Accepted Manuscript

Title: A novel approach to calibrate the Hemodynamic Model using functional Magnetic Resonance Imaging (fMRI) measurements

Author: Nafiseh Khoram Chadia Zayane Rabia Djellouli
Taous-Meriem Laleg-Kirati

PII: S0165-0270(16)00032-7
DOI: <http://dx.doi.org/doi:10.1016/j.jneumeth.2016.01.015>
Reference: NSM 7433

To appear in: *Journal of Neuroscience Methods*

Received date: 5-9-2015
Revised date: 11-1-2016
Accepted date: 12-1-2016

Please cite this article as: Nafiseh Khoram, Chadia Zayane, Rabia Djellouli, Taous-Meriem Laleg-Kirati, A novel approach to calibrate the Hemodynamic Model using functional Magnetic Resonance Imaging (fMRI) measurements, *Journal of Neuroscience Methods* (2016), <http://dx.doi.org/10.1016/j.jneumeth.2016.01.015>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

- An efficient solution methodology for estimating the parameters of the brain response model is proposed.
- This method distinguishes itself from existing calibrating techniques by employing intelligently (a) the Newton algorithm, (b) a Tikhonov regularization approach, and (c) a Kalman filtering procedure.
- Both synthetic and real fMRI measurements were used to assess the performance of this method.
- The fast convergence, the accuracy, and the robustness to the noise effect of this method are clearly demonstrated by the reported numerical results.
- This methods outperforms existing methods.

A novel approach to calibrate the Hemodynamic Model using functional Magnetic Resonance Imaging (fMRI) measurements

Nafiseh Khoram^a, Chadia Zayane^b, Rabia Djellouli^a, Taous-Meriem Laleg-Kirati^b

^a*Department of Mathematics & Interdisciplinary Research Institute for the Sciences, IRIS, California State University Northridge (CSUN), Northridge, USA.*

^b*Department of Applied Mathematics and Computational Science, King Abdullah University of Science and Technology (KAUST), KSA*

Abstract

Background

The calibration of the hemodynamic model that describes changes in blood flow and blood oxygenation during brain activation is a crucial step for successfully monitoring and possibly predicting brain activity. This in turn has the potential to provide diagnosis and treatment of brain diseases in early stages.

New Method

We propose an efficient numerical procedure for calibrating the hemodynamic model using some fMRI measurements. The proposed solution methodology is a regularized iterative method equipped with a Kalman filtering-type procedure. The Newton component of the proposed method addresses the nonlinear aspect of the problem. The regularization feature is used to ensure the stability of the algorithm. The Kalman filter procedure is incorporated here to address the noise in the data.

Results

Numerical results obtained with synthetic data as well as with real fMRI measurements are presented to illustrate the accuracy, robustness to the noise, and the cost-effectiveness of the proposed method.

Email addresses: nafiseh.khoram.25@my.csun.edu (Nafiseh Khoram), chadia.zayane@kaust.edu.sa (Chadia Zayane), rabia.djellouli@csun.edu (Rabia Djellouli), taousmeriem.laleg@kaust.edu.sa (Taous-Meriem Laleg-Kirati)

Comparison with Existing Method(s)

We present numerical results that clearly demonstrate that the proposed method outperforms the Cubature Kalman Filter (CKF), one of the most prominent existing numerical methods.

Conclusion

We have designed an iterative numerical technique, called the TNM-CKF algorithm, for calibrating the mathematical model that describes the single-event related brain response when fMRI measurements are given. The method appears to be highly accurate and effective in reconstructing the BOLD signal even when the measurements are tainted with high noise level (as high as 30%).

Keywords: Brain response, Balloon model, fMRI measurements, Nonlinear hemodynamic model, Parameter estimation, Newton method, Tikhonov regularization, Cubature Kalman filter

1. Introduction

Since its advent in the early 1990s, functional Magnetic Resonance Imaging (fMRI) has proven to be a powerful noninvasive tool for providing three-dimensional images of the brain per unit of time, which allows physicians to detect the activated regions in the brain. The principle of fMRI is relatively simple: it is a Magnetic Resonance Imaging (MRI) procedure imaging the brain over time. More specifically, it measures the brain activity by detecting associated changes in blood flow and produces three-dimensional images of the brain based on the Blood Oxygenation Level Dependent (BOLD) contrast [1]. Indeed, the BOLD signal is triggered by the variations of both the cerebral blood flow (CBF) and the cerebral metabolic rate of oxygen (CMRO₂). The BOLD signal reflects the decrease in the deoxyhemoglobin concentration at the site of the neural activity [2, 3].

Expressing the observed phenomena of the BOLD signal as the output of a mathematical model remains one of the most outstanding issues. Two main approaches have been so far adopted to address this issue: the General Linear Modeling (GLM) and the nonlinear biophysical modeling frameworks. In the GLM approach, statistical analysis tools are used to assess the convolution of the neural activity signal with a predefined convolution kernel called the Hemodynamic Response Function (HRF). Several basis functions have been used to represent HRF including Poisson functions [4], Gaussian functions

[5], Gamma functions [6, 7], and inverse Logit functions [8]. However, this class of methods is blind to the physiological aspects that underlie the BOLD transients and has the main drawback of excluding the nonlinear effects of the BOLD, as shown in [9, 10, 11, 12]. Due to these shortfalls, nonlinear biophysical modeling approaches emerged with the pioneer work of Buxton et al. [10]. Their model acknowledges – for the first time – the dependence of the BOLD signal on the variations of the normalized cerebral blood flow, volume, and deoxyhemoglobin content. Mandeville et al. [13] modified the suggested model by considering the venous compartment’s structure as a Balloon in which the stimulus, which induces a local neuronal activity, leads to an increase in blood flow [13]. However, the pathway to the latter phenomenon was not specified. Note that since this increase exceeds $CMRO_2$, it then reduces the concentration of deoxyhemoglobin, which in turn results in an increase in the magnetic resonance signal. The missing relationship between the neural activity and CBF dynamics was introduced for the first time in [14]. More specifically, assuming that the synaptic activity and the regional CBF are linearly dependent, the neurovascular coupling between the neuronal activity and CBF has been described with a linear second order differential equation. We must point out that mathematical models which take into account metabolic effect such that the glucose variations, have been also proposed in attempt to better describe the brain activity (see, e.g., [15]).

The construction of such a reliable nonlinear biophysical model, called the Hemodynamic Model (HDM), has raised the challenging question of determining or accurately estimating the biophysiological parameters, the hidden states, and ultimately the neural activity. To the best of our knowledge, the first important attempt was made by Friston et al. [14] who proposed a deterministic approach based on Volterra Kernel-type expansion to characterize the hemodynamic response. The bayesian framework was introduced in [16] so that the restriction induced by the use of temporal basis was replaced by Gaussian priors on the parameters. In addition, the nonlinear dynamic equation was also approximated using a bilinear equation to facilitate the likelihood maximization. Furthermore, in order to account for physiological noise, a Wiener process was added to the dynamics equation of the model proposed in [17]. More specifically, a Local Linearization Filter (LLF) based on a truncated Ito-Taylor expansion of the dynamics equation was employed to estimate both the state and the parameters of the Balloon model. It is interesting to note that the proposed approach uses a fixed number of radial basis functions to approximate the neural activity. Other attempts have

been made to infer model states and parameters using similar filtering approaches with various but limited successes. Examples of such approaches include the iterative extended Kalman filtering method coupled with simplex search method [18], the particle filtering method [19], the particle smoothing method [20], and the unscented Kalman filtering method [21]. Note that all these methods employ different strategies to add the prior knowledge that makes the estimation problem well-posed in the stability sense (see, e.g., [22]). For example, radial basis functions were adapted to express the input in [17], whereas Gaussian priors were used for the parameters in [23]. These small prior variances are needed to overcome the identifiability issues of some parameters. A nonlinear neural network method has also been used in [24] for the estimation of the states and input, and observer techniques have been tested for state and input estimation in [25, 26]. The cubature Kalman filter (CKF) appears to be among the most prominent parameter estimation techniques. The CKF method was originally designed by Arasaratnam and Haykin in [27] for solving nonlinear state estimation problems such as tracking a maneuvering aircraft. It was later applied by Havlicek et al. [23] to estimate the parameters of the Balloon model. The success of CKF in accurately estimating the parameters was however accomplished when applying this procedure in a pre-asymptotic convergence region, that is, when the values of initial guess of the parameters are the sought-after values tainted with a low noise level. In the absence of a priori knowledge on the parameters' values, which is the case in practice since these values are not measurable, the CKF procedure fails dramatically to estimate these parameters with a reasonable accuracy level, as demonstrated in this paper (see Figure 4 in Section 4.1.1). Given that, the quest for efficiently and accurately estimating the model parameters remains an ongoing effort of pressing importance.

