 \left( x_1(t) \frac{1-(1-\theta_6)^{1/x_1(t)}}{\theta_6} - x_3^{(\theta_1-1)}(t)x_4(t) \right).
\] (2.11)

Note that (2.10) and (2.11) depend on the inflow, \(x_1(t)\), and so we need an expression for the dynamics of this physical quantity in order to quantify the BOLD response. To this end, we use the relationship chosen in [12]:

\[
\frac{dx_1}{dt} = x_2(t),
\] (2.12)

where the change in signal is also given by [12] as

\[
\frac{dx_2}{dt} = \theta_2 u(t, \vec{p}) - \theta_3 x_2(t) - \theta_4 (x_1(t) - 1).
\] (2.13)

Combining (2.10)-(2.13), the balloon model is given by

\[
\begin{align*}
\dot{x}_1(t) &= x_2(t) \\
\dot{x}_2(t) &= \theta_2 u(t, \vec{p}) - \theta_3 x_2(t) - \theta_4 (x_1(t) - 1) \\
\dot{x}_3(t) &= \theta_5 \left( x_1(t) - x_3^{\theta_1(t)}(t) \right) \\
\dot{x}_4(t) &= \theta_5 \left( x_1(t) \frac{1-(1-\theta_6)^{1/x_1(t)}}{\theta_6} - x_3^{(\theta_1-1)}(t)x_4(t) \right)
\end{align*}
\] (2.14)

that is, the operator \(A\) in the process equation in (2.3) is

\[
A(\vec{x}(t), u(t, \vec{p}), \vec{\theta}) = \begin{cases} 
 x_2(t) \\
 \theta_2 u(t, \vec{p}) - \theta_3 x_2(t) - \theta_4 (x_1(t) - 1) \\
 \theta_5 \left( x_1(t) - x_3^{\theta_1(t)}(t) \right) \\
 \theta_5 \left( x_1(t) \frac{1-(1-\theta_6)^{1/x_1(t)}}{\theta_6} - x_3^{(\theta_1-1)}(t)x_4(t) \right) 
\end{cases}. 
\] (2.15)

### 2.1.2 Derivation of the BOLD Signal

While the balloon model describes the physiological changes in cerebral blood during brain activation, our ultimate goal is to connect the model with experimental fMRI. To this end, there have been numerous attempts to quantify the relationship between the BOLD signal and blood volume and deoxyhemoglobin content, using experimental data [34], numerical Monte Carlo simulations [28, 34], and analytical calculations [3, 35].

The BOLD effect that results from the extravascular signal changes are primarily due to changes in the total deoxyhemoglobin content, \(x_4\) in a voxel of tissue [28]. However, the work of Boxerman et al. [2] suggests that intravascular signal changes also play a
significant role in the total BOLD response. With this in mind, Buxton, et al. [3] model the BOLD signal as a volume-weighted sum of the extravascular ($S_e$) and intravascular ($S_i$) signal:

$$S = (1 - V)S_e + VS_i$$  \quad (2.16)

where $V = \theta x_3$ is the blood volume fraction. Then, for small signal changes $\Delta S$:

$$\Delta S = (1 - \theta)\Delta S_e - \Delta V S_e + \theta \Delta S_i + \Delta V S_i.$$  \quad (2.17)

Factoring $\theta$ out of (2.17) and $S_e$ out of (2.16) and (2.17), the fractional change in the BOLD signal can be written as:

$$\frac{\Delta S}{S} = \frac{\theta}{1 - \theta + \theta \frac{S_i}{S_e}} \left[ \left( \frac{1}{\theta} - 1 \right) \frac{\Delta S_e}{S_e} + (1 - x_3) + \frac{\Delta S_i}{S_e} - (1 - x_3(t)) \right]$$  \quad (2.18)

and

$$\frac{\Delta S_i}{S_e} = 2 \left( 1 - \frac{x_4(t)}{x_3(t)} \right),$$  \quad (2.22)

for some scaling factor $a$. Then, substituting (2.20)-(2.22) in (2.19), we have:

$$\frac{\Delta S}{S} = \theta \left[ k_1 (1 - x_4(t)) + 2 \left( 1 - \frac{x_4(t)}{x_3(t)} \right) + k_3 (1 - x_3(t)) \right],$$  \quad (2.23)

where $k_1 \cong 7 \theta_6$ and $k_3 \cong 2 \theta_6 - 0.2$ based on the results of [2] and [28]. Then, substituting the values of $k_1$ and $k_3$ into (2.23), the BOLD signal operator $B = \Delta S/S$ is given by:

$$B(\vec{x}(t), \vec{\theta}) = \theta \left[ 7 \theta_6 (1 - x_4(t)) + 2 \left( 1 - \frac{x_4(t)}{x_3(t)} \right) + (2 \theta_6 - 0.2)(1 - x_3(t)) \right]$$  \quad (2.24)
2.1.3 The Hemodynamic Model: Summary

Our goal is to construct a state-space model of the form (2.3) to describe the hemodynamic activity of the brain in response to a single exogenous input. In Section 2.1.1, we developed the balloon model, which describes the underlying physical changes in cerebral blood during local activation. In Section 2.1.2, we derived the BOLD signal equation, which provides the relationship between the physical activity in the brain and the fMRI measurement output. The coupling of the differential system and the algebraic equation introduced in 2.1.1 and 2.1.2, respectively, is known as the hemodynamic model (HDM), and is given by:

\[
\begin{align*}
\dot{x}(t) &= A(x(t), u(t, p), \theta) + \nu_t \\
y(t) &= B(x(t), \theta) + \omega_t \\
x(0) &= x_0
\end{align*}
\] (HDM) \tag{2.25}

where the vector-valued function \( A \) is given by (2.15), \( B \) is given by (2.24), and \( x_0 = (1, 0, 1, 1)^T \) is the resting value of the state vector, \( x \).

2.2 The Inverse Problem: Parameter Estimation

The dynamical system given by (2.25) defines an operator \( F \) that maps the biophysical parameters, \( \theta \), and the external stimulus characteristics, \( p \), to the BOLD signal, \( y \). Therefore, the problem of simultaneously determining the biophysical parameters \( \theta \) and the external stimulus characteristics \( p \) from the knowledge of a measured BOLD signal can be formulated as the following inverse problem:

\[
\begin{align*}
\text{Given an initial measured state } \tilde{x}_0 \text{ and a measured BOLD signal } \tilde{y}, \\
\text{find the biophysical parameters } \tilde{\theta}, \text{ control input parameters } \tilde{p}, \\
\text{and state vector function } \tilde{x}(t) \text{ such that:} \\
F(\tilde{\theta}, \tilde{p}; \tilde{x}(t)) = \tilde{y}(t)
\end{align*}
\] \tag{2.26}

where the tilde denotes a noisy quantity. For the initial state, this represents some level of activity in the brain, i.e., the brain is not fully at rest. For the BOLD signal, the “noise” corresponds to possible errors associated with measurement.

Though \( F \) represents a continuous operator, in practice the BOLD signal is measured at discrete time points, that is, for some number \( N_m > 0 \) of BOLD signal measurements,
(2.26) can be re-formulated as:

\[
\begin{cases}
\text{Given } \tilde{x}_0 \text{ and } \tilde{y} = (\tilde{y}_0, \tilde{y}_1, \ldots, \tilde{y}_{N_m})^T, \\
\text{find } \tilde{\theta}, \tilde{p}, \text{ and } \tilde{x}(t) \text{ such that:} \\
B(\tilde{\theta}, \tilde{p}, \tilde{x}(t_j)) = \tilde{y}_j; \quad j = 0, 1, \ldots, N_m,
\end{cases}
\] (2.27)

Note that the problem defined by (2.26) is a nonlinear inverse problem, which falls into the category of identifying the parameters of an ordinary differential system.
Chapter 3
Mathematical Study

The main goal of this chapter is to analyze the mathematical properties of the solution to the hemodynamic model given by (2.25). To this end, we first conduct a mathematical investigation of a class of first-order, nonlinear, ordinary differential equations. Then, we analyze the properties of the solution to the linear system given by the first two equations of (2.15). Next, we analyze the properties of the solution to the third equation of (2.15). Finally, we analyze the properties of the solution to the fourth equation of (2.15) and, subsequently, the properties of the BOLD signal (2.24).

3.1 General Study of a First-Order, Nonlinear Ordinary Differential Equation

The goal of this section is to analyze the properties of the solutions of the following class of first-order initial value problems:

\[
\begin{align*}
    y'(t) &= ay(t)|y(t)|^\theta + f(t) \\
    y(0) &= 1
\end{align*}
\]

where:

- \( a \) is a negative real number, that is, \( a < 0 \).
- \( \theta \) is a positive real number, that is, \( \theta > 0 \).
- \( t \rightarrow f(t) \) is a continuous function on \([0, \infty)\) such that \( \lim_{t \rightarrow \infty} f(t) = c > 0 \)

The results established in this section do not appear to be standard, and may be of independent interest.

**Theorem 1.** The first-order initial value problem (3.1) admits a unique solution \( t \rightarrow y(t) \), defined on \([0, \infty)\). In addition, we have

\[
\lim_{t \rightarrow \infty} y(t) = \left( -\frac{c}{a} \right)^{1/(\theta+1)}.
\]

Note that \( t \rightarrow y(t) \), the solution to (3.1) exists uniquely on \([0, T^*)\) for some \( T^* > 0 \). This is an immediate consequence of applying the Cauchy-Lipschitz Theorem (see, e.g., [32]). Hence, all we need is to prove that \( T^* = \infty \), as well as to prove that the limit of \( y(t) \)
as \( t \) tends to \(+\infty\) is given by (3.2). To this end, we first establish the following intermediate results, which are stated as lemmas.

**Lemma 1.** The solution \( t \to y(t) \) of the first-order initial value problem (3.1) is bounded on \([0, T^\ast)\), that is, there is a positive number \( M \) such that:

\[
|y(t)| \leq M; \quad \forall t \in [0, T^\ast).
\] (3.3)

**Proof.** First observe that the function \( t \to f(t) \) is bounded, i.e., there exists \( K > 0 \) such that

\[
|f(t)| \leq K; \quad \forall t \in [0, \infty).
\] (3.4)

Indeed, since \( \lim_{t \to \infty} f(t) = c \), then

\[
\forall \varepsilon > 0, \exists t^\ast > 0 \mid \forall t \geq t^\ast : |f(t) - c| < \varepsilon.
\] (3.5)

Hence, \( \forall t \geq t^\ast \):

\[
-c < f(t) - c < \varepsilon \quad \Rightarrow \quad c - \varepsilon < f(t) < c + \varepsilon
\] (3.6)

Let \( \varepsilon = c/2 \). Then, there is \( t^\ast > 0 \) such that:

\[
\frac{c}{2} < f(t) < \frac{3c}{2}; \quad \forall t \geq t^\ast.
\] (3.7)

Consequently,

\[
|f(t)| < \frac{3c}{2}; \quad \forall t \geq t^\ast.
\] (3.8)

In addition, \( f \) is continuous on \([0, t^\ast] \). Therefore, the function is bounded on this interval. Hence, there is a positive number \( L \) such that:

\[
|f(t)| \leq L; \quad \forall t \in [0, t^\ast].
\] (3.9)

Let

\[
K = \max \left\{ L, \frac{3c}{2} \right\}.
\] (3.10)

Then it follows from (3.8)-(3.10) that:

\[
|f(t)| \leq K; \quad \forall t \in [0, \infty).
\] (3.11)
Next, we set
\[ M_1 = \max \left\{ 1, \left( \frac{1 + K}{|a|} \right)^{\frac{1}{\theta+1}} \right\}. \tag{3.12} \]
Let \( M \) be any positive number such that \( M > M_1 \). It follows from (3.12) that:
\[ aM^{\theta+1} + K < -1. \tag{3.13} \]
On the other hand, since \( y(0) = 1 < M \), and since \( t \to y(t) \) is continuous, there is \( t'_0 \) such that:
\[ |y(t)| < M; \quad \forall t \in [0, t'_0]. \tag{3.14} \]
Let \( t_0 \) be the largest time for which (3.14) is satisfied, that is,
\[ t_0 = \sup \{ t'_0 < T^* \mid |y(t)| < M; \, \forall t \in [0, t'_0] \}. \tag{3.15} \]
If \( t_0 = T^* \), then \( t \to y(t) \) is bounded for all \( t \geq 0 \).

If \( t_0 < T^* \), then either \( y(t_0) = M \) or \( y(t_0) = -M \). Assume that \( y(t_0) = M \). Then, as illustrated in Fig. 3.1, \( t \to y(t) \) is increasing as \( t \) approaches \( t_0 \) from the left. Therefore, \( y'_l(t_0) \), the left-hand derivative of \( y \) at \( t = t_0 \) must be positive, that is,
\[ y'_l(t_0) = \lim_{h \to 0^-} \frac{y(t_0 + h) - y(t_0)}{h} > 0. \tag{3.16} \]
On the other hand, using the differential equation in (3.1), we also have that
\[ y'_l(t_0) = ay(t_0)|y(t_0)|^\theta + f(t_0) = aM^{\theta+1} + f(t_0). \tag{3.17} \]
It follows from (3.11), (3.13), and (3.17) that
\[ y'_l(t_0) < aM^{\theta+1} + K < -1, \tag{3.18} \]
which contradicts (3.16). Therefore, (3.15) is valid for all \( 0 \leq t \leq T^* \), that is,
\[ |y(t)| < M; \quad \forall t \in [0, T^*). \tag{3.19} \]
Similarly, assume \( y(t_0) = -M \). Then \( t \to y(t) \) is decreasing as \( t \) approaches \( t_0 \) from the left, that is,
\[ y'_l(t_0) = \lim_{h \to 0^-} \frac{y(t_0 + h) - y(t_0)}{h} < 0. \tag{3.20} \]
On the other hand, from (3.1), we have
\[ y'(t_0) = ay(t_0)|y(t_0)|^{\theta} + f(t_0) = -aM^{\theta} + f(t_0) \] (3.21)

It follows from (3.11), (3.13), and (3.21), that
\[ y'(t_0) \geq -aM^{\theta} - K > 1, \] (3.22)

contradicting (3.20). From here, we conclude that (3.15) is valid for all \( 0 \leq t \leq T^* \), that is,
\[ |y(t)| < M; \quad \forall t \in [0, T^*), \] (3.23)

which concludes the proof of Lemma 1.

The next results show that \( T^* \) is infinite, that is, \( t \rightarrow y(t) \) is bounded for all \( t \in [0, \infty) \).

**Corollary 1.** \( t \rightarrow y(t) \) exists and is bounded for all \( t \in [0, \infty) \).

**Proof.** It follows from Lemma 1 that there is \( T^* > 0 \) such that \( t \rightarrow y(t) \) is bounded on \([0, T^*)\). Since \( t \rightarrow y(t) \) is continuous, there is \( y_0 \in [-M, M] \) and a sequence \( (t_n) \subseteq [0, T^*) \) such that \( (t_n) \rightarrow T^* \) and \( y(t_n) \rightarrow y_0 \). Using Cauchy-Lipschitz Theorem [32], we deduce the existence of \( \bar{t} = \bar{t}(y_0, T^*) > 0 \) such that \( y(t_m + \bar{t}) \) exists for all \( n \). On the other hand, \( t_n + \bar{t} \rightarrow T^* + \bar{t} > T^* \). Moreover, using the continuity of \( y \), we also have

![Figure 3.1: Illustrative behavior of \( t \rightarrow y(t) \) in the neighborhood of \( t = t_0 \), where \( y(t_0) = M \), \( M \) being a positive number satisfying (3.13)](image)

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15
\[ y(t_n + \bar{t}) \rightarrow y(T^* + \bar{t}), \text{ which contradicts } T^* \text{ being the largest time for which } y \text{ exists.} \]

Therefore, \( T^* = +\infty. \)

To establish (3.2) of Theorem 1, we will need to use the following two auxiliary results, which are stated as lemmas. To this end, we introduce the following preliminary notations and assumptions.

Let \( \ell \) be a positive number such that:

\[ a\ell^{\theta+1} + c = 0. \quad (3.24) \]

Hence,

\[ \ell = \left( -\frac{c}{a} \right)^{1/(\theta+1)}. \quad (3.25) \]

Let \( t_0 \) be a time large enough such that, for all \( t \geq t_0 \), the following inequalities hold

\[ \left| \left( \ell \pm \frac{1}{t} \right)^{\theta+1} - \ell^{\theta+1} \mp \frac{(\theta+1)\ell^\theta}{t} \right| \leq \frac{(\theta+1)\ell^\theta}{4t}, \quad (3.26) \]

\[ |f(t) - c| \leq |a|\frac{(\theta + 1)\ell^\theta}{4t}, \quad (3.27) \]

and

\[ |a|\frac{(\theta + 1)\ell^\theta}{2t} > \frac{1}{\ell^2}. \quad (3.28) \]

Next, we introduce the following two functions:

\[ \varphi_1(t) = \ell + \frac{1}{t}; \ t > 0 \quad (3.29) \]

and

\[ \varphi_2(t) = \ell - \frac{1}{t}; \ t > 0. \quad (3.30) \]

The curves of \( \varphi_1 \) and \( \varphi_2 \) are depicted in Fig. 3.2.
Lemma 2. The flow of $t \to y(t)$, the solution to (3.1), is incoming on $\varphi_1$ and $\varphi_2$, given by (3.29) and (3.30), respectively. More specifically, for $t_1 \geq t_0$:

(i) If $y(t_1) = \varphi_1(t_1)$, then $y'(t_1) < \frac{d\varphi_1}{dt}(t_1) = -\frac{1}{t_1^2}$.

(ii) If $y(t_1) = \varphi_2(t_1)$, then $y'(t_1) > \frac{d\varphi_2}{dt}(t_1) = \frac{1}{t_1^2}$.

Proof. The proofs for both statements are similar. Hence, we establish statement (ii) only. Assume that $y(t_1) = \varphi_2(t_1)$. Using the differential equation in (3.1) and (ii), we deduce that

$$y'(t_1) = a\varphi_2(t_1)|\varphi_2(t_1)|^\theta + f(t_1) = a\varphi_2^{\theta+1}(t_1) + f(t_1).$$

Hence, it follows from (3.30) and (3.31) that

$$y'(t_1) = a\left(\ell - \frac{1}{t_1}\right)^{\theta+1} + f(t_1).$$

On the other hand, it follows from (3.26) that:

$$-\frac{(\theta + 1)\ell^\theta}{4t} \leq \left(\ell - \frac{1}{t}\right)^{\theta+1} - \frac{(\theta + 1)\ell^\theta}{t} \leq \frac{(\theta + 1)\ell^\theta}{4t}$$

$$\left(\ell - \frac{1}{t}\right)^{\theta+1} \leq \ell^{\theta+1} - \frac{(\theta + 1)\ell^\theta}{t} + \frac{(\theta + 1)\ell^\theta}{4t}$$

Figure 3.2: Graphs of the functions $\varphi_1$ and $\varphi_2$, given by (3.29) and (3.30), respectively.
and, since $a < 0$, we obtain:

$$a \left( \ell - \frac{1}{t} \right)^{\theta + 1} \geq a \left( \ell^{\theta + 1} - \frac{(\theta + 1)\ell^\theta}{t} \right) + a \frac{(\theta + 1)\ell^\theta}{4t}. \quad (3.33)$$

Moreover, it follows from (3.27) that:

$$-|a|\frac{(\theta + 1)\ell^\theta}{4t} \leq f(t) - c \leq |a|\frac{(\theta + 1)\ell^\theta}{4t}$$

$$c + a\frac{(\theta + 1)\ell^\theta}{4t} \leq f(t). \quad (3.34)$$

Hence, using (3.33) and (3.34), we deduce that:

$$a \left( \ell - \frac{1}{t_1} \right)^{\theta + 1} + f(t_1) \geq a \left( \ell^{\theta + 1} - \frac{(\theta + 1)\ell^\theta}{t_1} \right) + a \frac{(\theta + 1)\ell^\theta}{4t_1} + c + a \frac{(\theta + 1)\ell^\theta}{4t_1} \quad (3.35)$$

By substituting (3.24) in (3.35), we deduce that:

$$a \left( \ell - \frac{1}{t_1} \right)^{\theta + 1} + f(t_1) \geq a\ell^{\theta + 1} + c - a\frac{(\theta + 1)\ell^\theta}{2t_1}. \quad (3.36)$$

Consequently, it follows from (3.28), (3.32) and (3.36) that:

$$y'(t_1) \geq |a|\frac{(\theta + 1)\ell^\theta}{2t_1} > \frac{1}{t_1^2} = \frac{d}{dt}\varphi_2(t_1), \quad (3.37)$$

which is the desired result.

Next, we consider the region $A$ between the graphs of $\varphi_1$ and $\varphi_2$ given by (3.29) and (3.30), respectively, as depicted in Fig. 3.2. The region $A$ is given by:

$$A = \left\{ (t, y) \mid t \geq t_0, \ |y - 1| \leq \frac{1}{t} \right\} \quad (3.38)$$

Observe that the previous result states that, if there is $t_1 \geq t_0$ such that $(t_1, y(t_1)) \in A$, then $(t, y(t)) \in A$ for all $t \geq t_1$. The next result proves the existence of the time $t_1$.

**Lemma 3.** Let $t \to y(t)$ be the solution to (3.1). and $A$ the region given by (3.38). Then there is $t_1 \geq t_0$ such that $(t_1, y(t_1)) \in A$. 

Proof. We prove this result by contradiction. Assume that such \( t_1 \) does not exist. Then \((t, y(t)) \notin A\) for all \( t \geq t_0 \). Since \( t \to y(t) \) is continuous, then we have the following alternatives:

either

\[
y(t) > \varphi_1(t); \quad \forall t \geq t_0,
\]

or

\[
y(t) < \varphi_2(t); \quad \forall t \geq t_0.
\]

Without loss of generality, assume that (3.40) is true. It follows from the differential equation in (3.1), (3.30), and (3.40), that

\[
y'(t) = ay(t)|y(t)|^\theta + f(t) > a \left( \ell - \frac{1}{t} \right)^{\theta+1} + f(t).
\]

It follows from (3.33), (3.34), and (3.41),

\[
y'(t) > a \left( \ell^{\theta+1} - \frac{(\theta + 1)\ell^\theta}{t} + \frac{(\theta + 1)\ell^\theta}{4t} \right) + c + a \frac{(\theta + 1)\ell^\theta}{4t}.
\]

Consequently, we deduce from (3.24) and (3.42) that

\[
y'(t) > -a \frac{(\theta + 1)\ell^\theta}{2t} > 0.
\]

Hence, \( t \to y(t) \) is increasing. Moreover, since it is bounded above (see Lemma 1), then \( t \to y(t) \) admits a limit as \( t \) tends to \( +\infty \). Let \( \ell \) be this limit. Then,

\[
\lim_{t \to \infty} y(t) = \ell
\]

and

\[
\ell < \ell.
\]

It follows from the differential equation in (3.1), (3.44), and (3.45) that

\[
\lim_{t \to \infty} y'(t) = a\ell |\ell|^\theta + c \neq 0.
\]

Therefore,

\[
y(t) \sim \left( a\ell |\ell|^\theta + c \right) t; \quad t \to \infty.
\]

Thus, we must have

\[
\lim_{t \to \infty} y(t) = \infty \quad \text{or} \quad \lim_{t \to \infty} y(t) = -\infty,
\]
which contradicts Lemma 1. This concludes the proof of Lemma 3. □

Proof of Theorem 1. It follows from Lemma 3, that:

\[ \exists t_1 > t_0 \mid \varphi_2(t) < y(t) < \varphi_1(t); \quad \forall t \geq t_1. \]  
(3.49)

Thus,

\[ |y(t) - \ell| \leq \frac{1}{t}; \quad \forall t \geq t_1. \]  
(3.50)

Consequently, it follows from substituting (3.25) into (3.50), that:

\[ \lim_{t \to \infty} y(t) = \ell = \left(-\frac{c}{a}\right)^{1/(\theta+1)} \]  
(3.51)

□

3.2 Mathematical Study of the Hemodynamic Model

The goal of this section is to analyze mathematically the properties of the state vector \( t \to \vec{x}(t) \) and the corresponding BOLD signal solution to the hemodynamic model given by (2.25).

3.2.1 Properties of the Cerebral Blood Flow and the Flow Inducing Signal

We analyze in this section the properties of the cerebral blood flow \( t \to x_1(t) \) and the flow inducing signal \( t \to x_2(t) \) of the hemodynamic model given by (2.25). These state components are the solution to the following coupled first-order differential system:

\[
\begin{cases}
    x_1'(t) = x_2(t) \\
    x_2'(t) = \theta_2 u(t) - \theta_3 x_2(t) - \theta_4 x_1(t) + \theta_4 \\
    x_1(0) = 1, \quad x_2(0) = 0
\end{cases}
\]  
(3.52)

where

\[ u(t) = \begin{cases} 
    1 & : t \in [t_1, t_2] \\
    0 & : t \not\in [t_1, t_2]
\end{cases} \]  
(3.53)

is the considered On-Off external stimulus, for some \( t_1, t_2 \in \mathbb{R}^+ \) representing the start and end times of the stimulus, respectively.

Lemma 4. The explicit expression of \((x_1(t), x_2(t))\), the solution to the differential system (3.52) is given by:
(i) If $\theta_3^2 = 4\theta_4$,
\[
x_1(t) = \begin{cases} 
\beta \left[ e^{-\alpha(t-t_1)}(1 + \alpha(t-t_2)) - e^{-\alpha(t-t_2)}(1 + \alpha(t-t_2)) \right] + 1 & : t \in (t_2, \infty) \\
\beta e^{-\alpha(t-t_1)}(1 + \alpha(t-t_1)) - \beta + 1 & : t \in [t_1, t_2] \\
1 & : t \in [0, t_1)
\end{cases}
\]
\[
x_2(t) = \begin{cases} 
-\alpha^2 \beta \left[ (t-t_1)e^{-\alpha(t-t_1)} - (t-t_1)e^{-\alpha(t-t_1)} \right] & : t \in (t_2, \infty) \\
-\alpha^2 \beta (t-t_1)e^{-\alpha(t-t_1)} & : t \in [t_1, t_2] \\
0 & : t \in [0, t_1)
\end{cases}
\]

(ii) If $\theta_3^2 > 4\theta_4$,
\[
x_1(t) = \begin{cases} 
k \left[ (\lambda_2 e^{\lambda_1(t-t_1)} - \lambda_1 e^{\lambda_2(t-t_1)}) - (\lambda_2 e^{\lambda_1(t-t_2)} - \lambda_1 e^{\lambda_2(t-t_2)}) \right] + 1 & : t \in (t_2, \infty) \\
k \left( \lambda_2 e^{\lambda_1(t-t_1)} - \lambda_1 e^{\lambda_2(t-t_1)} \right) - \beta + 1 & : t \in [t_1, t_2] \\
1 & : t \in [0, t_1)
\end{cases}
\]
\[
x_2(t) = \begin{cases} 
k \lambda_1 \lambda_2 \left[ (e^{\lambda_1(t-t_1)} - e^{\lambda_2(t-t_1)}) - (e^{\lambda_1(t-t_2)} - e^{\lambda_2(t-t_2)}) \right] & : t \in (t_2, \infty) \\
k \lambda_1 \lambda_2 \left( e^{\lambda_1(t-t_1)} - e^{\lambda_2(t-t_1)} \right) & : t \in [t_1, t_2] \\
0 & : t \in [0, t_1)
\end{cases}
\]

(iii) If $\theta_3^2 < 4\theta_4$,
\[
x_1(t) = \begin{cases} 
\beta \left[ e^{-\alpha(t-t_1)} \left( \cos \nu(t-t_1) + \frac{\alpha}{\nu} \sin \nu(t-t_1) \right) \\
-\alpha^2 e^{-\alpha(t-t_2)} \left( \cos \nu(t-t_2) + \frac{\alpha}{\nu} \sin \nu(t-t_2) \right) \right] + 1 & : t \in (t_2, \infty) \\
\beta e^{-\alpha(t-t_1)} \left( \cos \nu(t-t_1) + \frac{\alpha}{\nu} \sin \nu(t-t_1) \right) - \beta + 1 & : t \in [t_1, t_2] \\
1 & : t \in [0, t_1)
\end{cases}
\]
\[
x_2(t) = \begin{cases} 
-\frac{\beta}{\nu} \left( \alpha^2 + \nu^2 \right) \left[ e^{-\alpha(t-t_1)} \sin \nu(t-t_1) - e^{-\alpha(t-t_2)} \sin \nu(t-t_2) \right] & : t \in (t_2, \infty) \\
-\frac{\beta}{\nu} e^{-\alpha(t-t_1)} \left( \alpha^2 + \nu^2 \right) \sin \nu(t-t_1) & : t \in [t_1, t_2] \\
0 & : t \in [0, t_1)
\end{cases}
\]
where
\[ \alpha = \frac{\theta_3}{2}, \quad \beta = -\frac{\theta_2}{\theta_4}, \quad \nu = \frac{1}{2} \sqrt{4\theta_4 - \theta_2^2}, \]
\[ \lambda_1 = \frac{1}{2} \left( -\theta_3 + \sqrt{\theta_3^2 - 4\theta_4} \right), \quad \lambda_2 = \frac{1}{2} \left( -\theta_3 - \sqrt{\theta_3^2 - 4\theta_4} \right), \]
and
\[ k = \frac{\theta_2}{\theta_4(\lambda_1 - \lambda_2)}. \]

Lemma 5. The solution, \((x_1(t), x_2(t))\), to the differential system (3.52) satisfies
\[ \lim_{t \to \infty} x_1(t) = 1, \quad (3.57) \]
\[ \lim_{t \to \infty} x_2(t) = 0. \quad (3.58) \]
In addition, in cases (i) and (ii) we have:
\[ x_1(t) \geq 1; \quad \forall \; t \geq 0. \quad (3.59) \]

Proof. First, we reformulate the system (3.52) as a single, second order differential equation. To this end, we differentiate the first equation of (3.52) to obtain
\[ x_1''(t) = x_2'(t). \quad (3.60) \]
Then, substituting (3.60) and the first equation of (3.52) into the second equation of (3.52), we obtain
\[ \begin{cases} 
    x_1''(t) + \theta_3 x_1'(t) + \theta_4 x_1(t) = \theta_2 u(t) + \theta_4 \\
    x_1(0) = 1, \quad x_1'(0) = 0 
\end{cases} \quad (3.61) \]
Observe that the differential equation in (3.61) is linear, with constant coefficients. In addition, we have:
\[ \begin{cases} 
    x_1''(t) + \theta_3 x_1'(t) + \theta_4 x_1(t) = \theta_4 \\
    x_1(0) = 1, \quad x_1'(0) = 0 
\end{cases} \quad ; \quad 0 < t < t_1. \quad (3.62) \]
Consequently, we have
\[ x_1(t) = 1; \quad \forall \; t \in [0, t_1). \quad (3.63) \]
Moreover, it follows from the first equation in (3.51) and (3.63) that
\[ x_2(t) = 0; \quad \forall \; t \in [0, t_1). \quad (3.64) \]
Similarly, for \( t \in [t_1, t_2] \), (3.52) can be written as follows:

\[
\begin{cases}
  x''_1(t) + \theta_3 x'_1(t) + \theta_4 x_1(t) = \theta_2 + \theta_4; \quad t_1 \leq t \leq t_2. \\
  x_1(t_1) = 1, \quad x'_1(t_1) = 0
\end{cases}
\]  

(3.65)

Observe that

\[ x'_1(t) = \frac{\theta_2}{\theta_4} + 1. \]  

(3.66)

is a particular solution to (3.65). Let \( t \to x^H_1(t) \) be the solution to the associated homogeneous problem, that is,

\[
\begin{cases}
  x''^H_1(t) + \theta_3 x'^H_1(t) + \theta_4 x^H_1(t) = \theta_2 + \theta_4; \quad t_1 \leq t \leq t_2. \\
  x^H_1(t_1) = 1, \quad x'^H_1(t_1) = 0
\end{cases}
\]  

(3.67)

The expression of \( t \to x^H_1(t) \) depends on the value of \( \theta_3^2 - 4\theta_4 \). Specifically, we have the following three cases:

(i) \( \theta_3^2 = 4\theta_4 \).