We propose a new solution methodology for efficiently solving the problem of calibrating the Hemodynamic Model (HDM) [12] when BOLD signal measurements are given. This problem is formulated as an inverse problem that falls in the category of parameter identification of a dynamical system. It is a nonlinear and ill-posed problem in the sense of Hadamard [22]. For this reason, we propose a regularized Newton method equipped with a Kalman filtering type procedure. The Newton component of the proposed algorithm addresses the nonlinear aspect of the problem. The regularization feature is used to ensure the stability of the algorithm. The Kalman filter procedure is the Cubature Kalman Filter (CKF) [23]. It is incorporated here to address the noise in the data. We have conducted a numerical investi-

gation using synthetic data tainted with various noise levels to assess the performance of the proposed method. We present results to illustrate the potential of the proposed solution methodology to accurately and efficiently estimate the biophysiological parameters. These results clearly indicate that the proposed method outperforms the Cubature Kalman Filter (CKF) [23], and significantly extends the range of satisfactory convergence. Finally, we also present model calibration results obtained when using real fMRI measurements corresponding to two paradigms: a face repetition stimulus [28] and a finger tapping stimulus [24].

The remainder of this paper is organized as follows. We specify in Section 2 the nomenclature and assumptions used in this paper and we state the hemodynamic model as well as the corresponding inverse problem. Section 3 is devoted to the description of the proposed solution methodology. In Section 4, we present numerical results obtained by using both synthetic data and real fMRI measurements. Concluding remarks are presented in Section 5.

2. Problem Statement

2.1. Nomenclature and Assumptions

Throughout this paper, we adopt the following notations and assumptions:

- t is a positive number representing the time.
- $t \rightarrow f(t)$ is a real-valued function representing the cerebral blood flow.
- $t \rightarrow s(t)$ is a real-valued function representing the flow inducing signal.
- $t \rightarrow v(t)$ is a real-valued function representing the normalized cerebral blood volume.
- $t \rightarrow q(t)$ is a real-valued function representing the normalized total deoxyhemoglobin content level.
- $t \rightarrow \vec{x}(t) = (f(t), s(t), v(t), q(t))^T$ is the state vector-valued function.
- $\dot{\vec{x}}$ represents the derivative with respect to t of the state vector $\vec{x}$, that is $\dot{\vec{x}}(t) = \frac{d\vec{x}}{dt}(t)$.

- α is a positive number representing the stiffness exponent.
- ϵ is a positive number representing the neural efficacy. ϵ characterizes the increase in perfusion signal elicited by the neuronal activity. This neural efficacy is expressed in terms of the event density (i.e., the number of evoked transients per second).
- $\mathcal{K}$ is a positive number representing the rate of signal decaying.
- $\mathcal{X}$ is a positive number representing the rate of flow-dependent elimination.
- $\tau = \frac{1}{\tau_0}$, where τ_0 is a positive number representing the hemodynamic transit time, that is, the average time it takes for the venous compartment to be filled again. This parameter determines the dynamics of the signal.
- E_0 is a positive number representing the resting oxygen extraction fraction.
- V_0 is a positive number representing the resting blood volume.
- $\vec{\theta} = (\alpha, \epsilon, \mathcal{K}, \mathcal{X}, \tau, E_0, V_0)^T \in \mathbb{R}^7$ is a vector representing the biophysiological system parameters.
- $t \rightarrow u(t)$ is a real-valued function representing the input of the considered dynamical system. It represents the neuronal activity. In this study, we consider two categories of inputs that appear to be standard (see, e.g., [17]):

i. A *Gaussian* input given by:

$$u(t) = 2 \exp[-(t - \mu)^2 / 2\sigma^2], \quad (1)$$

where, μ and σ are two positive real numbers.

ii. A step-function input, also called the *On-Off* input:

$$u(t) = \begin{cases} 0 & 0 \leq t < t_1 \\ a & t_1 \leq t \leq t_2 \\ 0 & t_2 < t \leq t_f, \end{cases} \quad (2)$$

where the interval $[t_1, t_2]$ is the time period of applying the stimulus, and t_f is the duration of the experiment. a is a positive number representing the intensity of the stimulus. It has been reported in [29, 15] that the percent of change in neuronal signal is in the 25% – 50% ranges for excitatory activity during visual stimulation conditions, i.e., $a \in [0.25, 0.5]$.

- $t \rightarrow y(t)$ is a real-valued function representing the so-called Blood Oxygenation Level Dependent (BOLD) signal.
- $\mathcal{N}(\lambda, \Sigma)$ is the Gaussian distribution, with λ being the mean value and Σ being the covariance [30].
- δ_{ij} denotes the Kronecker delta function, that is, $\delta_{ij} = \begin{cases} 1 & i = j \\ 0 & i \neq j \end{cases}$

2.2. The Hemodynamic System: The Direct Problem

The mathematical model for describing hemodynamic brain response to an exogenous input can be formulated in the framework of dynamical system theory. The model we consider is called HDM. This mathematical model has been first introduced by Buxton et al. [10], and then revisited later by Friston et al., to account for the nonlinearities involved in the process and the measurement equations [31]. The HDM is a first-order nonlinear differential system given by:

$$(HDM) \quad \begin{cases} \dot{\vec{x}}(t) = A(\vec{\theta}; \vec{x}(t)) + \nu_t \\ y(t) = H(\vec{\theta}; \vec{x}(t)) + \omega_t \\ \vec{x}(0) = \vec{x}_0 \end{cases} ; t \geq 0, \quad (3)$$

where A is a nonlinear vector-valued function given by:

$$A(\vec{\theta}; \vec{x}(t)) = \begin{cases} s(t) \\ \epsilon u(t) - \mathcal{K}s(t) - \mathcal{X}(f(t) - 1) \\ \tau(f(t) - v(t)^{1/\alpha}) \\ \tau(f(t)^{\frac{1-(1-E_0)^{1/f(t)}}{E_0}} - q(t)v(t)^{(1/\alpha-1)}) \end{cases}, \quad (4)$$

and H is a real-valued function given by:

$$H(\vec{\theta}; \vec{x}(t)) = V_0 [k_1(1 - q(t)) + k_2(1 - q(t)/v(t)) + k_3(1 - v(t))]. \quad (5)$$

The following observations are noteworthy:

- The first equation of HDM(3) describes the underlying physiology of the continuous hemodynamic system.
- The second equation of HDM(3) models the observations, that is, the BOLD signal.
- The third equation of HDM(3) is the initial conditions indicating the values of the state variables at rest. Note that the HDM (3) is normalized around the values at rest. $\vec{x}_0$ is a prescribed state vector whose typical value is $\vec{x}_0 = (1, 0, 1, 1)^T$ [10].
- $\nu_t \sim \mathcal{N}(0, Q_t)$ is a random vector with zero mean and 4×4 positive semidefinite covariance matrix, Q_t , depending on t . The function $t \rightarrow \nu_t$ represents the level and distribution of the noise in the system.
- $\omega_t \sim \mathcal{N}(0, R_t)$ is a random variable with zero mean and non-negative real-valued covariance, R_t , depending on t . The function $t \rightarrow \omega_t$ represents the level and distribution of the noise on the measurements.
- k_1, k_2 and k_3 are positive constants. These parameters are scanner-dependent and dimensionless. They have been evaluated in previous studies for a 1.5T scanner and $TE^1=40\text{ms}$ [10]:

$$\begin{cases} k_1 = 7E_0 \\ k_2 = 2 \\ k_3 = 2E_0 - 0.2. \end{cases} \quad (6)$$

2.3. The Inverse Problem

The HDM given by Eqs. (3)-(6), defines an operator $\mathcal{F}$ that maps the biophysiological parameters $\vec{\theta} = (\alpha, \epsilon, \mathcal{K}, \mathcal{X}, \tau, E_0, V_0)^T \in \mathbb{R}^7$ to the BOLD signal $y(t)$. Therefore, the problem of identifying the unknown parameters $\vec{\theta}$, from the knowledge of a measured BOLD signal $y(t)$ can be formulated as the following inverse parameter problem:

¹Echo Time (TE), represents the time in milliseconds between the application of the 90 pulse and the peak of the echo signal in Spin Echo and Inversion Recovery pulse sequences.

$$(IPP) \quad \left\{ \begin{array}{l} \text{Given an initial measured state } \tilde{x}_0, \text{ an input } u(t), \text{ and a measured} \\ \text{BOLD signal } \tilde{y}, \text{ find the biophysiological parameters vector } \vec{\theta} \\ \text{and its corresponding state vector-valued function } \vec{x}(t), \\ \text{such that,} \end{array} \right. \quad \mathcal{F}(\vec{\theta}; \vec{x}(t)) = \tilde{y}(t), \quad (7)$$

where the tilde notation indicates a noisy quantity. For the initial state it indicates that the brain is not completely at rest, whereas for the BOLD signal it characterizes possible error on the measurements.