In this case, we have

\[ x^H_1(t) = c_1 e^{-\frac{\theta_3}{2}t} + c_2 e^{-\frac{\theta_3}{2}t}, \]

where \( c_1 \) and \( c_2 \) are some constants to be determined by the initial conditions. Then

\[
x_1(t) = x^H_1(t) + x'_1(t) \\
= c_1 e^{-\frac{\theta_3}{2}t} + c_2 e^{-\frac{\theta_3}{2}t} + \frac{\theta_2}{\theta_4} + 1
\]  

(3.68)

and, using the initial conditions,

\[
x_1(t_1) = c_1 e^{-\frac{\theta_3}{2}t_1} + c_2 t_1 e^{-\frac{\theta_3}{2}t_1} + \frac{\theta_2}{\theta_4} + 1 = 1
\]

\[
c_1 + c_2 t_1 = -\frac{\theta_2}{\theta_4} e^{-\frac{\theta_3}{2}t_1}
\]  

(3.69)

\[
x'_1(t_1) = -\frac{\theta_3}{2} c_1 e^{-\frac{\theta_3}{2}t_1} + c_2 e^{-\frac{\theta_3}{2}t_1}(1 - \frac{\theta_3}{2} t_1) = 0
\]

\[
-\frac{\theta_3}{2} c_1 + c_2 (1 - \frac{\theta_3}{2} t_1) = 0
\]  

(3.70)

Let

\[ \alpha = \frac{\theta_3}{2}, \]  

(3.71)
\[ \beta = -\frac{\theta_2}{\theta_4}, \]  
(3.72)

and

\[
A = \begin{bmatrix}
1 & t_1 \\
-\alpha & (1 - \alpha t_1)
\end{bmatrix}.
\]  
(3.73)

Note that

\[ \det A = (1 - \alpha t_1) + \alpha t_1 = 1, \]  
(3.74)

so

\[
A^{-1} = \begin{bmatrix}
(1 - \alpha t_1) & -t_1 \\
\alpha & 1
\end{bmatrix}.
\]  
(3.75)

Then, from (3.69), (3.70), and (3.75),

\[
\begin{bmatrix}
  c_1 \\
  c_2
\end{bmatrix} = \begin{bmatrix}
  (1 - \alpha t_1) & -t_1 \\
  \alpha & 1
\end{bmatrix} \begin{bmatrix}
  \beta e^{\alpha t_1} \\
  0
\end{bmatrix},
\]  
(3.76)

that is,

\[ c_1 = \beta e^{\alpha t_1}(1 - \alpha t_1) \]  
(3.77)

\[ c_2 = \alpha \beta e^{\alpha t_1}. \]  
(3.78)

We substitute (3.77) and (3.78) into (3.68). We obtain:

\[ x_1(t) = \beta e^{\alpha(t-t_1)}(1 + \alpha(t - t_1)) - \beta + 1. \]  
(3.79)

Moreover, it follows from the first equation of (3.52) and (3.79) that

\[ x_2(t) = -\alpha^2 \beta (t - t_1) e^{-\alpha(t-t_1)}. \]  
(3.80)

Note that since \( x_1(t_1) = 1 \) and \( x_1'(t) \geq 0 \) for all \( t \in [t_1, t_2] \) (see (3.80)), we can conclude that \( x_1(t) \geq 1 \) and \( x_2(t) \geq 0 \) for all \( t \in [t_1, t_2] \).

(ii) \( \theta_3^2 > 4\theta_4 \).

In this case, we have

\[ x_1^H(t) = c_1 e^{\lambda_1 t} + c_2 e^{\lambda_2 t}, \]
where
\[ \lambda_1 = \frac{1}{2} \left( -\theta_3 + \sqrt{\theta_3^2 - 4\theta_4} \right) \] (3.81)
and
\[ \lambda_2 = \frac{1}{2} \left( -\theta_3 - \sqrt{\theta_3^2 - 4\theta_4} \right). \] (3.82)

Note that \( \lambda_2 < \lambda_1 < 0 \). Then we have
\[ x_1(t) = x_1^H(t) + x_1^P(t) = c_1 e^{\lambda_1 t} + c_2 e^{\lambda_2 t} + \frac{\theta_2}{\theta_4} + 1. \] (3.83)

Using the initial conditions,
\[ x_1(t_1) = c_1 e^{\lambda_1 t_1} + c_2 e^{\lambda_2 t_1} + \frac{\theta_2}{\theta_4} + 1 = 1 \] (3.84)
\[ c_1 e^{\lambda_1 t_1} + c_2 e^{\lambda_2 t_1} = -\frac{\theta_2}{\theta_4} \] (3.85)
\[ x_1'(t_1) = \lambda_1 c_1 e^{\lambda_1 t_1} + \lambda_2 c_2 e^{\lambda_2 t_1} = 0 \] (3.86)

Let
\[ A = \begin{bmatrix} 1 & 1 \\ \lambda_1 & \lambda_2 \end{bmatrix}. \] (3.87)

Note that
\[ \det A = \lambda_2 - \lambda_1, \] (3.88)
so
\[ A^{-1} = \begin{bmatrix} \frac{\lambda_2}{\lambda_2 - \lambda_1} & -\frac{1}{\lambda_2 - \lambda_1} \\ \frac{\lambda_1}{\lambda_2 - \lambda_1} & -\frac{1}{\lambda_2 - \lambda_1} \end{bmatrix}. \] (3.89)

Then from (3.84), (3.85), and (3.86),
\[ \begin{bmatrix} c_1 e^{\lambda_1 t_1} \\ c_2 e^{\lambda_2 t_1} \end{bmatrix} = \begin{bmatrix} \frac{\lambda_2}{\lambda_2 - \lambda_1} & -\frac{1}{\lambda_2 - \lambda_1} \\ -\frac{\lambda_1}{\lambda_2 - \lambda_1} & \frac{1}{\lambda_2 - \lambda_1} \end{bmatrix} \begin{bmatrix} \frac{\theta_2}{\theta_4} \\ 0 \end{bmatrix}, \] (3.90)
that is,

\[ c_1 e^{\lambda_1 t_1} = \frac{\lambda_2 \theta_2}{\theta_4 (\lambda_1 - \lambda_2)} \]
\[ c_1 = \frac{\lambda_2 \theta_2}{\lambda_1 \theta_2} e^{-\lambda_1 t_1}, \quad (3.90) \]
\[ c_2 e^{\lambda_2 t_1} = -\frac{\lambda_1 \theta_2}{\theta_4 (\lambda_1 - \lambda_2)} \]
\[ c_2 = -\lambda_1 \frac{\theta_2}{\theta_4 (\lambda_1 - \lambda_2)} e^{-\lambda_2 t_1} \quad (3.91) \]

We set

\[ k = \frac{\theta_2}{\theta_4 (\lambda_1 - \lambda_2)} > 0. \quad (3.92) \]

Then, substituting (3.90) and (3.91) into (3.83) leads to:

\[ x_1(t) = k \left( \lambda_2 e^{\lambda_1 (t-t_1)} - \lambda_1 e^{\lambda_2 (t-t_2)} \right) - \beta + 1. \quad (3.93) \]

Moreover, it follows from the first equation of (3.52) and (3.93) that:

\[ x_2(t) = k \lambda_1 \lambda_2 \left( e^{\lambda_1 (t-t_1)} - e^{\lambda_2 (t-t_1)} \right). \quad (3.94) \]

Because \( \lambda_2 < \lambda_1 < 0 \) and \( k > 0 \), \( x_1(t) \geq 0 \) for all \( t \in [t_1, t_2] \) (see (3.94)), we conclude again that \( x_1(t) \geq 1 \) and \( x_2(t) \geq 0 \) for all \( t \in [t_1, t_2] \).

\( (iii) \) \( \theta_3^2 < 4\theta_4. \)

In this case, we have

\[ x_1^H(t) = e^{-\alpha t} \left( c_1 \cos \nu t + c_2 \sin \nu t \right), \]

where \( \alpha \) is given by (3.71),

\[ \nu = \frac{1}{2} \sqrt{4 \theta_4 - \theta_3^2}, \quad (3.95) \]

and \( c_1 \) and \( c_2 \) are constants whose values depend on the initial conditions. Then

\[ x_1(t) = x_1^H(t) + x_1^P(t) = e^{-\alpha t} \left( c_1 \cos \nu t + c_2 \sin \nu t \right) - \beta + 1, \quad (3.96) \]
with \( \beta \) given by (3.72). Using the initial conditions,

\[
x_1(t_1) = e^{-\alpha t_1} (c_1 \cos \nu t_1 + c_2 \sin \nu t_1) - \beta + 1 = 1
\]

\[c_1 \cos \nu t_1 + c_2 \sin \nu t_1 = \beta e^{\alpha t_1}, \tag{3.97}\]

\[
x_1'(t_1) = -\alpha e^{-\alpha t_1} (c_1 \cos \nu t_1 + c_2 \sin \nu t_1) + \nu e^{-\alpha t_1} (c_2 \cos \nu t_1 - c_1 \sin \nu t_1) = 0
\]

\[-c_1 (\alpha \cos \nu t_1 + \nu \sin \nu t_1) + c_2 (\nu \cos \nu t_1 - \alpha \sin \nu t_1) = 0. \tag{3.98}\]

Let

\[A = \begin{bmatrix}
\cos \nu t_1 & \sin \nu t_1 \\
-\alpha \cos \nu t_1 - \nu \sin \nu t_1 & \nu \cos \nu t_1 - \alpha \sin \nu t_1
\end{bmatrix}. \tag{3.99}\]

Note that

\[
det A = \nu \cos^2 \nu t_1 - \alpha \sin \nu t_1 \cos \nu t_1 + \nu \sin^2 \nu t_1 + \alpha \sin \nu t_1 \cos \nu t_1
\]

\[= \nu \cos^2 \nu t_1 + \nu \sin^2 \nu t_1
\]

\[
det A = \nu, \tag{3.100}\]

so

\[A^{-1} = \begin{bmatrix}
\cos \nu t_1 - \frac{\alpha}{\nu} \sin \nu t_1 & -\frac{1}{\nu} \sin \nu t_1 \\
\frac{\alpha}{\nu} \cos \nu t_1 + \sin \nu t_1 & \frac{1}{\nu} \cos \nu t_1
\end{bmatrix}. \tag{3.101}\]

Then from (3.97), (3.98), and (3.101),

\[
\begin{bmatrix}
c_1 \\
c_2
\end{bmatrix} = \begin{bmatrix}
\cos \nu t_1 - \frac{\alpha}{\nu} \sin \nu t_1 & -\frac{1}{\nu} \sin \nu t_1 \\
\frac{\alpha}{\nu} \cos \nu t_1 + \sin \nu t_1 & \frac{1}{\nu} \cos \nu t_1
\end{bmatrix} \begin{bmatrix}
\beta e^{\alpha t_1} \\
0
\end{bmatrix}, \tag{3.102}\]

that is,

\[
c_1 = \beta e^{\alpha t_1} \left( \cos \nu t_1 - \frac{\alpha}{\nu} \sin \nu t_1 \right) \tag{3.103}\]

\[
c_2 = \beta e^{\alpha t_1} \left( \frac{\alpha}{\nu} \cos \nu t_1 + \sin \nu t_1 \right) \tag{3.104}\]
Then, substituting (3.103) and (3.104) into (3.96) leads to

\[ x_1(t) = \beta e^{-\alpha(t-t_1)} \left[ \cos \nu t_1 - \frac{\alpha}{\nu} \sin \nu t_1 \right] \cos \nu t - \frac{\alpha}{\nu} \left[ \cos \nu t_1 \cos \nu t - \frac{\alpha}{\nu} \sin \nu t_1 \cos \nu t \right] + \frac{\alpha}{\nu} \left[ \cos \nu t_1 \sin \nu t + \sin \nu t_1 \sin \nu t \right] - \beta + 1 \]

\[ x_1(t) = \beta e^{-\alpha(t-t_1)} \left[ \cos \nu(t-t_1) + \frac{\alpha}{\nu} \sin \nu(t-t_1) \right] - \beta + 1, \quad (3.105) \]

\[ x_1'(t) = x_2(t) = -\alpha \beta e^{-\alpha(t-t_1)} \left( \cos \nu(t-t_1) + \frac{\alpha}{\nu} \sin \nu(t-t_1) \right) + \beta e^{-\alpha(t-t_1)} (\alpha \cos \nu(t-t_1) - \nu \sin \nu(t-t_1)) \]

\[ x_2(t) = -\frac{\beta}{\nu} (\alpha^2 + \nu^2) e^{-\alpha(t-t_1)} \sin \nu(t-t_1). \quad (3.106) \]

It remains to prove that \( x_1(t) \geq 1 \) for all \( t \in [t_1, t_2] \). To do this, we minimize \( x_1 \) by finding the roots of \( x_1' = x_2 \). It follows from (3.106) that \( x_2(t) = 0 \) if and only if

\[ \sin \nu(t-t_1) = 0 \quad (3.107) \]

But if this is true then, since \( \beta < 0 \),

\[ \beta e^{-\alpha(t-t_1)} \left( \cos \nu(t-t_1) + \frac{\alpha}{\nu} \sin \nu(t-t_1) \right) = \beta e^{-\alpha(t-t_1)} \cos \nu(t-t_1) \]

\[ \beta e^{-\alpha(t-t_1)} \left( \cos \nu(t-t_1) + \frac{\alpha}{\nu} \sin \nu(t-t_1) \right) \geq \beta e^{-\alpha(t-t_1)} \]

\[ \beta e^{-\alpha(t-t_1)} \left( \cos \nu(t-t_1) + \frac{\alpha}{\nu} \sin \nu(t-t_1) \right) \geq \beta. \quad (3.108) \]

Then it follows from (3.105) and (3.108) that

\[ x_1(t) \geq \beta - \beta + 1 = 1, \quad (3.109) \]

that is,

\[ x_1(t) \geq 1; \quad \forall t \in [t_1, t_2]. \quad (3.110) \]

Finally, we consider the case where \( t > t_2 \). Here, again, the situation depends on the values of \( \theta_3^2 - 4\theta_4 \).
(i) $\theta_3^2 = 4\theta_4$.

In this case, (3.52) can be expressed as:

\[
\begin{cases}
  x_1''(t) + \theta_3 x_1'(t) + \theta_4 x_1(t) = \theta_4 \\
  x_1(t_2) = \beta e^{-\alpha(t_2-t_1)}(1 + \alpha(t_2 - t_1)) - \beta + 1; \ t > t_2. \\
  x_1'(t_2) = -\alpha^2 \beta (t_2 - t_1)e^{-\alpha(t_2-t_1)}
\end{cases}
\]  

(3.111)

A particular solution of (3.111) is given by:

\[ x_1^P(t) = 1. \]  

(3.112)

The solution to the homogeneous problem associated with (3.111) is given by

\[ x_1^H(t) = c_1 e^{-\alpha t} + c_2 t e^{-\alpha t}, \]

where $c_1$ and $c_2$ are two constants whose values are determined by the initial conditions. Therefore, the solution of (3.111) is given by:

\[
\begin{align*}
  x_1(t) &= x_1^H(t) + x_1^P(t) \\
  x_1(t) &= c_1 e^{-\alpha t} + c_2 t e^{-\alpha t} + 1.
\end{align*}
\]  

(3.113)

To determine the values of the constants $c_1$ and $c_2$, we use the initial conditions. We have:

\[
\begin{align*}
  x_1(t_2) &= \beta e^{-\alpha(t_2-t_1)}(1 + \alpha(t_2 - t_1)) - \beta + 1 \\
  c_1 + c_2 t_2 &= \beta e^{\alpha t_2}(1 + \alpha(t_2 - t_1)) - \beta e^{\alpha t_2} \\
  x_1'(t_2) &= -\alpha^2 \beta (t_2 - t_1)e^{-\alpha(t_2-t_1)} \\
  -\alpha c_1 + c_2(1 - \alpha t_2) &= -\alpha^2 \beta (t_2 - t_1)e^{\alpha t_1}
\end{align*}
\]  

(3.114)

(3.115)

Let

\[ A \begin{bmatrix} c_1 \\ c_2 \end{bmatrix} = b, \]  

(3.116)

where

\[ A = \begin{bmatrix} 1 & t_2 \\ -\alpha & (1 - \alpha t_2) \end{bmatrix}. \]  

(3.117)
and

\[ b = \begin{bmatrix} \beta e^{\alpha t_1} (1 + \alpha (t_2 - t_1)) - \beta e^{\alpha t_2} \\ -\alpha^2 \beta (t_2 - t_1)e^{\alpha t_1} \end{bmatrix} \]  \hspace{1cm} (3.118)

Note that

\[ \det A = (1 - \alpha t_2) + \alpha t_2 = 1. \]  \hspace{1cm} (3.119)

Hence, \( A \) is invertible, and we have:

\[ A^{-1} = \begin{bmatrix} (1 - \alpha t_2) & -t_2 \\ \alpha & 1 \end{bmatrix}. \]  \hspace{1cm} (3.120)

Then from (3.116), (3.118), and (3.120),

\[ \begin{bmatrix} c_1 \\ c_2 \end{bmatrix} = \begin{bmatrix} (1 - \alpha t_2) & -t_2 \\ \alpha & 1 \end{bmatrix} \begin{bmatrix} \beta e^{\alpha t_1} (1 + \alpha (t_2 - t_1)) - \beta e^{\alpha t_2} \\ -\alpha^2 \beta (t_2 - t_1)e^{\alpha t_1} \end{bmatrix}, \]  \hspace{1cm} (3.121)

that is,

\[ c_1 = \beta e^{\alpha t_1} (1 - \alpha t_1) - \beta e^{\alpha t_2} (1 - \alpha t_2) \]  \hspace{1cm} (3.122)
\[ c_2 = \alpha \beta (e^{\alpha t_1} - e^{\alpha t_2}) \]  \hspace{1cm} (3.123)

Substituting (3.122) and (3.123) into (3.113) leads to:

\[ x_1(t) = \beta \left[ e^{\alpha (t-t_1)} (1 + \alpha (t - t_1)) - e^{\alpha (t-t_2)} (1 + \alpha (t - t_2)) \right] + 1, \]  \hspace{1cm} (3.124)
\[ x_2(t) = -\alpha^2 \beta \left[ (t - t_1)e^{-\alpha (t-t_1)} - (t - t_2)e^{-\alpha (t-t_2)} \right]. \]  \hspace{1cm} (3.125)

Note that

\[ x_1'(t) < 0; \hspace{0.5cm} \forall t > \frac{t_2e^{\alpha t_2} - t_1e^{\alpha t_1}}{e^{\alpha t_2} - e^{\alpha t_1}}, \]  \hspace{1cm} (3.126)

i.e., \( t \to x_1(t) \) is eventually decreasing. Combining (3.57) and (3.126), and noting that \( x_1(t_2) > 1 \), we have:

\[ x_1(t) \geq 1; \hspace{0.5cm} \forall t > t_2 \]  \hspace{1cm} (3.127)

and, more generally,

\[ x_1(t) \geq 1; \hspace{0.5cm} \forall t \geq 0. \]  \hspace{1cm} (3.128)

\( (ii) \) \( \theta_3^2 > 4 \theta_4. \)
In this case, (3.52) can be written as:

\[
\begin{aligned}
x''_1(t) + \theta_3 x'_1(t) + \theta_4 x_1(t) &= \theta_2 + \theta_4 \\
x_1(t_2) &= k \left( \lambda_2 e^{\lambda_1(t_2 - t_1)} - \lambda_1 e^{\lambda_2(t_2 - t_1)} \right) - \beta + 1 ; \quad t > t_2. \\
x'_1(t_2) &= k \lambda_1 \lambda_2 \left( e^{\lambda_1(t_2 - t_1)} - e^{\lambda_2(t_2 - t_1)} \right)
\end{aligned}
\]  

(3.129)

A particular solution to (3.129) is given by

\[ x^P_1(t) = 1. \]  

(3.130)

The solution to the homogeneous problem associated with (3.129) is given by

\[ x^H_1(t) = c_1 e^{\lambda_1 t} + c_2 t e^{\lambda_2 t}, \]

where \( c_1 \) and \( c_2 \) are arbitrary real numbers whose values are determined by the initial conditions. Hence, the solution to (3.129) is given by:

\[ x_1(t) = x^H_1(t) + x^P_1(t) \]

\[ x_1(t) = c_1 e^{\lambda_1 t} + c_2 t e^{\lambda_2 t} + 1, \]  

(3.131)

where \( c_1 \) and \( c_2 \) satisfy,

\[
A \begin{bmatrix} c_1 e^{\lambda_1 t_2} \\ c_2 e^{\lambda_2 t_2} \end{bmatrix} = b,
\]  

(3.132)

with

\[
A = \begin{bmatrix} 1 & 1 \\ \lambda_1 & \lambda_2 \end{bmatrix}
\]  

(3.133)

and

\[
b = \begin{bmatrix} k \left( \lambda_2 e^{\lambda_1(t_2 - t_1)} - \lambda_1 e^{\lambda_2(t_2 - t_1)} \right) - \beta \\ k \lambda_1 \lambda_2 \left( e^{\lambda_1(t_2 - t_1)} - e^{\lambda_2(t_2 - t_1)} \right) \end{bmatrix}.
\]  

(3.134)

Note that

\[
\det A = \lambda_2 - \lambda_1.
\]  

(3.135)
Therefore, $A$ is invertible and its inverse is given by:

$$
A^{-1} = \begin{bmatrix}
\frac{\lambda_2}{\lambda_2 - \lambda_1} & -\frac{1}{\lambda_2 - \lambda_1} \\
\frac{\lambda_1}{\lambda_2 - \lambda_1} & \frac{1}{\lambda_2 - \lambda_1}
\end{bmatrix}.
$$

(3.136)

Then from (3.132), (3.134), and (3.136),

$$
\begin{bmatrix}
c_1 e^{\lambda_1 t_2} \\
c_2 e^{\lambda_2 t_2}
\end{bmatrix} = A^{-1} b.
$$

(3.137)

Consequently, we have

$$
c_1 = k\lambda_2 \left( e^{-\lambda_1 t_1} - e^{-\lambda_1 t_2} \right),
$$

(3.138)

$$
c_2 = -k\lambda_1 \left( e^{-\lambda_2 t_1} - e^{-\lambda_2 t_2} \right)
$$

(3.139)

Substituting (3.138) and (3.139) into (3.131) leads to

$$
x_1(t) = k \left[ (\lambda_2 e^{\lambda_1 (t-t_1)} - \lambda_1 e^{\lambda_2 (t-t_1)}) - (\lambda_2 e^{\lambda_1 (t-t_2)} - \lambda_1 e^{\lambda_2 (t-t_2)}) \right] + 1,
$$

(3.140)

and

$$
x_2(t) = k\lambda_1 \lambda_2 \left[ (e^{\lambda_1 t(t-t_1)} - e^{\lambda_2 (t-t_1)}) - (e^{\lambda_1 t(t-t_2)} - e^{\lambda_2 (t-t_2)}) \right].
$$

(3.141)

Note that

$$
x_1'(t) < 0; \quad \forall t > \frac{1}{\lambda_1 - \lambda_2} \ln \left( \frac{e^{-\lambda_2 t_1} - e^{-\lambda_2 t_2}}{e^{-\lambda_1 t_1} - e^{-\lambda_1 t_2}} \right),
$$

(3.142)

i.e., $t \to x_1(t)$ is eventually decreasing. Combining (3.57) and (3.142), and noting that $x_1(t_2) > 1$, we have:

$$
x_1(t) \geq 1; \quad \forall t > t_2
$$

(3.143)

and, more generally,

$$
x_1(t) \geq 1; \quad \forall t \geq 0.
$$

(3.144)

(iii) $\theta_3^2 < 4\theta_4$. 

32
In this case, (3.52) can be written as follows:

\[
\begin{aligned}
x''_1(t) + \theta_3 x'_1(t) + \theta_4 x_1(t) &= \theta_2 + \theta_4 \\
x_1(t_2) &= \beta e^{-\alpha(t_2-t_1)} \left[ \cos \nu(t_2-t_1) + \frac{\alpha}{\nu} \sin \nu(t_2-t_1) \right] - \beta + 1; \quad t > t_2, \\
x'_1(t_2) &= -\frac{\beta}{\nu} (\alpha^2 + \nu^2) e^{-\alpha(t_2-t_1)} \sin \nu(t_2-t_1)
\end{aligned}
\]  

(3.145)

where \( \alpha, \beta, \) and \( \nu \) are given by (3.71), (3.72), and (3.95), respectively. A particular solution to (3.145) is

\[
x_1^p(t) = 1.
\]  

(3.146)

The solution to the homogeneous problem associated with (3.145) is given by:

\[
x_1^H(t) = e^{-\alpha t} (c_1 \cos \nu t + c_2 \sin \nu t),
\]  

where \( c_1 \) and \( c_2 \) are arbitrary constants whose values are determined by the initial conditions. Hence,

\[
x_1(t) = x_1^H(t) + x_1^p(t) = e^{-\alpha t} (c_1 \cos \nu t + c_2 \sin \nu t) + 1,
\]  

(3.147)

where \( c_1 \) and \( c_2 \) satisfy

\[
A \begin{bmatrix} c_1 \\ c_2 \end{bmatrix} = b,
\]  

(3.148)

with

\[
A = \begin{bmatrix} \cos \nu t_2 & \sin \nu t_2 \\ -\alpha \cos \nu t_2 - \nu \sin \nu t_2 & \nu \cos \nu t_2 - \alpha \sin \nu t_2 \end{bmatrix}
\]  

(3.149)

and

\[
b = \begin{bmatrix} \beta e^{\alpha t_1} \left[ \cos \nu(t_2-t_1) + \frac{\alpha}{\nu} \sin \nu(t_2-t_1) \right] - \beta e^{\alpha t_2} \\ -\frac{\beta}{\nu} (\alpha^2 + \nu^2) e^{\alpha t_1} \sin \nu(t_2-t_1) \end{bmatrix}.
\]  

(3.150)

Note that

\[
det A = \nu \cos^2 \nu t_2 - \alpha \sin \nu t_2 \cos \nu t_2 + \nu \sin^2 \nu t_2 + \alpha \sin \nu t_2 \cos \nu t_2 \\
= \nu \cos^2 \nu t_2 + \nu \sin^2 \nu t_2
\]  

(3.151)
Therefore A is invertible, and

\[
A^{-1} = \begin{bmatrix}
\cos \nu t_2 - \frac{\alpha}{\nu} \sin \nu t_2 & -\frac{1}{\nu} \sin \nu t_2 \\
\frac{\alpha}{\nu} \cos \nu t_2 + \sin \nu t_2 & \frac{1}{\nu} \cos \nu t_2
\end{bmatrix}.
\]

(3.152)

Then from (3.148), (3.150), and (3.152),

\[
\begin{bmatrix}
c_1 \\
 c_2
\end{bmatrix} = A^{-1}b,
\]

(3.153)

that is,

\[
c_1 = \beta \left[ e^{\alpha t_1} \left( \cos \nu t_1 - \frac{\alpha}{\nu} \sin \nu t_1 \right) - e^{\alpha t_2} \left( \cos \nu t_2 - \frac{\alpha}{\nu} \sin \nu t_2 \right) \right]
\]

(3.154)

\[
c_2 = \beta \left[ e^{\alpha t_1} \left( \frac{\alpha}{\nu} \cos \nu t_1 + \sin \nu t_1 \right) - e^{\alpha t_2} \left( \frac{\alpha}{\nu} \cos \nu t_2 + \sin \nu t_2 \right) \right]
\]

(3.155)

Then, by plugging (3.154) and (3.155) into (3.147), we have

\[
x_1(t) = \beta \left[ e^{-\alpha(t-t_1)} \left( \cos \nu(t-t_1) + \frac{\alpha}{\nu} \sin \nu(t-t_1) \right) - e^{-\alpha(t-t_2)} \left( \cos \nu(t-t_2) + \frac{\alpha}{\nu} \sin \nu(t-t_2) \right) \right] + 1,
\]

(3.156)

\[
x_2(t) = -\frac{\beta}{\nu} \left( \alpha^2 + \nu^2 \right) \left( e^{-\alpha(t-t_1)} \sin \nu(t-t_1) - e^{-\alpha(t-t_2)} \sin \nu(t-t_2) \right) .
\]

(3.157)


**Remark 1.** We have not proved that \( x_1(t) > 0 \) for all \( t \geq 0 \) in the case where \( \theta_3^2 < 4\theta_4 \). However, our conjecture is that this property holds.

### 3.2.2 Properties of the Cerebral Blood Volume

We study in this section the properties of \( t \to x_3(t) \), the cerebral blood flow. It follows from the statement of the hemodynamic model (2.25) that this component of the state vector, \( t \to x_3(t) \), is the solution to the first-order initial value problem

\[
\begin{aligned}
x_3'(t) &= -\theta_3 x_3^5(t) + \theta_5 x_1(t) \\
x_3(0) &= 1
\end{aligned}
\]

(3.158)

where \( t \to x_1(t) \) represents the cerebral blood flow, i.e., the solution to (3.52). The next result pertains to the global existence and uniqueness of \( t \to x_3(t) \).
Proposition 1. Assume $\theta_3^2 \geq 4\theta_4$. Then the solution $t \to x_3(t)$ to the initial value problem given by (3.158) exists and is unique for all $t \geq 0$.

Proof. Using Cauchy-Lipschitz Theorem [32], we deduce that there is $t^* > 0$ such that $t \to x_3(t)$ exists uniquely for all $t \in [0, t^*)$. In addition, we have

$$x_3(t) > 0 \text{ for all } t \in [0, t^*). \quad (3.159)$$

We set

$$T^* = \sup \{t^* \mid x_3(t) > 0 \text{ for all } t \in [0, t^*)\}. \quad (3.160)$$

If $T^* = \infty$, then the solution exists for all $t \geq 0$, which concludes the proof of Theorem 3. Suppose $T^* < +\infty$. Then, necessarily,

$$x_3(T^*) = 0. \quad (3.161)$$

Let

$$x_{3d}(T^*) = \lim_{h \to 0^-} \frac{x_3(T^* + h) - x_3(T^*)}{h}. \quad (3.162)$$

Then, since $t \to x_3(t)$ decreases to zero, we must have

$$x_{3d}(T^*) < 0. \quad (3.163)$$

On the other hand, we have from the differential equation given by (3.158), that:

$$x_{3d}(T^*) = -\theta_5 x_3(T^*) + \theta_5 x_1(T^*). \quad (3.164)$$

Using (3.161) and (3.164), and since $x_1(t) > 0$ for all $t \geq 0$, we deduce that:

$$x_{3d}(T^*) > 0, \quad (3.165)$$

which contradicts (3.163). Therefore, $T^* = +\infty$, that is,

$$x_3(t) > 0; \quad \forall t \geq 0. \quad (3.166)$$

Remark 2. If $x_1(t) > 0$ for all $t \geq 0$ in the case where $\theta_3^2 < 4\theta_4$, then Proposition 1 as well as the following results hold for all values of $\theta_3$ and $\text{theta}_4$. 