Since in practice the BOLD signal is measured at a discrete finite set of time $(t_j)_{j=0}^M$, IPP(7) is then reformulated as follows:

$$\left\{ \begin{array}{l} \text{Given an initial state } \tilde{x}_0, \text{ a control input vector } \vec{u} = (u(t_0), u(t_1), \dots, u(t_M))^T, \\ \text{and BOLD signal measurements } \tilde{y} = (\tilde{y}_0, \tilde{y}_1, \dots, \tilde{y}_M)^T, \text{ find } \vec{\theta} \text{ and } \vec{x}(t) \\ \text{such that:} \end{array} \right. \quad \tilde{H}(\vec{\theta}; \vec{x}(t_j)) = \tilde{y}_j; \quad j = 0, 1, \dots, M \quad (8)$$

where $\vec{x}(t_j)$ is the solution of differential system HDM(3) evaluated at time t_j .

3. Parameter Estimation: The Solution Methodology

The parameter identification problem IPP(7) is an inverse problem that falls into the category of design problems. This problem is difficult to solve, especially from a numerical point of view, because it is nonlinear and ill-posed in the sense of Hadamard [22]. In practice, this means that small errors in the measured BOLD signal can induce large errors in the estimate of the parameters. To solve IPP(7), we propose a solution methodology that is based on the Tikhonov regularized Newton method (TNM) [32, 33], since regularized iterative methods appear to be the primary candidates for solving nonlinear and ill-posed problems (see, e.g., [34], and the references therein). The Newton algorithm addresses the nonlinear aspect of IPP(7), whereas the Tikhonov regularization procedure is incorporated to address its ill-posed nature [35, 36]. Note that TNM has been applied successfully in the biomedical field to calibrate the mathematical model that describes the fibrous capsule

tissue growth around biomaterials [37]. However, we have observed that TNM by itself delivers inaccurate estimates of the biophysiological parameters when the data are highly noisy (see Figure 7 in Section 4.1.2). For this reason, a Kalman-type de-noising procedure is built within the proposed method to “filter” the noise contaminating the considered model [38]. More specifically, we employ the so-called cubature Kalman filter (CKF) that was originally designed by Arasaratnam and Haykin in [27] for solving nonlinear state estimation problems such as tracking a maneuvering aircraft, and then applied later by Havlicek et al. to solve IPP(7) [23]. Note that, in the absence of an a priori knowledge on the parameters’ values, which is the case in practice since these values are not measurable, we have observed that the use of the CKF algorithm by itself fails dramatically to solve IPP(7) (see Figure 4 in Section 4.1.1). Hence, the proposed solution methodology can be viewed as a two-step iterative procedure that alternates between TNM for the non-linearity aspect and CKF for the de-noising procedure. For this reason, we named it TNM-CKF. To the best of our knowledge, this is the first time that these two methods (TNM and CKF) have been combined successively, resulting in a novel procedure with a great potential for solving IPP(7) efficiently and accurately, as illustrated by the results reported in Section 4.1 and Section 4.2 .

3.1. The Regularized Newton Algorithm (TNM)

3.1.1. The Newton Equation

The solution of the nonlinear system (see (8)) by the Newton algorithm incurs, at each iteration m , the solution of the linearized problem of the form:

$$\tilde{H}^{(m)}(\vec{\theta}^{(m)}; \vec{x}^{(m)}(t_j)) + \frac{\partial \tilde{H}^{(m)}}{\partial \vec{\theta}}(\vec{\theta}^{(m)}; \vec{x}^{(m)}(t_j)) \delta \vec{\theta}^{(m)} = \tilde{y}_j; \quad j = 0, 1, \dots, M, \quad (9)$$

and then we update

$$\vec{\theta}^{(m+1)} = \vec{\theta}^{(m)} + \delta \vec{\theta}^{(m)}. \quad (10)$$

Therefore, at iteration $m + 1$ we solve the following equation:

$$\sum_{l=1}^7 \left(\frac{\partial \tilde{H}^{(m)}}{\partial \theta_l}(\vec{\theta}^{(m)}; \vec{x}^{(m)}(t_j)) \delta \theta_l^{(m)} \right) = \tilde{y}_j - y^{(m)}(t_j); \quad j = 0, \dots, M, \quad (11)$$

where

$$y^{(m)}(t) = \tilde{H}^{(m)}(\vec{\theta}^{(m)}; \vec{x}^{(m)}(t)). \quad (12)$$

In general, the number of measurement points M is greater than 7, the number of the parameters. Consequently, the linear system given by Eq. (11) is typically overdetermined, and therefore is solved in a least-squares sense as follows:

$$\sum_{j=1}^M \sum_{l=1}^7 \left(\frac{\partial \tilde{H}^{(m)}}{\partial \theta_k}(\vec{\theta}^{(m)}; \vec{x}^{(m)}(t_j)) \frac{\partial \tilde{H}^{(m)}}{\partial \theta_l}(\vec{\theta}^{(m)}; \vec{x}^{(m)}(t_j)) \delta \theta_l^{(m)} \right) = \sum_{j=1}^M \frac{\partial \tilde{H}^{(m)}}{\partial \theta_k}(\vec{\theta}^{(m)}; \vec{x}^{(m)}(t_j)) (\tilde{y}_j - y^{(m)}(t_j)); \quad k = 1, \dots, 7, \quad (13)$$

Observe that Eq. (13) is a 7×7 linear system.

3.1.2. The Regularized Newton

Since the linear system given by Eq. (13) is severely ill-conditioned, we employ the classical Tikhonov regularization procedure to restore the stability. Consequently, Eq (13) is replaced by the following regularized system:

$$\sum_{j=1}^M \sum_{l=1}^7 \left(\frac{\partial \tilde{H}^{(m)}}{\partial \theta_k}(\vec{\theta}^{(m)}; \vec{x}^{(m)}(t_j)) \frac{\partial \tilde{H}^{(m)}}{\partial \theta_l}(\vec{\theta}^{(m)}; \vec{x}^{(m)}(t_j)) + \gamma \right) \delta \theta_l^{(m)} = \sum_{j=1}^M \frac{\partial \tilde{H}^{(m)}}{\partial \theta_k}(\vec{\theta}^{(m)}; \vec{x}^{(m)}(t_j)) (\tilde{y}_j - y^{(m)}(t_j)); \quad k = 1, \dots, 7, \quad (14)$$

where the positive real number γ represents the Tikhonov regularization parameter.

Note that large values for γ have the effect of improving the condition number of the matrix, which stabilizes the linear system given by Eq.(14). On the other hand, small values of γ improve the accuracy of the solution. Hence, the choice of γ is a balancing act between stability and accuracy, and finding its optimal value is generally difficult. Moreover, experience shows that the convergence of the Newton method strongly depends on the value of γ , which can be found using theoretical considerations such as Morozov's discrepancy principal [39, 40]. Roughly speaking, there are in general two strategies for choosing the regularization parameter γ when solving an ill-posed inverse problem: the *a priori* rules where the parameter γ is defined as a function of the noise level, and the *a posteriori* rules where γ depends both on the noise level and the actual data. Examples of methods for selecting γ include the

generalized cross-validation method [41] and the L-curve method [42].

In this work, we chose to use a trial and error strategy for finding the optimal value of γ . This “brute force” approach consists of sweeping γ over a large interval of positive real numbers, evaluating the residual for each value of γ , and then choosing the value that leads to the minimum residual (up to the noise level). Note that such an approach can be applied at each Newton iteration, leading to an adaptive strategy. In this work, we decided to freeze the value of γ obtained at the first Newton iteration and use it for the subsequent iterations. Choosing this method appears to be convenient for this particular problem because (a) it is a simple procedure, and (b) the computational cost remains reasonable since it involves solving a small linear system (7×7) several times without having to reconstruct the matrix each time.

3.1.3. Evaluation of the Derivatives

The critical step in the numerical implementation of the regularized Newton method is the computation, at each iteration m , of the Jacobian $J_H^{(m)} = \left[\frac{\partial \tilde{H}}{\partial \theta_l}(\tilde{\theta}^{(m)}; \vec{x}^{(m)}(t_j)) \right]$ for $j = 1, \dots, M$ and $l = 1, \dots, 7$. Such computation must be executed with a high level of accuracy to ensure the stability, fast convergence, and computational efficiency of the proposed Newton algorithm. We compute J_H using the following expression of the derivative of the BOLD signal:

$$\begin{aligned} \frac{\partial \tilde{H}}{\partial \theta_l}(\tilde{\theta}; \vec{x}(t)) &= \delta_{7l} \left[7E_0(1 - q(t)) + 2\left(1 - \frac{q(t)}{v(t)}\right) + (1 - v(t))(2E_0 - 0.2) \right] \\ &+ \delta_{6l} [7V_0(1 - q(t)) + (1 - v(t))2V_0] \\ &- \frac{\partial q}{\partial \theta_l} V_0 \left[7E_0 + \frac{2}{v(t)} \right] + \frac{\partial v}{\partial \theta_l} V_0 \left[\frac{2q(t)}{v^2(t)} - 2E_0 + 0.2 \right]; \quad l = 1, \dots, 7. \end{aligned} \quad (15)$$

Hence, the evaluation of the derivatives of the measurement equation given by Eq. (15) requires the computation of the derivatives of the state vector $\vec{x}$ with respect to the parameters $\tilde{\theta}$. The characterization of these derivatives is given by the following theorem that can be easily established using the chain rule.

Theorem 1. For $i = 1, \dots, 4$ and $l = 1, \dots, 7$, let $z_{li}(t) = \frac{\partial x_i}{\partial \theta_l}(t)$ be the derivative of the i^{th} coordinate of the state vector $\vec{x}$ with respect to θ_l . Then,

$\vec{z}_l(t) = (z_{l1}(t), z_{l2}(t), z_{l3}(t), z_{l4}(t))$ is the solution of the following initial value problem:

$$\begin{cases} \dot{\vec{z}}(t) = B(\vec{\theta}; \vec{z}(t)) + G(\vec{\theta}; \vec{x}(t)) \\ \vec{z}(0) = \vec{0} \end{cases} \quad (16)$$

where

$$B(\vec{\theta}; \vec{z}(t)) = \begin{cases} z_{l2}(t) \\ -\mathcal{K}z_{l2}(t) - \mathcal{X}z_{l1}(t) \\ \tau \left[z_{l1}(t) - 1/\alpha v(t)^{1/\alpha-1} z_{l3}(t) \right] \\ \tau \left[\frac{z_{l1}(t)}{E_0} \left((1 - (1 - E_0)^{1/f(t)}) + \frac{(1-E_0)^{1/f(t)} \ln(1-E_0)}{f(t)} \right) - \right. \\ \left. v(t)^{(1/\alpha-1)} z_{l4}(t) - (1/\alpha - 1)q(t)v(t)^{(1/\alpha-2)} z_{l3}(t) \right] \end{cases} \quad (17)$$

and

$$G(\vec{\theta}; \vec{x}(t)) = \begin{cases} 0 \\ \delta_{l2}u(t) - \delta_{l3}s(t) - \delta_{l4}(f(t) - 1) \\ \delta_{5l}(f(t) - v(t)^{1/\alpha}) - \delta_{l1}\tau v(t)^{1/\alpha} \ln v(t) \\ \tau \left[\frac{\delta_{6l}}{E_0} \left((1 - E_0)^{1/f(t)-1} - \frac{f(t)}{E_0} (1 - (1 - E_0)^{1/f(t)}) \right) - \right. \\ \left. q(t)v(t)^{(1/\alpha-1)} \delta_{l1} \ln v(t) \right] + \\ \delta_{5l} \left(f(t) \frac{1-(1-E_0)^{1/f(t)}}{E_0} - q(t)v(t)^{(1/\alpha-1)} \right) \end{cases} \quad (18)$$

Remark 1. Theorem 1 reveals that the derivatives of the state vector $\vec{x}^{(m)}(t)$, with respect to the parameters θ_j , are the solutions of the same initial value problem with different right-hand-sides. The computational implication of this theoretical result is that, at each regularized Newton iteration, we evaluate the Jacobian entries $\frac{\partial \tilde{H}}{\partial \theta_i}(\vec{\theta}^{(m)}; \vec{x}^{(m)}(t_j))$ by solving a single ordinary differential system with 7 different right-hand-sides.

3.2. The Cubature Kalman Filtering (CKF)

The CKF procedure is a nonlinear filter that belongs to the class of Kalman filtering methods [38]. It distinguishes itself from existing ones by its highly efficient numerical integration procedure: the cubature quadrature rule [43]. This procedure is derivative-free and, more importantly, the number of integration points, called the cubature points, increases linearly with the state-vector dimension. More specifically, one needs to use $2n$ cubature points if n is the state-vector dimension. For these reasons, CKF is

considered to be among the most accurate and cost-effective nonlinear filters for computing multivariate moment integrals encountered in the nonlinear Bayesian filtering framework. Nevertheless, as indicated in [27], CKF does not overcome completely the challenging issue of the dimensionality since the computational cost in terms of *flops* is $O(n^3)$. Next, we present the algebraic formulation of the CKF algorithm, as applied here to HDM(3). A detailed description and performance analysis of CKF can be found in [23]-[27].

The CKF algorithm evaluates the BOLD signal in two steps: (a) a time update step in which *predicted* estimates of the state-vector and error covariance matrix are delivered at the next time step, and (b) a measurement update step in which *corrected* estimates of the *predicted* values are calculated.

3.2.1. The Time-Update Step in CKF

For $l = 0, 1, \dots, M$, let $\vec{x}_l$ (resp. P_l) be an estimated value of the state vector $\vec{x}(t_l)$ (resp. the corresponding error covariance matrix $P(t_l)$). Suppose that $\vec{x}_l$ and P_l have been evaluated up to $l = j$ where $j \leq M - 1$. Then, in order to compute $\vec{x}_{j+1}$ and P_{j+1} , we first calculate in this step $\hat{\vec{x}}_{j+1}$ (resp. $\hat{P}_{j+1}$) a *predicted* estimate of the state vector (resp. the corresponding error covariance matrix). We evaluate $\hat{\vec{x}}_{j+1}$, by first calculating the cubature vectors as follows:

$$\vec{c}_{i,j} = S_j \vec{\xi}_i + \vec{x}_j; \quad i = 1, 2, \dots, 8, \quad (19)$$

where S_j results from the Cholesky factorization of the error covariance matrix P_j , that is, $P_j = S_j S_j^T$ and $\vec{\xi}_i$ is the given i^{th} column vector of the cubature points matrix (see Eq. 7, page 2112 in [23]). Then, using the process equation in HDM(3) and the cubature vectors given by (19), we solve the following first order differential system

$$\begin{cases} \dot{\vec{z}}_i = A(\vec{\theta}; \vec{z}_i) \\ \vec{z}_i = \vec{c}_{i,j} \end{cases} ; \quad i = 1, \dots, 8, \quad (20)$$

and evaluate the i^{th} “propagated” cubature vectors at time t_{j+1} , that is, $\vec{z}_{i,j+1} = \vec{z}_i(t_{j+1})$. Note that, the differential system given by Eq. (20) is solved here using Runge-Kutta methods of order 4 (see, e.g., [44]).

The *predicted* estimate for the state at time t_{j+1} is then calculated as follows:

$$\hat{\vec{x}}_{j+1} = \frac{1}{8} \sum_{i=1}^8 \vec{z}_{i,j+1}. \quad (21)$$

Furthermore, the *predicted* estimate for the corresponding error covariance matrix $\hat{P}_{j+1}$ at time t_{j+1} is evaluated as follows:

$$\hat{P}_{j+1} = \frac{1}{8} \sum_{i=1}^8 \vec{z}_{i,j+1} \vec{c}_{i,j+1}^T - \hat{\vec{x}}_{j+1} \hat{\vec{x}}_{j+1}^T + Q_{j+1}; \quad (22)$$

where $Q_{j+1} = Q_{t_{j+1}}$ is the process noise covariance matrix defined in Section 2.2.

3.2.2. The Measurement-Update Step in CKF

This step is called the correction step. The goal here is to calculate x_{j+1} and P_{j+1} by “correcting” the predicted values $\hat{x}_{j+1}$ and $\hat{P}_{j+1}$, and then to deduce y_{j+1} , the estimated BOLD signal at time t_{j+1} . To this end, we first evaluate $\vec{x}_{j+1}$ as follows:

$$\vec{x}_{j+1} = \hat{\vec{x}}_{j+1} + (\tilde{y}_{j+1} - \hat{y}_{j+1}) \vec{W}_{j+1}, \quad (23)$$

where:

- $\tilde{y}_{j+1}$ is the given measured BOLD signal at time t_{j+1} .
- $\hat{y}_{j+1}$ is the *predicted* BOLD signal at time t_{j+1} . It is calculated by applying the cubature quadrature rule to the measurement equation given in HDM(3) as follows:

$$\hat{y}_{j+1} = \frac{1}{8} \sum_{i=1}^8 H(\vec{\theta}; \hat{\vec{c}}_{i,j+1}), \quad (24)$$

with $\hat{\vec{c}}_{i,j+1}$ being the i^{th} “*predicted*” cubature vector obtained as follows:

$$\hat{\vec{c}}_{i,j+1} = \hat{S}_{j+1} \vec{\xi}_i + \hat{\vec{x}}_{j+1}; \quad i = 1, 2, \dots, 8, \quad (25)$$

where the matrix $\hat{S}_{j+1}$ results from the Cholesky factorization of the *predicted* error covariance matrix $\hat{P}_{j+1}$ at time t_{j+1} , that is, $\hat{P}_{j+1} = \hat{S}_{j+1} \hat{S}_{j+1}^T$.