35
Corollary 2. Assume $\theta_3^2 \geq 4\theta_4$. Then the solution $t \to x_3(t)$ to (3.158) satisfies

$$\lim_{t \to \infty} x_3(t) = 1.$$  \hfill (3.167)

Proof. Since $x_3(t) > 0$ for all $t \geq 0$, we can rewrite (3.158) as follows:

$$\begin{cases}
  x'_3(t) = ax_3(t)|x_3(t)|^\theta + f(t), \\
  x_3(0) = 1
\end{cases}$$

where

$$a = -\theta_5,$$  \hfill (3.169)

$$\theta = \theta_1 - 1,$$  \hfill (3.170)

and

$$f(t) = \theta_5x_1(t).$$  \hfill (3.171)

Observe that

$$\lim_{t \to \infty} f(t) = \lim_{t \to \infty} \theta_5x_1(t) = \theta_5.$$  \hfill (3.172)

Hence, we are in a position to apply Theorem 1 and conclude that:

$$\lim_{t \to \infty} x_3(t) = \left(-\frac{\theta_5}{-\theta_5}\right)^{1/\theta_1} = 1.$$  \hfill (3.173)

Proposition 2. Assume $\theta_3^2 \geq 4\theta_4$. Then the solution $t \to x_3(t)$ of the initial value problem given by (3.158) satisfies:

$$x_3(t) = 1 + O\left(e^{-\theta_1\theta_5t}\right) + O\left(e^{pt}\right); \quad \text{as } t \to \infty,$$  \hfill (3.174)

where

$$p = \begin{cases}
  -\alpha & \text{if } \theta_3^2 = 4\theta_4 \\
  \lambda_2 & \text{if } \theta_3^2 > 4\theta_4
\end{cases}$$  \hfill (3.175)

where $\alpha$ and $\lambda_2$ are given by (3.71) and (3.82), respectively.

Proof. Since $x_3(t) \to 1$ as $t \to \infty$ (see Corollary 2), then there is a continuously differen-
tiable function $t \to \xi(t)$ such that:

$$x_3(t) = 1 + \xi(t) \quad (3.176)$$

and

$$\lim_{t \to \infty} \xi(t) = 0. \quad (3.177)$$

Consequently, for $t > t_2$, since $x_1(t) \approx 1 + O(e^{pt})$, making the substitutions in the differential equation in (3.158),

$$\xi'(t) = -\theta_5(1 + \xi(t))^{\theta_1} + \theta_5 \left(1 + O(e^{pt})\right) \quad (3.178)$$

Thus,

$$\xi'(t) = -\theta_5(1 + \theta_1 \xi(t)) + O(\xi^2(t)) + \theta_5 + O(e^{pt}), \quad (3.179)$$

that is,

$$\xi'(t) = -\theta_1 \theta_5 \xi(t) + O(e^{pt}) + O(\xi^2(t)). \quad (3.180)$$

Therefore, we must have

$$\xi(t) = O(e^{-\theta_1 \theta_5 t}) + O(e^{pt}). \quad (3.181)$$

We then conclude the proof of (3.174) by combining (3.176) and (3.181). \qed

### 3.2.3 Properties of the Total Deoxyhemoglobin Content Level

Next, we analyze the existence and uniqueness of the total deoxyhemoglobin content level $t \to x_4(t)$, the solution of the first-order initial value problem

$$\left\{ \begin{array}{l}
x_4'(t) = \theta_5 \left( x_1(t) \frac{1 - (1 - \theta_6)^{1/x_1(t)}}{\theta_6} - x_4(t)x_3^{\theta_1 - 1}(t) \right), \\
x_4(0) = 1 \end{array} \right. \quad (3.182)$$

where $t \to x_1(t)$ is the cerebral blood flow and $t \to x_3(t)$ represents the cerebral blood volume analyzed in Sections 3.2 and 3.3, respectively.

**Theorem 2.** Assume $\theta_3^2 \geq 4 \theta_4$. Then the solution $t \to x_4(t)$ exists and is unique for all $t \geq 0$. In addition,

$$x_4(t) > 0 \text{ for all } t \geq 0. \quad (3.183)$$

**Proof.** From Lemma 5 and Proposition 1, respectively, we have $x_1(t) > 0$ and $x_3(t) > 0$ for all $t \geq 0$. Then (3.182) is a linear, first-order initial value problem whose coefficients are
defined for all \( t \geq 0 \). Therefore, \( t \rightarrow x_4(t) \) exists and is unique for all \( t \geq 0 \). Furthermore, since \( x_4(0) = 1 \), then there is \( t^* > 0 \) such that \( x_4(t) > 0 \) for all \( t \in [0, t^*] \). We set

\[
T^* = \sup \{ t^* \mid x_4(t) > 0 \text{ for all } t \in [0, t^*] \} .
\] (3.184)

If \( T^* = \infty \), then \( x_4(t) > 0 \) for all \( t \geq 0 \), which concludes the proof. Suppose \( T^* < +\infty \). Then we must have \( x_4(T^*) = 0 \). Let

\[
x_4'(T^*) = \lim_{h \to 0} \frac{x_4(T^* + h) - x_4(T^*)}{h} .
\] (3.185)

Then

\[
x_4'(T^*) < 0 .
\] (3.186)

On the other hand, it follows from the differential equation in (3.182) that:

\[
x_4'(T^*) = \theta_5 \left( x_1(T^*) \frac{1 - (1 - \theta_6)^{1/x_3(T^*)}}{\theta_6} - x_4(T^*)x_3^{1/(T^*)} \right) = \theta_5 x_1(T^*) \frac{1 - (1 - \theta_6)^{1/x_3(T^*)}}{\theta_6} > 0 ,
\] (3.187)

which contradicts (3.186). Therefore \( T^* = \infty \), that is, \( x_4(t) > 0 \) for all \( t \geq 0 \). \( \square \)

**Proposition 3.** Assume \( \theta_3^2 \geq 4\theta_4 \). Then for \( t \) large enough,

\[
x_4(t) = 1 + O \left( e^{-\theta_4 t} \right) + O \left( e^{\theta_4 t} \right) .
\] (3.188)

**Proof.** Recall that for \( t > t_2 \), \( x_1(t) \approx 1 + O \left( e^{\theta_4 t} \right) \) and \( x_3 = 1 + O \left( e^{-\theta_1 \theta_5 t} \right) + O \left( e^{\theta_4 t} \right) \). Making the appropriate substitutions in the differential equation in (3.182), we have that, for \( t > t_2 \),

\[
x_4'(t) = \theta_5 \left[ 1 + O \left( e^{\theta_4 t} \right) - x_4(t) \left( 1 + O \left( e^{-\theta_1 \theta_5 t} \right) + O \left( e^{\theta_4 t} \right) \right) \right] .
\] (3.189)

This equation can be solved using variation of parameters:

\[
x_4'(t) = -\theta_5 x_4(t) \left( 1 + O \left( e^{-\theta_1 \theta_5 t} \right) + O \left( e^{\theta_4 t} \right) \right)
\]

\[
\frac{x_4'(t)}{x_4(t)} = -\theta_5 \left( 1 + O \left( e^{-\theta_1 \theta_5 t} \right) + O \left( e^{\theta_4 t} \right) \right)
\]

\[
\ln |x_4(t)| = -\theta_5 \left( t + O \left( e^{-\theta_1 \theta_5 t} \right) + O \left( e^{\theta_4 t} \right) \right) + c
\]

\[
x_4(t) = K(t) \exp \left[ -\theta_5 \left( t + O \left( e^{-\theta_1 \theta_5 t} \right) + O \left( e^{\theta_4 t} \right) \right) \right]
\] (3.190)
Differentiating (3.190) with respect to $t$,

\[ x_4'(t) = K'(t) \exp \left[ -\theta_5 \left( t + O \left( e^{-\theta_1 t} \right) + O \left( e^{pt} \right) \right) \right] \\
- \theta_5 K(t) \exp \left[ -\theta_5 \left( t + O \left( e^{-\theta_1 \theta_5 t} \right) + O \left( e^{pt} \right) \right) \right] \left( 1 + O \left( e^{-\theta_1 t} \right) + O \left( e^{pt} \right) \right) \]

(3.191)

and making the substitution (3.190) in (3.191),

\[ x_4'(t) = K'(t) \exp \left[ -\theta_5 \left( t + O \left( e^{-\theta_1 \theta_5 t} \right) + O \left( e^{pt} \right) \right) \right] - \theta_5 x_4(t) \left( 1 + O \left( e^{-\theta_1 \theta_5 t} \right) + O \left( e^{pt} \right) \right). \]

(3.192)

Making the approximation

\[ \exp \left[ -\theta_5 \left( t + O \left( e^{-\theta_1 \theta_5 t} \right) + O \left( e^{pt} \right) \right) \right] \approx e^{-\theta_5 t} \]

(3.193)

and equating the right-hand sides of (3.190) and (3.192)

\[ K'(t) e^{-\theta_5 t} \approx \theta_5 + O \left( e^{pt} \right) \]
\[ K'(t) \approx \theta_5 e^{\theta_5 t} + O \left( e^{(p+\theta_5)t} \right) \]
\[ K(t) \approx e^{\theta_5 t} + O \left( e^{(p+\theta_5)t} \right) + c. \]

(3.194)

Plugging (3.194) into (3.190) and using (3.193) again, we have that, for $t > t_2$,

\[ x_4(t) \approx 1 + ce^{-\theta_5 t} + O \left( e^{pt} \right). \]

(3.195)

\[ \square \]

**Corollary 3.**

\[ \lim_{t \to \infty} x_4(t) = 1. \]

(3.196)

Corollary 3 follows directly from Proposition 3.

### 3.2.4 Properties of the BOLD Signal

Finally, we come to the BOLD signal:

\[ B(t) = \theta_7 \left[ 7\theta_6 \left( 1 - x_4(t) \right) + 2 \left( 1 - \frac{x_3(t)}{x_4(t)} \right) + (2\theta_6 - 0.2) \left( 1 - x_3(t) \right) \right] \]

(3.197)
Proposition 4. \( t \to B(t) \) is well-defined for all \( t \geq 0 \). Furthermore,

\[
B(t) = O(e^{\alpha t})
\]  
(3.198)

for large enough \( t \), where

\[
\alpha = \begin{cases} 
-\theta_1 \theta_5 & \text{if } \theta_1 > 1 \\
-\theta_5 & \text{if } \theta_1 \leq 1
\end{cases}
\]  
(3.199)

Proof. In view of (3.197), it is easy to see that \( B(t) \) exists for all \( t \geq 0 \) because \( x_3(t) \) and \( x_4(t) \) exist for all \( t \geq 0 \), and \( x_4 \) is strictly positive. For \( t > t_2 \), the rational term in (3.196) is

\[
\frac{x_4(t)}{x_3(t)} = \frac{1 + O(e^{-\theta_5 t})}{1 + O(e^{-\theta_5 t})} = \frac{1}{1 + O(e^{-\theta_5 t})}.
\]  
(3.200)

Expanding as a geometric series,

\[
\frac{1}{1 + O(e^{-\theta_5 t})} = 1 + O(e^{-\theta_1 \theta_5 t}) + \cdots
\]  
(3.201)

and therefore

\[
\frac{x_4(t)}{x_3(t)} = \left(1 + O(e^{-\theta_5 t})\right) \left(1 + O(e^{-\theta_1 \theta_5 t})\right) = 1 + O(e^{\alpha t}).
\]  
(3.202)

Then for \( t > t_2 \),

\[
B(t) = \theta_7 \left[ 7\theta_6 \left(1 - (1 - O(e^{-\theta_5 t})) + 2 \left(1 - (1 + O(e^{\alpha t}))\right) \right) + (2\theta_6 - 0.2) \left(1 - (1 - O(e^{-\theta_1 \theta_5 t}))\right) \right]
\]

\[
= \theta_7 \left[ 7\theta_6 O(e^{-\theta_5 t}) + 2O(e^{\alpha t}) + (2\theta_6 - 0.2) O(e^{-\theta_1 \theta_5 t}) \right]
\]

\[
= O(e^{-\theta_5 t}) + O(e^{\alpha t}) + O(e^{-\theta_1 \theta_5 t})
\]

\[
B(t) = O(e^{\alpha t}),
\]  
(3.203)

\[
\square
\]

Corollary 4.

\[
\lim_{t \to \infty} B(t) = 0
\]  
(3.204)

This result is an immediate consequence of Proposition 4.
3.3 Determination of the Jacobian Matrix of the Direct Mapping

Implementation of the Tikhonov-Regularized Newton Method requires solving at each iteration the equation

\[
(J_B^T J_B + \mu I) \delta \bar{z} = J_B^T (\bar{y} - y),
\]

(3.205)

where \( J_B \) is the Jacobian matrix of the BOLD Signal operator \( B \) and \( \bar{z} \) is the target parameters vector, that is \( \bar{z} = \bar{\theta} \) or \( \bar{z} = \bar{p} \). Without digressing too much toward the description and derivation of this equation (that is left for Section 4.1.1), we instead turn our attention here to the Jacobian matrix, \( J_B \). Indeed, accurate computation of the Jacobian matrix is essential for the stability as well as for the high convergence speed and computational efficiency of the regularized Newton Algorithm. Note that we have two choices for the target parameters vector, \( \bar{z} \). With this in mind, we compute the Jacobian first with respect to \( \bar{\theta} \), and then with respect to \( \bar{p} \).