- $\vec{W}_{j+1}$ is the *Kalman gain* at time t_{j+1} . $\vec{W}_{j+1}$ is given by:

$$\vec{W}_{j+1} = M_{j+1}^{-1} \vec{N}_{j+1}, \quad (26)$$

where:

- the real number M_{j+1} , called the *innovation covariance* value, is given by:

$$M_{j+1} = \frac{1}{8} \sum_{i=1}^8 \left(H(\vec{\theta}; \hat{c}_{i,j+1}) \right)^2 - \hat{y}_{j+1}^2 + R_{j+1}, \quad (27)$$

and $R_{j+1} = R_{t_{j+1}}$ is the measurement noise covariance value, as defined in Section 2.2.

- the vector $\vec{N}_{j+1}$, called the *cross covariance* vector, is given by:

$$\vec{N}_{j+1} = \frac{1}{8} \sum_{i=1}^8 H(\vec{\theta}; \hat{c}_{i,j+1}) \vec{z}_{i,j+1} - \hat{y}_{j+1} \hat{x}_{j+1}, \quad (28)$$

The *corrected* error covariance matrix is then evaluated as follows:

$$P_{j+1} = \hat{P}_{j+1} - M_{j+1} \vec{W}_{j+1} \vec{W}_{j+1}^T, \quad (29)$$

where $\hat{P}_{j+1}$, M_{j+1} , and $\vec{W}_{j+1}$ are given by Eqs. (22), (27), and (26) respectively.

Last, we deduce the estimated BOLD signal at time t_{j+1} as follows:

$$y_{j+1} = H(\vec{\theta}, \vec{x}_{j+1}). \quad (30)$$

3.3. Algorithm Summary

The proposed TNM-CKF algorithm can be summarized as follows (see figure 1):

- **Step 0: Initialization.** TNM-CKF requires the following initial data:

$$\tilde{x}_0 \in \mathbb{R}^4, \quad \vec{\theta}^{(0)} \in \mathbb{R}^7, \quad \tilde{y} \in \mathbb{R}^M, \quad (31)$$

where $\tilde{x}_0$ is the estimated initial state vector at rest and $\vec{\theta}^{(0)}$ is the initial parameters vector. Since $\vec{\theta}^{(0)}$ is not measurable, its value is selected arbitrarily, that is, $\vec{\theta}^{(0)}$ is a “blind” guessed value. $\tilde{y}$ is the given measured BOLD signal.

- **Step 1: Application of the CKF procedure.**

Using the initial data $\vec{\theta}^{(0)}$ and $\vec{x}_0^{(0)} = \vec{x}_0$, we apply CKF, as indicated in Section 3.2, and evaluate the BOLD signal $\vec{y}^{(0)}$.

Then, we check whether $\vec{y}^{(0)}$ is a “good” approximation for the measured BOLD signal $\vec{y}$, that is, if:

$$\frac{\|\vec{y} - \vec{y}^{(0)}\|_2}{\|\vec{y}\|_2} < \epsilon, \quad (32)$$

where ϵ is a desired tolerance. If the relative *residual* given by Eq. (32) is satisfied, then the algorithm stops. In this case, $\vec{\theta}^{(0)}$ is the sought-after estimate for the biophysiological parameters, and $\vec{y}^{(0)}$ is the corresponding reconstructed BOLD signal. Otherwise, we go to step 2.

- **Step 2: Application of the TNM method.**

We apply TNM, as described in Section 3.1, to solve the regularized linear system given by Eq. (14) with the initial value $\vec{\theta}^{(0)}$. We evaluate $\delta\vec{\theta}^{(0)}$, and update the biophysiological parameters as follows:

$$\vec{\theta}^{(1)} = \vec{\theta}^{(0)} + \delta\vec{\theta}^{(0)}. \quad (33)$$

Then, we go back to Step 1, using the initial data $\vec{\theta}^{(1)}$ given by Eq. (33) and $\vec{x}_0^{(1)} = \vec{x}_M^{(0)}$, where $\vec{x}_M^{(0)}$ is the state vector at the final time t_M computed at the previous iteration.

Figure 1: Schematic diagram of the TNM-CKF algorithm

3.4. Computational Complexity

The proposed iterative solution methodology (TNM-CKF) outlined in Section 3.3 to estimate the biophysiological parameters from the knowledge of a measured BOLD signal at M different times, requires at each Newton iteration m , the following calculations:

- Solving one ordinary differential system (see Eq. (20)) with $8M$ different initial values to evaluate the *propagated cubature points*. This is accomplished using Runge-Kutta method of order 4.
- Performing $2M$ Cholesky factorization of a small matrix (4×4) to evaluate both the *cubature points* and the *predicted cubature points*.
- Solving seven ordinary differential equation given by Eq. (16) that are different from each other only by the right-hand-sides, to evaluate the Jacobian matrix needed for the regularized Newton iteration system (14).
- Applying one LU factorization to solve one small linear system (7×7) to determine the update values of the parameters $\vec{\delta\theta}^{(m)}$.

4. Parameter Estimation: Illustrative Numerical Results

We present numerical results to illustrate the potential of the proposed solution methodology for calibrating efficiently the HDM(3) when given a discrete set of BOLD signal measurements. These results were obtained for two groups of numerical experiments. The first category of results were obtained by performing numerical experiments using synthetic data, whereas the second group of results were obtained using real data corresponding to (a) finger tapping fMRI measurements [24], and (b) face repetition fMRI measurements [28].

4.1. Parameter Estimation with Synthetic Data

We have conducted an extensive numerical investigation to assess the performance (accuracy and convergence) as well as the stability (robustness to the noise effect) of the proposed method [45]. For illustrative purposes, we present here the results of two sets of numerical calibration experiments that differ by the control input. In the first experiments, a Gaussian input (see Eq. (1)) is employed whereas in the second ones an On-Off input (see Eq.

(2)) is used. We must point out that in all of these experiments, we used the Runge-Kutta method of order 4 to solve HDM(3). More specifically, we used the “*gsl_odeiv2_step_rk4*” routine available in the GSL library [46]. On the other hand, the synthetic BOLD signal measurements are generated using another routine, namely “*gsl_odeiv2_step_rkf45*” [46], to avoid the so-called *inverse crime* [47].

4.1.1. Case of a Gaussian Input

In these experiments, we use a Gaussian input given by Eq. (1) with $\mu = 25$, $\sigma = 6$. The synthetic BOLD signal (see Figure 2) is generated by solving the noise free ($Q_t = [0]$ and $R_t = 0$, for all $t \geq 0$) HDM (3) with the initial state vector $\vec{x}_0 = (1, 0, 1, 1)^T$ and the biophysiological system parameters $\vec{\theta}^*$ whose coordinates’ values were used in [23] and are listed in Table 1. Note that we have selected these values for comparison purposes. Moreover, because in practice only a discrete set of BOLD signal measurements is available, we consider a set of 60 measurements ($M = 60$) taken every one second ($\Delta t = 1$ s), that is, $\tilde{\vec{y}} \in \mathbb{R}^{60}$ and $\tilde{y}_j = \tilde{y}(j)$ (See Figure 2).

Next, we analyze the sensitivity of the performance efficiency of the proposed solution methodology to the noise level in the data. To this end, we present the results of the following two experiments.

Experiment I. The goal of this experiment is to investigate the effect of the noise level in the measured BOLD signal. We also compare the obtained results to the ones delivered by the CKF algorithm when applied, as suggested in [23], to the extended Hemodynamic model (see Eq. (9), p. 2112 in [23]) to calibrate HDM(3). We must point out that the CKF algorithm was implemented using both the forward and backward pass, as described in [23]. This comparison illustrates the importance of using the TNM procedure in conjunction with the CKF algorithm for calibrating accurately HDM(3).

In this experiment, the initial state vector $\vec{x}_0$ (resp. the process equation) is tainted with a fixed white noise level of 5% (resp. 1%). Furthermore, the exact BOLD signal vector denoted by $\vec{y}^{ex}$ is tainted with four different noise levels: 1%, 10%, 20% and 30% (see Figure 2). The resulting noisy BOLD signal vectors are denoted by $\vec{y}^{meas}$.

For the four considered measurements, we employ TNM-CKF to calibrate HDM(3) using an initial biophysiological parameters vector $\vec{\theta}^{(0)}$ whose components are all arbitrarily set to .5 (see Table 1). For every noise level, the value of the regularization parameter γ was selected through a trial and error strategy. This “brute force” approach allowed to determine values for γ

intervals in which the proposed algorithm delivers results with a comparable accuracy level. For illustration purpose, we have reported in Table 2 the selected values of γ for obtaining the results depicted in Figures 3 and 4, and Table 3-5.

Parameters $\vec{\theta}$	α	ϵ	$\mathcal{K}$	$\mathcal{X}$	τ	E_0	V_0
Target $\vec{\theta}^*$	.34	.54	.65	.38	.98	.32	.04
Initial guess $\vec{\theta}^{(0)}$	.5	.5	.5	.5	.5	.5	.5

Table 1: Target vs. initial biophysiological parameters. Experiment I: Gaussian input and 60 points of BOLD signal measurements.

Noise level (%)	1%	10%	20%	30%
γ	8×10^{-5}	2×10^{-3}	5×10^{-3}	10^{-2}

Table 2: Selected regularization parameter values for various noise levels on the measured BOLD signal. Experiment I: Gaussian input, 60 measurements, 5% white noise in $\vec{x}_0$, and 1% white noise in the differential system of HDM(3).

The following observations are noteworthy:

- Table 1 indicates that the initial parameters' values $\vec{\theta}^{(0)}$ are selected outside the pre-asymptotic convergence region. Indeed, the relative error in the euclidean norm is over 50%. In addition, Figure 2 shows that the use of this initial guess $\vec{\theta}^{(0)}$ in HDM(3) leads to the computation of an initial BOLD signal profile $\vec{y}^{(0)}$ that is very far from the target BOLD signal $\vec{y}^{ex}$. More specifically, the relative error on the BOLD signal at iteration 0, is over 300%, as indicated in Table 3. Clearly, these numerical experiments are performed without using any a priori knowledge on the sought-after biophysiological parameters $\vec{\theta}^*$ or the BOLD signal $\vec{y}^{ex}$.
- Figure 3 illustrates the fast convergence and the robustness to the noise of the proposed TNM-CKF. Indeed, one can clearly observe that, regardless of the noise level on the data, the relative residual drops from the initial value (over 300%) to the noise level after at most 9 iterations only.

- At convergence, the TNM-CKF algorithm delivers a BOLD signal $\vec{y}^{app}$ with an excellent accuracy level for all considered noise levels. This is clearly demonstrated in Figure 4. Indeed, the third column in Table 3 shows that, at convergence, the relative error varies from 1.3% to 11.7% depending on the noise level in the data.
- The comparison with the results obtained when applying the CKF algorithm only, as suggested in [23], reveals that (a) the TNM-CKF method outperforms the CKF algorithm (see Figure 4 and the fourth column of Table 3) and (b) the CKF algorithm fails dramatically to calibrate the HDM(3) in the absence of a priori knowledge on the values of the biophysiological parameters, particularly when the measured BOLD signal is contaminated with a relatively high noise level. We must point out that the results reported in [23] with a good accuracy level were obtained using an initial value $\vec{\theta}^{(0)}$ set to be the target value $\vec{\theta}^*$ tainted with a low white noise level. In practice, the value of $\vec{\theta}^*$ is not available, and therefore it is not possible to guarantee that the selected initial guess $\vec{\theta}^{(0)}$ will be in the neighborhood of $\vec{\theta}^*$. These observations tend to indicate that the CKF algorithm is not suitable for calibrating HDM(3). In addition, these numerical experiments clearly illustrate the importance of employing the TNM procedure in conjunction with CKF to reconstruct the BOLD signal with an acceptable accuracy level when starting the calibration process from a blind guess for the biophysiological parameters's values.
- Figure 5 provides a comparison between the exact biophysiological parameters' values and the ones computed by the proposed TNM-CKF algorithm and by the CKF algorithm, as proposed in [23]. These results clearly demonstrate that the TNM-CKF approach outperforms the CKF algorithm. Indeed, for all considered noise levels, the CKF algorithm computes the parameters with a relative error above 40%, which is an unacceptable accuracy level. On the other hand, as indicated in Table 4, the relative error in the case of the proposed TNM-CKF algorithm remains acceptable given the noise level in both the model and the data.

(a) Noise level on the measured BOLD signal $\vec{y}^{meas}$: 1%

(b) Noise level on the measured BOLD signal $\vec{y}^{meas}$: 10%

(c) Noise level on the measured BOLD signal $\vec{y}^{meas}$: 20%

(d) Noise level on the measured BOLD signal $\vec{y}^{meas}$: 30%

Figure 2: Comparison between the BOLD signal profiles for various noise levels: Target BOLD signal $\vec{y}^{ex}$ (solid-black), measured BOLD signal $\vec{y}^{meas}$ (dotted-red), and initial BOLD signal $\vec{y}^{(0)}$ (solid-magenta). Experiment I: Gaussian input, 60 BOLD signal measurements, 5% white noise in $\vec{x}_0$, and 1% white noise in the differential system of HDM(3).

(a) Noise level on the measured BOLD signal $\vec{y}^{meas}$: 1%

(b) Noise level on the measured BOLD signal $\vec{y}^{meas}$: 10%

(c) Noise level on the measured BOLD signal $\vec{y}^{meas}$: 20%

(d) Noise level on the measured BOLD signal $\vec{y}^{meas}$: 30%

Figure 3: Convergence history of the TNM-CKF algorithm for various noise levels. Experiment I: Gaussian input, 60 points BOLD signal measurements, 5% white noise in $\vec{x}_0$, and 1% white noise in the differential system of HDM(3).

(a) Noise level on the measured BOLD signal $\vec{y}^{meas}$: 1%

(b) Noise level on the measured BOLD signal $\vec{y}^{meas}$: 10%

(c) Noise level on the measured BOLD signal $\vec{y}^{meas}$: 20%

(d) Noise level on the measured BOLD signal $\vec{y}^{meas}$: 30%

Figure 4: Computed vs. exact BOLD signal for various noise levels in the measurements: Exact BOLD signal (black), computed with TNM-CKF (blue), computed with CKF (red). Experiment I: Gaussian input, 60 points BOLD signal measurements, 5% white noise in $\vec{x}_0$, and 1% white noise in the differential system of HDM(3).

(a) Noise level on the measured BOLD signal $\vec{y}^{meas}$: 1%

(b) Noise level on the measured BOLD signal $\vec{y}^{meas}$: 10%

(c) Noise level on the measured BOLD signal $\vec{y}^{meas}$: 20%

(d) Noise level on the measured BOLD signal $\vec{y}^{meas}$: 30%

Figure 5: Computed vs. exact biophysiological parameters for various noise levels: Exact (black), computed with TNM-CKF (blue), computed with CKF (red). Experiment I: Gaussian input, 60 points BOLD signal measurements, 5% white noise in $\vec{x}_0$, and 1% white noise in the differential system of HDM(3).

Noise Level on the BOLD signal (%)	$\frac{\ \vec{y}^{ex} - \vec{y}^{(0)}\ _2}{\ \vec{y}^{ex}\ _2} (\%)$	$\frac{\ \vec{y}^{ex} - \vec{y}^{app}\ _2}{\ \vec{y}^{ex}\ _2} (\%)$	
		TNM-CKF	CKF
1	317.3	1.3	5.6
10	327.6	4.7	23.9
20	358.9	8.2	38.6
30	393.3	11.7	54.2

Table 3: Sensitivity of the relative error on the BOLD signal $\vec{y}$ to the noise level: Comparison between the performance of TNM-CKF and CKF algorithm. Experiment I: Gaussian input, 60 points BOLD signal measurements, 5% white noise in $\vec{x}_0$, and 1% white noise in the differential system of HDM(3).

Noise Level on the BOLD signal (%)	$\frac{\ \vec{\theta}^{ex} - \vec{\theta}^{app}\ _2}{\ \vec{\theta}^{ex}\ _2} (\%)$
	TNM-CKF
1	9.0
10	17
20	19.8
30	23.9

Table 4: Sensitivity of the relative error on the biophysiological parameters to the noise level. Experiment I: Gaussian input, 60 points BOLD signal measurements, 5% white noise in $\vec{x}_0$, and 1% white noise in the differential system of HDM(3).

Experiment II. The goal of this experiment is to investigate the effect of uncertainties on the initial state $\vec{x}_0$. We also compare the obtained results to the ones delivered by the TNM algorithm only when applied to IPP(7) to calibrate HDM(3). This comparison illustrates the importance of the use of the CKF procedure in conjunction with the TNM algorithm for calibrating HDM(3) accurately. In this experiment, the BOLD signal vector $\vec{y}$ is with a fixed white noise level of 30%, which is a very high noise level. On the other hand the initial state $\vec{x}_0$ is tainted with four different noise levels: 5%, 10%, 20% and 30%. For the four considered initial guess values, we apply TNM-CKF to calibrate HDM(3) using the same blind guess for the initial biophysiological parameters vector $\vec{\theta}^{(0)}$ as in previous experiments (see Table 1). The value of the regularization parameter γ was selected through the trial and error strategy. For all of these experiments the selected regularization

parameter is $\gamma = 10^{-3}$.