In the first case, our goal is to build the Jacobian matrix of (2.24) with respect to \( \bar{\theta} \), the vector of biophysiological parameters of the hemodynamic model. For each component \( \theta_i \), \( i = 1, 2, \ldots, 7 \), of the vector,

\[
\frac{\partial B}{\partial \theta_i}(t) = \delta_{7,i} \left[ 7\theta_6 (1 - x_4(t)) + 2 \left( 1 - \frac{x_4(t)}{x_3(t)} \right) + 2 (\theta_6 - 0.2) (1 - x_3(t)) \right]
+ \delta_{6,i} \theta_7 \left[ 7 (1 - x_1(t)) + 2 (1 - x_3(t)) \right]
+ (1 - \delta_{7,i}) \theta_7 \left[ -7\theta_6 w_{4,i}(t) - 2 \left( \frac{w_{4,i}(t)}{x_3(t)} - \frac{w_{3,i}(t)x_4(t)}{x_3^2(t)} \right) - 2 (\theta_6 - 0.2) w_{3,i}(t) \right],
\]

(3.206)

where

\[
\delta_{j,i} = \begin{cases} 
1 & : i = j \\
0 & : i \neq j
\end{cases}
\]

(3.207)

and \( w_{j,i} = \frac{\partial x_j}{\partial \theta_i} \), whose values are found by differentiating the differential system

\[
A \left( \vec{x}(t), \vec{\theta}, \bar{p} \right) = \begin{cases} 
\dot{x}_1(t) = x_2(t) \\
\dot{x}_2(t) = \theta_2 u(t) - \theta_3 x_2(t) - \theta_4 (x_1(t) - 1) \\
\dot{x}_3(t) = \theta_5 \left( x_1(t) - x_3^\theta_1(t) \right) \\
\dot{x}_4(t) = \theta_5 \left( x_1(t) \frac{1 - (1 - \theta_6)^{1/x_1(t)}}{\theta_6} - x_4(t)x_3^{\theta_1-1}(t) \right)
\end{cases}
\]

(3.208)
and solving with initial value $\vec{w}_i(0) = 0$, that is, $\vec{w}_i = (w_{1,i}, w_{2,i}, w_{3,i}, w_{4,i})^T$ is the solution of the following initial value problem:

$$
\begin{align*}
\dot{w}_{1,i}(t) &= w_{2,i}(t) \\
\dot{w}_{2,i}(t) &= -\theta_3 w_{2,i}(t) - \theta_4 w_{1,i}(t) + \delta_2 u(t) - \delta_3 x_2(t) - \delta_4 (x_1(t) - 1) \\
\dot{w}_{3,i}(t) &= \theta_5 [w_{1,i}(t) - \theta_1 x_3^{\theta_1-1}(t) w_{3,i}(t)] + \delta_5 (x_1(t) - x_3^{\theta_1}(t)) - \delta_{1,i} \theta_5 x_3^{\theta_1}(t) \ln(x_3(t)) \\
\dot{w}_{4,i}(t) &= \theta_5 \left[ \frac{w_{1,i}(t)}{\theta_6} \left( 1 - (1 - \theta_6)^{1/x_1(t)} \right) \left( \frac{1}{x_1(t)} \frac{(1 - \theta_6)^{1/x_1(t)} \ln(1 - \theta_6)}{x_1(t)} \right) - w_{4,i}(t) x_3^{\theta_1-1}(t) - (\theta_1 - 1) w_{3,i}(t) x_1(t) x_3^{\theta_1-2}(t) + \delta_{5,i} \frac{x_4(t)}{\theta_5^2} + \delta_{1,i} \left( (1 - \theta_6)^{1/x_1(t)} - x_1(t) \frac{1}{\theta_6} \left( 1 - (1 - \theta_6)^{1/x_1(t)} \right) \right) - \delta_1 x_4(t) x_3^{\theta_1-1}(t) \ln(x_3(t)) \right] \\

w_{1,i}(0) &= w_{2,i}(0) = w_{3,i}(0) = w_{4,i}(0) = 0
\end{align*}
$$

(3.209)

Then the Jacobian matrix is given by

$$
J_B = \begin{bmatrix}
\frac{\partial B}{\partial \theta_1}(t_1) & \frac{\partial B}{\partial \theta_2}(t_1) & \cdots & \frac{\partial B}{\partial \theta_7}(t_1) \\
\frac{\partial B}{\partial \theta_1}(t_2) & \frac{\partial B}{\partial \theta_2}(t_2) & \cdots & \frac{\partial B}{\partial \theta_7}(t_2) \\
\vdots & \vdots & \ddots & \vdots \\
\frac{\partial B}{\partial \theta_1}(t_{N_m}) & \frac{\partial B}{\partial \theta_2}(t_{N_m}) & \cdots & \frac{\partial B}{\partial \theta_7}(t_{N_m})
\end{bmatrix},
$$

(3.210)

where $N_m$ is the number of measurements taken.

Next, we build the Jacobian matrix of (2.24) with respect to $\vec{p} = (\bar{t}, a)^T$, the parameters
of the \( \text{On-Off} \) function

\[
u(t) = \chi \left( \frac{t - \bar{\ell}}{a} \right),\]

(3.211)

Differentiating (2.24) with respect to \( \bar{\ell} \) and setting \( \frac{\partial \bar{\ell}}{\partial \bar{\ell}} = \bar{\ell} \),

\[
\frac{\partial B}{\partial \bar{\ell}}(t) = -7\theta_7\theta_6 w_4(t) - 2\theta_7 \left( \frac{w_4(t)}{x_3(t)} - \frac{x_4(t)w_3(t)}{x_3^2(t)} \right) - (2\theta_7\theta_6 - 0.2\theta_7)w_3(t),
\]

(3.212)

where \( \bar{\ell}(t) \) is the solution to

\[
\begin{align*}
\dot{w}_1(t) &= w_2(t) \\
\dot{w}_2(t) &= \theta_2 \frac{\partial u}{\partial \bar{\ell}}(t) - \theta_3 w_2(t) - \theta_4 w_1(t) \\
\dot{w}_3(t) &= \theta_5 (w_1(t) - \theta_1 x_3^{\theta_1 - 1}(t) w_3(t)) \\
\dot{w}_4(t) &= \theta_5 \left( w_1(t) \frac{1 - (1 - \theta_6)^{1/x_1(t)}}{\theta_6} + \frac{w_1(t)}{x_1(t)} \left( \frac{1 - \theta_6}{\theta_6} \right) \ln(1 - \theta_6) \right) \\
&\quad \quad - \theta_5 (w_4(t) x_3^{\theta_1 - 1}(t) + (\theta_1 - 1) x_4(t) x_3^{\theta_1 - 2}(t) w_3(t)) \\

w_1(0) &= w_2(0) = w_3(0) = w_4(0) = 0
\end{align*}
\]

(3.213)

with

\[
\frac{\partial u}{\partial \bar{\ell}}(t) = -\frac{1}{a} (\delta(t - \bar{\ell}) + \delta(t - (\bar{\ell} + a))).
\]

(3.214)

Similar calculations can be done to show that

\[
\frac{\partial B}{\partial a}(t) = -7\theta_7\theta_6 w_4(t) - 2\theta_7 \left( \frac{w_4(t)}{x_3(t)} - \frac{x_4(t)w_3(t)}{x_3^2(t)} \right) - (2\theta_7\theta_6 - 0.2\theta_7)w_3(t),
\]

(3.215)
with $\vec{w} = \frac{\partial u}{\partial a}$ the solution to the system

$$
\begin{align*}
\dot{w}_1(t) &= v_2(t) \\
\dot{w}_2(t) &= \theta_2 \frac{\partial u}{\partial a}(t) - \theta_3 w_2(t) - \theta_4 w_1(t) \\
\dot{w}_3(t) &= \theta_5 (w_1(t) - \theta_1 x_3^{\theta_1-1}(t)w_3(t)) \\
\dot{w}_4(t) &= \theta_5 \left( w_1(t) \frac{1 - (1 - \theta_6)^{1/x_1(t)}}{\theta_6} + \frac{w_1(t)}{x_1(t)} \frac{(1 - \theta_6)^{1/x_1(t)}}{\theta_6} \ln(1 - \theta_6) \right) \\
&\quad - \theta_5 (w_4(t)x_3^{\theta_1-1}(t) + (\theta_1 - 1)x_4(t)x_3^{\theta_1-2}(t)w_3(t)) \\
\end{align*}
$$

(3.216)

$$
\begin{align*}
w_1(0) = w_2(0) = w_3(0) = w_4(0) = 0
\end{align*}
$$

and

$$
\frac{\partial u}{\partial a}(t) = \frac{t - t}{a^2} \left( \delta(t - \bar{t}) + \delta(t - (\bar{t} + a)) \right),
$$

(3.217)

where $\bar{t} = t_1$, and $a = t_2 - t_1$. Then the Jacobian matrix is given by

$$
J_B = \begin{bmatrix}
\frac{\partial B}{\partial t}(t_1) & \frac{\partial B}{\partial a}(t_1) \\
\frac{\partial B}{\partial t}(t_2) & \frac{\partial B}{\partial a}(t_2) \\
\vdots & \vdots \\
\frac{\partial B}{\partial t}(t_{N_m}) & \frac{\partial B}{\partial a}(t_{N_m})
\end{bmatrix}.
$$

(3.218)

Remark 3. The Jacobian for the Gaussian input function is constructed in the same manner, by making the appropriate substitutions:

$$
u(t) = 2 \exp \left( -\frac{(t - \bar{t})^2}{2a^2} \right).
$$

(3.219)

$$
\frac{\partial u}{\partial t} = \frac{2}{a^2} \exp \left( -\frac{(t - \bar{t})^2}{2a^2} \right) (t - \bar{t}) = \frac{(t - \bar{t})}{a^2} u(t).
$$

(3.220)

and

$$
\frac{\partial u}{\partial a} = \frac{2(t - \bar{t})}{a^3} \exp \left( -\frac{(t - \bar{t})^2}{2a^2} \right) = \frac{(t - \bar{t})^2}{a^3} u(t).
$$

(3.221)
Chapter 4

Solution Methodology

One of the greatest challenges in constructing a realistic model that describes event-related brain activity is the estimation of the model parameters and hidden states. Pioneering work was carried out by Karl Friston, who proposed the use of Volterra Kernel expansion to characterize the hemodynamic response [12] and, subsequently, introduced Bayesian inference as a tool for parameter estimation in fMRI studies [7]. The use of a local linearization filter by Riera, et al. [30] was significant because it accounted for possible physiological noise, whereas the previous methods had only accounted for errors in the measurements. Different types of filters were developed in the wake of Riera’s work, including particle filtering [20], particle smoothing [26], and unscented Kalman filtering [18].

The major drawback of these methods is their reliance on some a priori knowledge about the values of the model parameters. This poses a problem because, in practice, these parameters cannot be measured within any interval of confidence. In addition, these methods can estimate the neuronal activation without knowing the input, i.e., the external stimulus [13]. Recently, Khoram et al. developed the Regularized Newton Algorithm equipped with a cubature Kalman filter (RNA-CKF) [21]. In spite of this method’s efficiency and superiority over its predecessors (including the standalone CKF [1]) for determining the biophysiological parameters only, the RNA-CKF method seems to fail dramatically when applied to estimate simultaneously the biophysiological parameters and the external stimulus characteristics.

In this chapter we introduce a new method for calibrating the hemodynamic model (2.23). The method makes use of the previously developed RNA-CKF algorithm to estimate the biophysiological parameters of the system and the characteristic parameters of the considered external stimulus. Specifically, we use the RNA-CKF algorithm in a multi-step framework to successively predict and correct each set of parameters separately. In Section 4.1, we describe the RNA-CKF algorithm. Section 4.2 is devoted to describing the proposed new solution for solving the inverse problem. In Section 4.3, we address issues pertaining to the numerical implementation of the proposed algorithm.

4.1 The RNA-CKF Method

Some of the most commonly used inversion methods in fMRI studies include dynamic expectation Modeling (DEM), CKF, sequential Monte Carlo (SMC), and square root cuba-
ture Kalman filtering (SCKF) [13]. A common trait of these methods is that they all rely on some a priori information about the parameters of the system. Since, in practice, these parameters are not directly measurable, there is a clear need for a method that is capable of estimating the parameters absent knowledge of their true values. The RNA-CKF algorithm is a procedure that successively employs a Tikhonov-regularized Newton technique, called RNA [21], to address the nonlinearity of the problem, and a cubature Kalman filter (CKF) [1] to handle the effect of the noise. As is demonstrated by Khoram, et al. [21], the RNA-CKF method is both efficient and accurate in estimating the biophysiological parameters without any prior knowledge of the true values. In this section, we describe these two components of the considered RNA-CKF algorithm.

4.1.1 The Regularized Newton Algorithm

The inverse problem given by (2.25) consisting of determining the parameters of the system corresponding to a given BOLD signal is a difficult one to solve. Specifically, the problem is nonlinear and ill-posed in the sense of Hadamard [16], which causes difficulties from a numerical standpoint. In order to remedy these issues, the iterative Newton method—which addresses the nonlinearity of the problem—is equipped with a Tikhonov-type regularization procedure to account for the ill-posedness and restore the stability of the problem.

At iteration \( m \), the standard Newton method requires solving the following linear system:

\[
J_B^{(m)} \delta \bar{z}^{(m)} = \bar{y} - y^{(m)}
\]

and updating

\[
\bar{z}^{(m+1)} = \bar{z}^{(m)} + \delta \bar{z}^{(m)}
\]

for the next iteration. \( J_B \) is the Jacobian of the matrix of the BOLD signal (2.22), given by:

\[
[J_B]_{i,j} = \frac{\partial B}{\partial z_j} \left( \bar{\theta}^{(m)}, \bar{\theta}^{(m)}; \bar{z}^{(m)} \right)
\]

for \( i = 1, 2, \ldots, N_m, j = 1, 2, \ldots, N_z^{(m)} \). \( \bar{z} \) is the target parameters vector (\( \bar{z} = \bar{\theta} \) or \( \bar{z} = \bar{p} \)). \( N_z^{(m)} \) represents the size of \( \bar{z} \) at iteration \( m \) (\( N_z^{(m)} = 7 \) if \( \bar{z} = \bar{\theta} \), \( N_z^{(m)} = 2 \) if \( \bar{z} = \bar{p} \)). Note that for \( N_m > 7 \), which is the case in any practical situation, the system given by (4.1) is overdetermined. Thus, we solve the system in the least squared sense:

\[
J_B^{T(m)} J_B^{(m)} \delta \bar{z}^{(m)} = J_B^{T(m)} (\bar{y} - y^{(m)})
\]
Another problem arises here in the fact that (4.4) is ill-conditioned. Therefore, we add a Tikhonov regularization procedure so that, at iteration $m$, we solve the following linearized system:

$$
(J_B^T(m) J_B(m) + \mu I) \delta \tilde{z}^{(m)} = J_B^T(m) (\tilde{y} - y^{(m)})
$$

(4.5)

where $I$ is the identity matrix and $\mu$ is the Tikhonov regularization parameter, whose value is selected using a trial and error procedure.

### 4.1.2 The Cubature Kalman Filter

The Kalman filter is a set of mathematical equations that provides an efficient recursive solution of the least square method. The key aspect, which makes the Kalman filter a powerful tool, is its ability to support estimations of past, present, and future states. In addition, it can do so when the precise nature of the modeled system is unknown. Another feature that distinguishes the Kalman filter from other parameter estimation methods is its recursive nature, that is, at each time step, the Kalman filter refines the previous estimate by incorporating new information from the model and from the output [23, 21].

The Kalman filter assumes that the dynamical system to which it is applied is linear. The hemodynamic model given by (2.23), however, is nonlinear. With this in mind, we turn to the cubature Kalman filter (CKF), which was designed in the Kalman filtering framework to handle such nonlinear systems. Along with being nonlinear, the CKF procedure is derivative-free, and the number of points of integration—called the cubature points—increases linearly with the dimension of the state vector, $\vec{x}$. Specifically, the number of cubature points $m = 2n$, where $n$ is the size of the state vector. In this case, $n = 4$, i.e., the number of cubature points $m = 8$. The CKF algorithm evaluates the BOLD signal in two steps: (i) a time update step and (ii) a measurement update step.

#### Time Update

In the time update step, predicted estimates of the state vector and its associated error covariance are delivered for the next time step. Assume that the state vector $\vec{x}_j$ and covariance $P_j$ have been computed for $j = 0, 1, \ldots, t$. Then the state vector and covariance for the next time step, $\vec{x}_{t+1}$, $P_{t+1}$, respectively, are computed by first finding predicted estimates $\tilde{\vec{x}}_{t+1}$ and $\tilde{P}_{t+1}$ as follows:

1. We begin by evaluating the cubature points,

$$
\tilde{c}_{i,t} = S_t \vec{c}_i + \vec{x}_t; \quad i = 1, 2, \ldots, 8
$$

(4.6)
where \( S_t \) is computed by a Cholesky factorization of \( P_t \), that is,
\[
P_t = S_t S_t^T,
\]
(4.7)
and \( \xi_i \) is the \( i \)th column of the cubature points matrix \( \xi \) given by:
\[
\xi = \begin{bmatrix}
2 & 0 & 0 & 0 & -2 & 0 & 0 & 0 \\
0 & 2 & 0 & 0 & 0 & -2 & 0 & 0 \\
0 & 0 & 2 & 0 & 0 & 0 & -2 & 0 \\
0 & 0 & 0 & 2 & 0 & 0 & 0 & -2 \\
\end{bmatrix}
\]
(4.8)

2. Next, we evaluate the process at the cubature points to obtain the propagated cubature points at time \( t + 1 \), which requires solving the following differential system:
\[
\begin{cases}
\dot{\vec{z}}_i = A(\vec{\theta}, \vec{p}; \vec{z}_i) \\
\vec{z}_{i,t} = \vec{c}_{i,t} 
\end{cases}
; \quad i = 1, 2, \ldots, 8,
\]
(4.9)
where \( A \) is given by (2.13).