Noise Level on the initial state $\tilde{x}^{(0)}$ (%)	$\frac{\ \vec{y}^{ex} - \vec{y}^{app}\ _2}{\ \vec{y}^{ex}\ _2}$ (%)	
	TNM-CKF	TNM
5	9.6	9.7
10	9.7	10.1
20	9.7	11
30	9.7	11.9

Table 5: Sensitivity of the reconstruction of the BOLD signal to the noise levels. Comparison between the performance of TNM-CKF and TNM algorithm. Experiment I: Gaussian input, 60 points BOLD signal measurements, 30% white noise on the BOLD signal measurements, and 1% white noise in the differential system of HDM(3).

The following observations are noteworthy:

- As reported in Table 1, the initial parameters' values $\vec{\theta}^{(0)}$ are selected outside the pre-asymptotic convergence region. Indeed, Figure 2 shows that the use of this initial guess with HDM(3) leads to an initial BOLD signal profile that is very far from the target. Hence, these experiments are performed without using any a priori knowledge on the sought-after BOLD signal.
- Figure 6 illustrates the convergence and the robustness of the TNM-CKF and TNM algorithm to the presence of the noise in the initial state. Indeed, Figure 6 indicates that for all considered noise levels, both algorithms require at most 4 iterations to converge to the noise level on the BOLD signal (see the third and fourth columns of Table 3).
- The results depicted in Figure 7 reveal that the TNM-CKF algorithm delivers a BOLD signal with an excellent accuracy level. Indeed, as reported in the fourth row of Table 5, relative *error* on the BOLD signal remains in an acceptable accuracy range even when the initial state is highly tainted with noise.
- The comparison with the results obtained when applying the TNM algorithm only shows that (a) the TNM-CKF method is more accurate than the TNM algorithm (see Figure 7 and Table 5) and (b) the TNM

algorithm fails to reconstruct the BOLD signal in the presence of noise on the initial state.

4.1.2. Case of an On-off Input

In this section, we consider the case of an *On-off* input given by Eq. (2) with $t_1 = 7\text{ s}$, $t_2 = 37\text{ s}$, $t_f = 72\text{ s}$ and $a = 1$. The BOLD signal was measured every 3 seconds ($\Delta t = 3\text{ s}$) during 72 seconds, that is, we have 25 measurements. The generated BOLD signal corresponds to the parameters $\vec{\theta}$ listed in Table 6. We added 10% white noise to generated signal and 5% white noise to the initial states. The result reported in Figure 9 indicates that TNM-CKF converges very quickly (in about 4 iterations). Moreover, the result depicted in Figure 10 shows that TNM-CKF is an accurate procedure. Indeed, the relative error on the BOLD signal is about 4.6 %. In addition, this experiment reveals that, similarly to the Gaussian control input, the CKF performs poorly. Indeed, CKF delivers a BOLD signal with a relative error of about 23%. Moreover, observe that unlike the BOLD signal constructed with TNM-CKF, the one obtained with CKF does not reflect the effect underlying neuronal activity which drives the BOLD signal response, as demonstrated by the post stimulus undershoot of the BOLD signal (see Figure 10 (left))

Parameters $\vec{\theta}$	α	ϵ	$\mathcal{K}$	$\mathcal{X}$	τ	E_0	V_0
Target $\vec{\theta}^*$	.45	.6	.4	.15	.4	.3	1.05
Initial guess $\vec{\theta}^{(0)}$	.5	.5	.5	.5	.5	.5	.5

Table 6: Target and initial parameters' values corresponding to the experiments with the On-Off input.

4.2. Parameter Estimation with Real Data

In this section, we assess the performance of the TNM-CKF algorithm for calibrating HDM(3) when the BOLD signal data are obtained from real fMRI measurements. We consider here fMRI measurements corresponding to two stimuli: a finger tapping stimulus and a face repetition stimulus.

4.2.1. Case of a Finger Tapping Stimulus

The BOLD signal measurements are obtained from a lab experiment in which one male subject was imaged while performing a finger tapping task.

(a) Noise level on the initial guess $\vec{x}_0$: 5%

(b) Noise level on the initial guess $\vec{x}_0$: 10%

(c) Noise level on the initial guess $\vec{x}_0$: 20%

(d) Noise level on the initial guess $\vec{x}_0$: 30%

Figure 6: Convergence history of the TNM (red) and TNM-CKF (blue) algorithm for various noise levels in the $\vec{x}_0$. Experiment II: Gaussian input, 60 points BOLD signal measurements, 30% white noise in the measurements.

(a) Noise level on the initial guess $\vec{x}_0$: 5%

(b) Noise level on the initial guess $\vec{x}_0$: 10%

(c) Noise level on the initial guess $\vec{x}_0$: 20%

(d) Noise level on the initial guess $\vec{x}_0$: 30%

Figure 7: Computed vs. exact BOLD signal for various noise levels in $\vec{x}_0$: Exact BOLD signal (black), computed with TNM-CKF (blue), computed with TNM (red). Experiment II: Gaussian input, 60 points BOLD signal measurements, 30% white noise in the measurements.

(a) Noise level on the initial guess $\vec{x}_0$: 5%

(b) Noise level on the initial guess $\vec{x}_0$: 10%

(c) Noise level on the initial guess $\vec{x}_0$: 20%

(d) Noise level on the initial guess $\vec{x}_0$: 30%

Figure 8: Computed vs. exact biophysiological parameters for various noise levels in $\vec{x}_0$: Exact (black), computed with TNM-CKF (blue), computed with TNM (red). Experiment II: Gaussian input, 60 points BOLD signal measurements, 30% white noise in the measurements.

Figure 9: Convergence history for the TNM-CKF algorithm. Experiment with an *On-off* input with 5% white noise in the $\vec{x}_0$ and 10% white noise in the measurements.

Figure 10: Computed vs. exact BOLD signal (left) and biophysiological parameters (right). Exact BOLD signal (black), computed with TNM-CKF (blue) and computed with CKF (red). Experiment with an *On-off* input with 5% white noise in the $\vec{x}_0$ and 10% white noise in the measurements and the regularization parameter $\gamma = 18$.

More specifically, 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 protocol followed a standard block design. The *On-Off* cycle was repeated six times for each scanning plane. The characteristics of this experiments as well as the collected data are reported in Table 4.2.1. Note that the considered study was approved by the Institutional Review Board (IRB) at Nationwide Childrens Hospital, Columbus, OH [24]. The *On-Off* input is characterized by $t_0 = 0\text{ s}$, $t_1 = 7\text{ s}$, $t_2 = 37\text{ s}$, $t_f = 72\text{ s}$ and $a = 0.2$ (see Eq. 5). Note that we have used a control input corresponding to 20% increase in neuronal activity. This choice seems to be reasonable due to the relatively mild nature of the considered audio stimulus. The final measurements of this experiment are over 72 seconds, with 25 data points, that is every 3 seconds one measurement has been taken, as indicated in Figure 11. The TNM-CKF algorithm was applied to estimate the biophysiological parameters starting from the same initial guess $\vec{\theta}^{(0)}$ used for the experiments with synthetic data (See Table 1) and using the regularization parameter $\gamma = 0.01$. The results are reported in Figure 12 and Table 8. Figure 12 clearly reveals that the TNM-CKF algorithm converges after 11 iterations only. It also provides a comparison between the measured bold signal and the computed one at convergence (after 11 iterations). The relative error between the two signals is about 6%. The estimated biophysiological parameters values delivered by the TNM-CKF algorithm are reported in Table 8. These values are physiologically plausible and fall within the range of typical value (see Fig. 7 in [14]).

4.2.2. Case of a Face Repetition Stimulus

Here, we consider the data measured from a repetition priming experiment performed using event-related fMRI. These open access data are available in [28]. In this experiment, the subject was asked to make fame judgments by making key presses. There are thus four event-types of interest: first and second presentations of famous and non-famous faces. We consider here the measurements corresponding to first presentations of famous faces only. This stimulus is characterized by an *On-Off* control input with $t_1 = 1\text{ s}$, $t_2 = 4\text{ s}$, $t_f = 32\text{ s}$, and $a = 0.5$. Note that we assume that there is a 50% increase in neural activity since the presentation of a famous face is a relatively and exciting visual stimulus. Sixteen BOLD measurements have been obtained by taking the average effect (see Figure 13). A fitting procedure has been applied to these data [28], leading to 385 data points (see Figure

Figure 11: Raw real BOLD signal measurements for the finger tapping stimulus experiment: 25 raw data points

(a) Convergence history

(b) BOLD signal: Computed vs. Measured

Figure 12: Parameters estimation using finger tapping stimulus measurements. The BOLD signal is computed after 11 iterations with the regularization parameter $\gamma = .01$

Origin	Children's Hospital, Columbus, OH
Subject	1 male
Stimulus	Right hand finger tapping
Duration	6 minutes followed by 6 minutes rest
Voxels distribution	20 slices of 8 mm
Temporal sampling	3 seconds
Preprocessing	Filtering, smoothing and convolution
Number of voxels	$128 \times 128 \times 20$
Sampling time	0.01 seconds
Resolution	22 mm

Table 7: Description of the real data corresponding to the finger tapping stimulus experiment.