3. The average of the cubature points found in step 2 serves as a prediction for the state at time \( t + 1 \), that is,
\[
\hat{\vec{x}}_{t+1} = \frac{1}{8} \sum_{i=1}^{8} \vec{z}_{i,t+1}
\]
(4.10)

4. The time update step ends with the calculation of the predicted error covariance, \( \hat{P}_{t+1} \):
\[
\hat{P}_{t+1} = \frac{1}{m} \sum_{i=1}^{8} \vec{z}_{i,t+1} \vec{z}_{i,t+1}^T - \hat{\vec{x}}_{t+1} \hat{\vec{x}}_{t+1}^T + Q_{t+1},
\]
(4.11)
where \( Q_{t+1} \) is the process noise covariance at time \( t + 1 \) defined in Chapter 2.

**Measurement Update**

The measurement update step can be thought of as the correction step, that is, in this step we correct the predicted values given by (4.10) and (4.11), in order to evaluate the BOLD signal at time \( t + 1 \). The measurement update goes as follows:

1. We begin by correcting \( \hat{\vec{x}}_{t+1}^{\text{corr}} \) to obtain \( \vec{x}_{t+1} \). To do so, we first evaluate the predicted
cubature points,
\[
\tilde{c}_{i,t+1} = \hat{S}_{t+1} \xi_i + \hat{x}_{t+1}; \quad i = 1, 2, \ldots, 8
\]  \hfill (4.12)

where \( \hat{S}_{t+1} \) is once again computed by the Cholesky factorization of \( \hat{P}_{t+1} \), that is,
\[
\hat{P}_{t+1} = \hat{S}_{t+1} \hat{S}_{t+1}^T. \tag{4.13}
\]

Next, and similarly to the predicted state vector, we obtain the predicted BOLD signal at time \( t + 1 \) by averaging the BOLD signal over the predicted cubature points (4.12):
\[
\hat{y}_{t+1} = \frac{1}{8} \sum_{i=1}^{8} B(\theta, \bar{p}; \tilde{c}_{i,t+1}). \tag{4.14}
\]

Using (4.10) and (4.14), we get the corrected value of \( \bar{x}_{t+1} \), given by:
\[
\bar{x}_{t+1} = \hat{x}_{t+1} + (\hat{y}_{t+1} - \hat{y}_{j+1}) \vec{W}_{t+1}, \tag{4.15}
\]

where \( \hat{y}_{t+1} \) is the measured BOLD signal at time \( t + 1 \), \( \vec{W}_{t+1} \) is the “Kalman gain” at time \( t + 1 \), given by:
\[
\vec{W}_{t+1} = M_{t+1}^{-1} \vec{N}_{t+1}, \tag{4.16}
\]

with
\[
M_{t+1} = \frac{1}{8} \sum_{i=1}^{8} \left( B(\theta, \bar{p}; \tilde{c}_{i,t+1}) \right)^2 - \hat{y}_{t+1}^2 + R_{t+1}, \tag{4.17}
\]

the innovation covariance, \( R_{t+1} \) the measurement noise covariance at time \( t + 1 \) as defined in Chapter 2, and
\[
\vec{N}_{t+1} = \frac{1}{8} \sum_{i=1}^{8} B(\theta, \bar{p}; \tilde{c}_{i,t+1}) \tilde{z}_{i,t+1} - \hat{y}_{t+1} \hat{x}_{t+1} \tag{4.18}
\]

is the cross-covariance vector.

2. Next, using (4.11), (4.16), and (4.17), we get the corrected error covariance:
\[
P_{t+1} = \hat{P}_{t+1} - M_{t+1} \vec{W}_{t+1}^2 \vec{W}_{t+1}^T \tag{4.19}
\]
3. Finally, we compute the corrected BOLD signal at time $t + 1$ as follows:

$$y_{t+1} = B \left( \vec{\theta}, \vec{p}; \vec{x}_{t+1} \right)$$  (4.20)

### 4.2 The Proposed Solution Methodology: A Multi-Step Strategy

As demonstrated in [21] the RNA-CKF algorithm is a very powerful tool for estimating the biophysiological parameters only. The problem with this method is that it relies on knowledge of the nature of the external stimulus characteristics, i.e., the exact values of the parameters vector $\vec{p}$ of the input function $u$. Since, in practice, this information may not be readily available, it is important to be able to identify both the biophysiological parameters $\vec{\theta}$ and the external stimulus characteristics $\vec{p}$. As illustrated in Fig. 5.1, RNA-CKF seems to fail dramatically when faced with the task of estimating both sets of parameters. Indeed, the method computed the parameters with a relative error of about 48% after 122 iterations—clearly an unacceptable level of accuracy as well as efficiency.

In view of these disappointing results, there is a clear need for a new algorithm that is capable of estimating simultaneously the biophysiological parameters of the hemodynamic model and the characteristics of the external stimulus. However, we should not dismiss the RNA-CKF algorithm altogether. After all, the results in [21] clearly demonstrate the algorithm’s ability to estimate the biophysiological parameters alone. Similarly, assuming knowledge of the biophysiological parameters, the RNA-CKF successfully estimates the parameters of the external stimulus, that is, the vector $\vec{p}$ of the input function $u$. With this in mind, we propose a new approach to solve the inverse problem given by (2.25). It consists of applying RNA-CKF in a multi-stage strategy to determine successively the bio-

![Figure 4.1: Parameter Values: Target (black) vs. Computed with RNA-CKF (red).](image)
physiological parameters, \( \tilde{\theta} \), and the control input parameters, \( \tilde{p} \). This iterative procedure—rather than searching for all the parameters simultaneously—consists of freezing the values of one parameter vector (either \( \tilde{\theta} \) or \( \tilde{p} \)), and updating the values of the other vector using the RNA-CKF algorithm. This process can be summarized as follows:

- **Step 0 (Initialization).** Start with a random initial guess \((\tilde{\theta}^{(0)}, \tilde{p}^{(0)})\). This step can be viewed as a random prediction of the biophysiological parameters \( \tilde{\theta} \) and the control function characteristics \( \tilde{p} \).

- **Step 1 (Update the Control Function Parameters).** Apply TNM-CKF to correct \( \tilde{p}^{(0)} \) and obtain \( \tilde{p}^{(m_1)} \), the updated values of the control function characteristics delivered by TNM-CKF at convergence or stagnation.

- **Step 2 (Update the Initial Guess).** Replace the current initial guess by the computed values, that is:
  \[
  (\tilde{\theta}^{(0)}, \tilde{p}^{(0)}) \leftarrow (\tilde{\theta}^{(0)}, \tilde{p}^{(m_1)}).
  \]

- **Step 3 (Update the Biophysiological Parameters).** Apply TNM-CKF to correct \( \tilde{\theta}^{(0)} \) and obtain \( \tilde{\theta}^{(m_1)} \), the updated values of the biophysiological parameters delivered by TNM-CKF at convergence or stagnation.

- **Step 4 (Update the Initial Guess).** Replace the current initial guess by the computed values, that is:
  \[
  (\tilde{\theta}^{(0)}, \tilde{p}^{(0)}) \leftarrow (\tilde{\theta}^{(m_1)}, \tilde{p}^{(0)}).
  \]

- **Step 5.** Go to Step 1 if the relative residual, in the Euclidean norm, on the BOLD signal is higher than a prescribed tolerance (the noise level).

Note that the convergence/stagnation of the algorithm is determined by comparing the relative residual of the BOLD signal, in the Euclidean norm, to the noise level.

### 4.3 Numerical Implementation of the Proposed Algorithm

The numerical implementation of the proposed solution methodology is, to some extent, straightforward and similar to the implementation of the standard RNA-CKF [21]. The only issue that deserves a special attention, in the context of the finite difference discretization, is the computation of the Jacobian entries given by (4.3) when updating the control function parameters, that is, when \( \tilde{z} = \tilde{p} \). Indeed, this computation requires the derivative of the
control input function which gives rise to the Dirac function $\delta$, as illustrated in Fig. 4.2. More specifically, we have:

$$\frac{\partial u}{\partial t} = -\frac{1}{a} (\delta(t - \bar{t}) - \delta(t - (\bar{t} + a))) \quad (4.23)$$

and

$$\frac{\partial u}{\partial a} = -\frac{t-\bar{t}}{a^2} \left(\delta(t - \bar{t}) - \delta(t - (\bar{t} + a))\right), \quad (4.24)$$

where $\bar{t} = T_{on}$, and $a = T_{off} - T_{on}$. The numerical computation of the Dirac delta function when evaluating the Jacobian entries is performed in two stages [33]. First, we approximate the Dirac at a given time $t^*$ by the following Gaussian function:

$$\delta(t - t^*) \approx \frac{1}{\Delta t \sqrt{2\pi}} \exp\left(-\frac{(t - t^*)^2}{2\Delta t^2}\right) \quad (4.25)$$

This approximation has the following two desirable features:

- The integral $\int_{-\infty}^{\infty} \delta(t) dt = 1$ for any choice of $\Delta t$.
- $\lim_{\Delta t \to 0} \frac{1}{\Delta t \sqrt{2\pi}} \exp\left(-\frac{t^2}{2\Delta t^2}\right) = \delta(t)$

Then, we use the values of the Gaussian function (4.25) at time $t_i$, as illustrated in Fig. 4.3.

Figure 4.2: $\frac{\partial u}{\partial t}$ with $\bar{t} = 7$, $a = 30$.

Figure 4.3: Numerical approximation of the Dirac delta function by the Gaussian function (12) at $t^* = 0$, $\Delta t = 0.4s$, and 21 values measured.
In this chapter, we present numerical results to demonstrate the ability of the proposed solution methodology to calibrate the brain response model. These results have been obtained by performing a numerical investigation in which both synthetic and real fMRI measurements have been used. The real data correspond to a finger-tapping experiment performed at Nationwide Children’s Hospital, Columbus, OH.

5.1 Performance Assessment with Synthetic Data

We present, in this section, the results of the numerical study we have conducted using synthetic data, that is, the BOLD signal measurements were created by solving the forward problem HDM (2.23) with a given set of parameters. Two sets of experiments have been performed that differ only by the considered external stimulus. In both cases, the forward problem HDM (2.23) was solved using Runge-Kutta order 4 [14]. It is important to note that a different solver—the Fehlberg method [14]—was used in the inversion scheme, in order to avoid the “inverse crime” [6].

5.1.1 Results with an On-Off Input

In this section, the synthetic BOLD signal measurements were generated using an On-Off control function, given by (3.53). The noise-free BOLD signal (Fig. 5.1) was computed by applying the Runge-Kutta method of order four [14] to the direct problem HDM (2.23), for the values of the biophysiological parameters $\vec{\theta}^*$ reported in Table 5.1 and the values of the control function characteristics $\vec{p}^*$ reported in Table 5.2. Since, in practice, the BOLD signal is measured at a prescribed time, we used 181 values measured every 0.4 seconds, which corresponds to a brain activation over a period of 72 seconds. We present the results of three numerical experiments.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>$\theta_1$</th>
<th>$\theta_2$</th>
<th>$\theta_3$</th>
<th>$\theta_4$</th>
<th>$\theta_5$</th>
<th>$\theta_6$</th>
<th>$\theta_7$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target ($\vec{\theta}^*$)</td>
<td>0.45</td>
<td>0.6</td>
<td>0.4</td>
<td>0.15</td>
<td>0.4</td>
<td>0.3</td>
<td>1.05</td>
</tr>
<tr>
<td>Initial Guess ($\vec{\theta}^{(0)}$)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 5.1: Biophysiological Parameters: Target vs. Initial Values, Case of an On-Off Stimulus

53
<table>
<thead>
<tr>
<th>Parameters</th>
<th>$T_{on}$</th>
<th>$T_{off}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target ($\bar{p}^*$)</td>
<td>7</td>
<td>37</td>
</tr>
<tr>
<td>Initial Guess ($\bar{p}^{(0)}$)</td>
<td>10</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 5.2: Control Function Characteristics: Target vs. Initial Values, Case of an On-Off Stimulus

Figure 5.1: Synthetic BOLD signal corresponding to the On-Off control input.

Experiment 1:

The proposed algorithm was tested by adding 5%, 10%, 20%, and 30% white noise to the synthetic signal, as depicted in Fig. 5.2, in order to demonstrate the robustness and efficiency of the proposed method in the presence of noise. Note that the last two cases are considered extreme scenarios since, in practice, the errors associated with measurement do not exceed 10%. The results of the experiments with these varying levels of noise are given in Figs. 5.3-5.5. The results seem to indicate that we have a very efficient and accurate solution methodology. The following observations are noteworthy:

- At convergence, the proposed algorithm delivers a very accurate estimation of the parameters, even in the presence of high noise levels. For example, in the case of 20% noise on the BOLD signal measurements, the control input parameters $\bar{p}$ are estimated with a relative error of about 1%, and the biophysiological parameters $\bar{\theta}$ are estimated with a relative error of about 16% (see Fig. 5.3 (c)). This appears to be an excellent accuracy level considering the relatively high noise level.

- The algorithm also delivers a highly accurate BOLD signal. In the case of 20% noise on the measurements, the BOLD signal is computed with a 6% relative error, as shown in Fig. 5.4 (c). This again appears to be an excellent accuracy level consider-
Experiment 2:

Next, we perform a numerical experiment with the same levels of noise on the BOLD signal measurements as in Experiment 1, that is, with 5%, 10%, 20%, and 30% noise added, but with an additional 5% noise added to the initial state, $\bar{x}_0$. Noise on the initial state corresponds to the situation where the brain is not fully “at rest.” The corresponding results
Figure 5.3: Target parameters (black) vs. estimated parameters using Multi-Step method (red). Case of an *On-Off* stimulus, Experiment 1: Different noisy measurements, no noise on the initial state $\bar{x}_0$ and the system ($\nu_t = 0$).
Figure 5.4: Target BOLD signal (solid-black) vs. reconstructed BOLD signal using Multi-Step method (dashed-red). Case of an On-Off stimulus, Experiment 1: Different noisy measurements, no noise on the initial state $\bar{x}_0$ and the system ($\nu_t = 0$).
Figure 5.5: Convergence history of the Multi-Step method (dashed-red). Case of an On-Off stimulus, Experiment 1: Different noisy measurements, no noise on the initial state \( \vec{x}_0 \) and the system \((\nu_t = 0)\). A blue line between iterations means that \( \vec{\rho} \) was updated; a red line indicates that \( \vec{\theta} \) was updated. The horizontal line represents the level of noise on the synthetic BOLD signal.
are given in Figs. 5.6-5.8. The following observations are noteworthy:

- The results in this case indicate that the proposed algorithm is not sensitive to noise on the initial state. Indeed, in the case of 20% noise on the BOLD signal measurements and 5% noise on the initial state, similar results are obtained as in Experiment 1: the control input parameters \( \vec{p} \) are estimated with a relative error of about 1%, and the biophysiological parameters \( \vec{\theta} \) are estimated with a relative error of about 16% (see Fig. 5.6 (c)).

- The algorithm once again delivers a high level of accuracy in the corresponding BOLD signal. For example, in the case of 20% noise on the measurements, the BOLD signal is computed with a 6% relative error, as shown in Fig. 5.7 (c). This appears to be an excellent accuracy level considering the relatively high noise level.

- The algorithm appears to remain efficient in the presence of noise on the initial state. For example, Fig. 5.8 (c) reveals that, in the case of 20% noise on the BOLD signal measurements, convergence is reached after 4 steps with a total of 4 iterations only.

**Experiment 3:**

Finally, we duplicated the conditions in Experiment 2 (5%, 10%, 20%, and 30% noise on the BOLD signal measurements, 5% noise on the initial state), and 1% process noise—which corresponds to some uncertainty in the accuracy of the model—was added to the system. Figs. 5.9-5.11 demonstrate the robustness of the method, even in the presence of this process noise. The following observations are noteworthy:

- The proposed algorithm continues to deliver accurately the parameters of the system. For example, in the case of 20% noise on the BOLD signal measurements, 5% noise on the initial state, and 1% noise on the system, and the control input parameters \( \vec{p} \) are estimated with a relative error of about 1%, and the biophysiological parameters \( \vec{\theta} \) are estimated with a relative error of about 17% (see Fig. 5.9 (c)).

- The algorithm again delivers a high level of accuracy in the corresponding BOLD signal. For example, in the case of 20% noise on the measurements, the BOLD signal is computed with a 6% relative error, as shown in Fig. 5.10 (c). This appears to be an excellent accuracy level considering the high noise level.

- The algorithm continues to operate efficiently in the presence of the process noise.
Figure 5.6: Target parameters (black) vs. estimated parameters using Multi-Step method (red). Case of an On-Off stimulus, Experiment 2: Different noisy measurements, 5% noise on $\bar{x}_0$, and no noise on the system ($\nu_t = 0$).
Figure 5.7: Target BOLD signal (solid-black) vs. reconstructed BOLD signal using Multi-Step method (dashed-red). Case of an On-Off stimulus, Experiment 2: Different noisy measurements, 5% noise on $\vec{x}_0$, and no noise on the system ($\nu_t = 0$).
Figure 5.8: Convergence history of the Multi-Step method (dashed-red). Case of an On-Off stimulus, Experiment 2: Different noisy measurements, 5% noise on $\vec{x}_0$, and no noise on the system ($\nu_t = 0$). A blue line between iterations means that $\vec{p}$ was updated; a red line indicates that $\vec{\theta}$ was updated. The horizontal line represents the level of noise on the synthetic BOLD signal.
Figure 5.9: Target parameters (black) vs. estimated parameters using Multi-Step method (red). Case of an On-Off stimulus with different noisy measurements, 5% noise on $\vec{x}_0$, and 1% process noise.

For example, Fig. 5.11 (c) shows that, in the case of 20% noise on the BOLD signal, convergence is reached after 4 steps with a total of 6 iterations only.

Comparison with RNA-CKF

In this section, we use the results from one experiment in which 30% white noise was added to the synthetic BOLD signal measurements (Fig. 5.2 (d)) to compare the proposed algorithm to the previously developed RNA-CKF algorithm. The proposed algorithm clearly outperforms the RNA-CKF algorithm when applied to determine all the parameters at once. Indeed, RNA-CKF computed the parameters with a relative error of about 48% after 122 iterations, leading to poor performance and a very inaccurate computation of the
Figure 5.10: Target BOLD signal (solid-black) vs. reconstructed BOLD signal using Multi-Step method (dashed-red). Case of an On-Off stimulus with different noisy measurements, 5% noise on $\vec{x}_0$, and 1% process noise.
Figure 5.11: Convergence history of the Multi-Step method (dashed-red). Case of an *On-Off* stimulus with different noisy measurements, 5% noise on $\vec{x}_0$, and 1% process noise. A blue line between iterations means that $\vec{p}$ was updated; a red line indicates that $\vec{\theta}$ was updated. The horizontal line represents the level of noise on the synthetic BOLD signal.
5.1.2 Results with a Gaussian Input

In this section, the synthetic BOLD signal measurements (Fig. 5.13) were generated by once again applying the Runge-Kutta method of order four [14] to the direct problem HDM (2.23) for the values of the biophysiological parameters $\vec{\theta}^*$ reported in Table 5.3, with a Gaussian control function given by (2.2), and the values of the control function characteristics $\vec{p}^*$ reported in Table 5.4. For this study, the BOLD signal was computed with a time step of 1 second and a total of 61 data points. We present the results of three numerical experiments.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>$\theta_1$</th>
<th>$\theta_2$</th>
<th>$\theta_3$</th>
<th>$\theta_4$</th>
<th>$\theta_5$</th>
<th>$\theta_6$</th>
<th>$\theta_7$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target ($\vec{\theta}^*$)</td>
<td>0.34</td>
<td>0.54</td>
<td>0.65</td>
<td>0.38</td>
<td>0.98</td>
<td>0.32</td>
<td>0.04</td>
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<td>Initial Guess ($\vec{\theta}^{(0)}$)</td>
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<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 5.3: Biophysiological Parameters: Target vs. Initial Values, Case of a Gaussian Stimulus

Experiment 1:

White noise was added to the noise-free BOLD signal in the amounts of 5%, 10%, 20%, and 30%. Noisy measurements are given in Fig. 5.14, and results are presented in Figs. 5.15-5.18. The following observations are noteworthy:
Table 5.4: Control Function Characteristics: Target vs. Initial Values, Case of a Gaussian Stimulus

<table>
<thead>
<tr>
<th>Parameters</th>
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<th>$a$</th>
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</thead>
<tbody>
<tr>
<td>Target ($\hat{p}^*$)</td>
<td>25</td>
<td>$\sqrt{7}$</td>
</tr>
<tr>
<td>Initial Guess ($\hat{p}^{(0)}$)</td>
<td>20</td>
<td>2</td>
</tr>
</tbody>
</table>

- At convergence, the algorithm delivers a highly accurate estimation of the BOLD signal. For example, in the case of 10% noise on the BOLD signal measurements, we obtain a BOLD signal reconstruction with a relative error of approximately 4% (Fig. 5.15 (b)).

- Surprisingly, in the case of the Gaussian input, the parameters are estimated with a higher relative error. In the case of 10% noise on the BOLD signal measurements, the parameters are estimated with a relative error of about 15% on the stimulus characteristics, $\hat{\mu}$, and a relative error of about 46% on the biophysiological parameters, $\hat{\theta}$ (Fig. 5.16(b)). In spite of this striking discrepancy, the BOLD signal is very well reconstructed, as indicated previously.

- The convergence of the algorithm in the case of the Gaussian input is slower than in the case of the \textit{On-Off} stimulus. For example, in the case of 10% noise on the BOLD signal measurements, the algorithm converges after 21 iterations (Fig. 5.17 (b)). However, because of the computational time per iteration ($t << 1$ second), the number of iterations to convergence still results in a very fast computation of the BOLD signal.

**Experiment 2:**

Next, we perform a numerical experiment with the same levels of noise on the BOLD signal measurements as in Experiment 1, that is, with 5%, 10%, 20%, and 30% noise added, but with an additional 5% noise added to the initial state, $\vec{x}_0$. We make the following observations from the results in Figs. 5.18-5.20:

- The algorithm in this case still seems to be robust to noise on the initial state. With 10% noise on the measurements and 5% noise on the initial state, $\vec{x}_0$, the BOLD signal is reconstructed with a relative error of about 5% (Fig. 5.18 (b)).

- The parameters are again estimated with a high relative error. For the case of 10% noise on the BOLD signal measurements, we obtain a relative error of about 12% on $\hat{\mu}$ and 50% on $\hat{\theta}$ at convergence (Fig. 5.19 (b)).
Figure 5.14: Target BOLD signal (solid-black) and noisy BOLD signal measurements (dots-blue). Case of a Gaussian stimulus.
Figure 5.15: Target BOLD signal (solid-black) vs. reconstructed BOLD signal using Multi-Step method (dashed-red). Case of a Gaussian stimulus, Experiment 1: different noisy measurements, no noise on the initial state $\vec{x}_0$ and the system ($\nu_t = 0$).
Figure 5.16: Target parameters (black) vs. estimated parameters using Multi-Step method (red). Case of a Gaussian stimulus, Experiment 1: different noisy measurements, no noise on the initial state $\bar{x}_0$ and the system ($\nu_t = 0$)
Figure 5.17: Convergence history of the Multi-Step method (dashed-red). Case of a Gaussian stimulus, Experiment 1: different noisy measurements, no noise on the initial state $\vec{x}_0$ and the system ($\nu_t = 0$). A blue line between iterations means that $\vec{p}$ was updated; a red line indicates that $\vec{\theta}$ was updated. The horizontal line represents the level of noise on the synthetic BOLD signal.
Noise on the initial state does not adversely effect the efficiency of the algorithm in this case. With 10% noise on the BOLD signal measurements, for example, the algorithm converges after 19 iterations (5.20 (b)).

**Experiment 3:**

Finally, we duplicated the conditions in Experiment 2 (5%, 10%, 20%, and 30% noise on the BOLD signal measurements, 5% noise on the initial state), and 1% process noise was added to the system. The following observations are noteworthy:

- The algorithm also appears to be sensitive to noise on the system in the case of the Gaussian stimulus. With 10% noise on the measurements, 5% noise on the initial
Figure 5.19: Target parameters (black) vs. estimated parameters using Multi-Step method (red). Case of a Gaussian stimulus, Experiment 2: different noisy measurements, 5\% noise on $\vec{x}_0$, and no noise on the system ($\nu_t = 0$).
Figure 5.20: Convergence history of the Multi-Step method (dashed-red). Case of a Gaussian stimulus, Experiment 2: different noisy measurements, 5% noise on $\vec{x}_0$, and no noise on the system ($\nu_t = 0$). A blue line between iterations means that $\vec{p}$ was updated; a red line indicates that $\vec{\theta}$ was updated. The horizontal line represents the level of noise on the synthetic BOLD signal.
Figure 5.21: Target BOLD signal (solid-black) vs. reconstructed BOLD signal using Multi-Step method (dashed-red). Case of a Gaussian stimulus, Experiment 3: different noisy measurements, 5% noise on $\vec{x}_0$, and 1% process noise.

- The BOLD signal is reconstructed with a relative error of about 10% (Fig. 5.21 (b)).

- The process noise also affects the parameter estimation: For the case of 10% noise on the BOLD signal measurements, the parameters are estimated with a relative error of 20% on $\vec{p}$ and 56% on $\vec{\theta}$ (Fig. 5.22 (b)).

- The algorithm appears to be more efficient in the presence of the process noise. For example, in the case of 10% noise on the BOLD signal measurements, the algorithm converges after 7 iterations only (Fig. 5.23 (b)).
Figure 5.22: Target parameters (black) vs. estimated parameters using Multi-Step method (red). Case of a Gaussian stimulus, Experiment 3: different noisy measurements, 5% noise on $\vec{x}_0$, and 1% process noise.
Figure 5.23: Convergence history of the Multi-Step method (dashed-red). Case of a Gaussian stimulus, Experiment 3: different noisy measurements, 5% noise on $\vec{x}_0$, and 1% process noise. A blue line between iterations means that $\vec{p}$ was updated; a red line indicates that $\vec{θ}$ was updated. The horizontal line represents the level of noise on the synthetic BOLD signal.
5.2 Performance Assessment with Real Data

5.2.1 Description of the Data

The considered data have been obtained from an fMRI scan of a male subject instructed to complete a finger-tapping task at the Nationwide Children’s Hospital in Columbus, Ohio [7].

Scanning Sequences:

The fMRI experiment was performed with a 3.0T GE Medical Systems Signal Excite and the BOLD-sensitive T2*-weighted echo-planar (EPI) sequence [31] using an 8-channel array head RF coil. Scanning protocol included a screening brain MR scan, including sagittal T1-weighted and axial T2-weighted scans, to exclude any anatomic brain abnormality. The task was performed with the following parameters: TE = 35 ms; TR = 3 s; flip angle = 90° single shot; full k-space, 128x128 acquisition matrix with a field of view (FOV)=25.6 cm, generating an in-plane resolution of 2 mm and slice thickness of 8 mm with a max total of 20 axial slices. A total of 120 volumes (time points) were acquired.

Stimulation Protocol:

The subject was instructed to begin and stop finger tapping every 30 seconds. Head motion was restricted by firm cushions packed around the head and by use of a head strap. The On-Off cycle was repeated six times for each scanning plane.

Data Processing:

fMRI data preprocessing was carried out using FEAT (fMRI Expert Analysis Tool) Version 5.98, part of FSL (fMRIBs Software Library, www.fmrib.ox.ac.uk/fsl). Motion correction using MCFLIRT [19], mean-based intensity normalization of all volumes by the same factor, and temporal high-pass filtering (using 60 s) was then performed on the data as well as a spatial smoothing of 5 mm (Gaussian) were applied as pre-statistics processing. The time-series for each voxel was then extracted for further analysis. The final measurements are taken every 3 seconds over 72 seconds, for a total of 25 data points. Fig. 5.24 shows the final BOLD signal measurements.

5.2.2 Numerical Results

The same initial guesses have been used for $\bar{\theta}$ and $\bar{p}$ as in Section 5.1.1 (see Tables 5.5-5.6) to apply the proposed solution methodology to the real data set. In this experiment, we
make the following observations:

- Figs. 5.25-5.26 illustrate the efficiency of the proposed algorithm in estimating the parameters to fit the BOLD signal output, reaching a relative error of 6.2% after 6 steps, totaling 10 iterations only.

- Though the exact parameter values are not directly measurable, the computed parameter values given in Tables 5.5-5.6 fall well within the range of the parameter values found in [21].

<table>
<thead>
<tr>
<th>Parameters</th>
<th>$\theta_1$</th>
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<tr>
<td>Initial Guess ($\hat{\theta}^{(0)}$)</td>
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<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
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<tr>
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Table 5.5: Biophysiological Parameters: Initial Guess vs. Computed Values, Finger-tapping Data

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</thead>
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<tr>
<td>Computed Values ($\hat{\mathbf{p}}^{(m)}$)</td>
<td>7.0</td>
<td>36.9</td>
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</table>

Table 5.6: Control Function Characteristics: Initial Guess vs. Computed Values, Finger-tapping Data

![Figure 5.24: Real BOLD signal: 25 measured points.](image)
Figure 5.25: Convergence history using real data.

Figure 5.26: Real BOLD signal (solid-black) vs. computed BOLD signal after 6 steps (dashed-red).
Chapter 6

Conclusion

We have investigated, mathematically and numerically, the problem of estimating the biophysiological parameters of the hemodynamic model as well as the external stimulus characteristics from the knowledge of some BOLD signal measurements. Solving this inverse parameter estimation problem is a preliminary step toward better understanding and more effective monitoring of brain activity.

Mathematically, we have analyzed the properties of the solutions of a class of first-order, nonlinear ordinary differential equations, some of the results of which may be of independent interest. In addition, we have analyzed the properties of the solutions to the equations of the hemodynamic model.

Numerically, we have proposed an efficient solution methodology to estimate the biophysiological parameters and the external stimulus characteristics to fit the BOLD signal output of the hemodynamic model. This technique uses an existing technique, RNA-CKF, in a multi-stage strategy to estimate successively each set of parameters. The defining features of this method are its ability to perform without a priori knowledge on the parameter values, as well as its ability to retrieve both the biophysiological parameters and the external stimulus characteristics. The numerical results presented have demonstrated the robustness and efficiency of the proposed method. In addition, the new method has been implemented to calibrate the hemodynamic model using real data, that is, from actual fMRI images. Another advantage of the method is its lack of computational complexity, i.e., the proposed algorithm can be run on any simple laptop or desktop machine.

The work presented herein is rooted in an effort to help improve the understanding of brain activity, and can be considered as preliminary tools to detect and treat diseases caused by abnormal brain activity at early stages. Though these results are promising, there is still much that is not understood about the brain, and there remains much work to be done. One possible direction for such future work is to upgrade the mathematical model to include some chemical contribution. Specifically, there is great interest in understanding and modeling the role of glucose utilization during brain activation.
References