Nomenclature	α	ϵ	$\mathcal{K}$	$\mathcal{X}$	τ	E_0	V_0
Computed values	.72	.92	.38	.09	.85	.35	.02

Table 8: Computed biophysiological parameters values after 5 iterations when using finger tapping stimulus measurements.

13). These fitted measurements were used to calibrate HDM.

The obtained results are depicted in Figure 14 and Table 9. Here again, Figure 14 demonstrates the convergence of the TNM-CKF algorithm. Indeed, the algorithm converges after 10 iterations. Note that the plateau of the convergence occurs at about 13% on the residual, which suggests that the data are tainted with a higher noise level than the ones obtained from the finger tapping stimulus experiment. Figure 14 also illustrates the performance accuracy of the TNM-CKF for reconstructing the BOLD signal. The relative error is about 12.5%.

The computed BOLD signal is overall in agreement with both the averaged and the fitted data. Observe that both the averaged and fitted BOLD signals exhibit a more pronounced post-stimulus undershoot than the computed BOLD signal. This apparent discrepancy may be due to the fact that the measured data were averaged over 26 instances of the associated event, and therefore are expected to be highly noisy. Indeed, Figure 13 and Figure 14 (b) indicate that the measured BOLD signal is negative at the time where the brain activity already returned to its baseline. On the other hand, the

Figure 13: Measured BOLD signal for face repetition

estimated biophysiological parameters values delivered by the TNM-CKF algorithm are reported in Table 9. The values appears to be physiologically plausible as they fall within the range of typical values (see Figure 7 in [14]).

Nomenclature	α	ϵ	$\mathcal{K}$	$\mathcal{X}$	τ	E_0	V_0
Computed values	.47	.75	1.18	.69	1.36	.01	.03

Table 9: Computed biophysiological parameters values after 15 iterations when using face repetition stimulus measurements.

Figure 14: Parameters estimation using face repetition stimulus measurements (385 data points). The BOLD signal is computed after 10 iterations with the regularization parameter $\gamma = .003$.

5. Conclusion

We have designed an efficient numerical technique, called the TNM-CKF algorithm, for calibrating the mathematical model that describes the single-event related brain response when fMRI measurements are given. This method employs a regularized Newton technique in conjunction with a Kalman filtering procedure. The method is simple to understand, easy to implement, and cost-effective. Indeed, our C code can run on a personal desktop and the algorithm converges in few iterations. This code is available upon request. The numerical results obtained when using either synthetic data or real data illustrate the accuracy, robustness to the noise, and the cost-effectiveness of the proposed algorithm. Indeed, even when the data are highly contaminated with noise (as high as 30%), the TNM-CKF converges in few iterations and delivers a BOLD signal with an acceptable accuracy level.

Acknowledgments

The authors would like to thank Dr. Nasser Kashou, Wright State University for the enlightening discussions.

References

- [1] S. Huettel, Functional magnetic resonance imaging, Sinauer Associates, Sunderland, Mass, 2008.
- [2] S. Ogawa, T. M. Lee, A. S. Nayak, P. Glynn, Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields, *Magnetic Resonance in Medicine* 14 (1) (1990) 68–78.
- [3] S. Ogawa, R. S. Menon, D. W. Tank, S. G. Kim, H. Merkle, J. M. Ellermann, K. Ugurbil, Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model., *Biophysical journal* 64 (3) (1993) 803–12.
- [4] K. J. Friston, P. Jezzard, R. Turner, Analysis of functional MRI time-series, *Human Brain Mapping* 1 (1994) 153–171.
- [5] J. C. Rajapakse, E. Kruggel, J. M. Maisog, D. Y. von Cramon, Modeling hemodynamic response for analysis of functional MRI time-series, *Human Brain Mapping* 6 (1998) 283–300.
- [6] K. J. Friston, P. Fletcher, O. Josephs, A. P. Holmes, M. D. Rugg, R. Turner, Event-related fMRI: characterizing different responses, *NeuroImage* 7 (1998) 30–40.
- [7] P. Ciuciu, J.-B. Poline, G. Marrelec, J. Idier, C. Pallier, H. Bendali, Unsupervised robust nonparametric estimation of the hemodynamic response function for any fMRI experiment, *IEEE Transactions on Medical Imaging* 22 (2003) 1235–1251.
- [8] M. Lindquist, T. Wager, Modeling the hemodynamic response function using inverse logit functions, in: *Proceedings of Human Brain Mapping Annual Meeting*, vol. 45, S187–S198., 2005.
- [9] R. B. Buxton, L. R. Frank, A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation, *Journal of Cerebral Blood Flow and Metabolism* 17 (1997) 64–72.
- [10] R. B. Buxton, E. C. Wong, L. R. Frank, Dynamics of blood flow and oxygenation changes during brain activation: The balloon model, *Mag. Reso. Med.* 39 (1998) 855–864.

- [11] K. J. Friston, O. Josephs, G. Rees, R. Turner, Nonlinear event-related responses in fMRI, *Mag. Reso. Med.* 39 (1998) 41–52.
- [12] K. J. Friston, E. Zarahn, O. Josephs, R. Henson, A. Dale, Stochastic design in event-related fMRI, *NeuroImage* 10 (1999) 607–619.
- [13] J. B. Mandeville, J. J. A. Marota, C. Ayata, G. Zaharchuk, M. A. Moskowitz, B. R. Rosen, R. M. Weisskoff, Evidence of a cerebrovascular postarteriole Windkessel with delayed compliance, *Journal of Cerebral Blood Flow and Metabolism* 9 (1999) 679–689.
- [14] K. Friston, A. Mechelli, R. Turner, C. Price, Nonlinear Responses in fMRI: The Balloon Model, Volterra Kernels, and Other Hemodynamics, *NeuroImage* 12 (4) (2000) 466 – 477.
- [15] R. C. Sotero, N. J. Trujillo-Barreto, Modeling the role of excitatory and inhibitory neuronal activity in the generation of the BOLD signal., *Neuroimage* 35 (2007) 149–165.
- [16] K. J. Friston, Bayesian estimation of dynamical systems: an application to fMRI., *NeuroImage* 16 (2) (2002) 513–30.
- [17] J. J. Riera, J. Watanabe, I. Kazuki, M. Naoki, E. Aubert, T. Ozaki, R. Kawashima, A state-space model of the hemodynamic approach: non-linear filtering of BOLD signals, *NeuroImage* 21 (2) (2004) 547–567.
- [18] T. Deneux, O. Faugeras, Using nonlinear models in fMRI data analysis: model selection and activation detection, *NeuroImage* 32 (4) (2006) 1669 – 1689.
- [19] L. A. Johnston, E. Duff, I. Mareels, G. F. Egan, Nonlinear estimation of the BOLD signal, *NeuroImage* 40 (2) (2008) 504–14, Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18203623>.
- [20] L. Murray, A. Storkey, Continuous Time Particle Filtering for fMRI, *Advances in Neural Information Processing Systems* 20 (2007) 1–8.
- [21] Z. Hu, X. Zhao, H. Liu, P. Shi, Nonlinear analysis of the BOLD signal, *EURASIP Journal on Advances in Signal Processing* 2009 (2009) 1–13.
- [22] J. Hadamard, *Lectures on Cauchy’s problem in linear partial differential equations*, New Haven, Yale University Press, 1923.

- [23] M. Havlicek, K. J. Friston, J. Jan, M. Brazdil, V. Calhoun, Dynamic Modeling of neural responses in fMRI using cubature Kalman filtering, *Neuroimage* 56 (2011) 2109–2128.
- [24] A. Karam, T. Laleg-Kirati, C. Zayane, N. Kashou, Nonlinear neural network for hemodynamic model state and input estimation using fMRI data, *Biomedical signal processing and control* (2014) 240–247.
- [25] T. Laleg-Kirati, H. Arabi, T. Tadjine, C. Zayane, Estimation of the Neuronal activation using fMRI data: an observer-based approach, *American Control Conference*, Washington, June 2013 .
- [26] C. Zayane-Aissa, T. Laleg-Kirati, A sliding mode observer for hemodynamic characterization under modeling uncertainties, *Mediterranean Control Conference*, June 2014 .
- [27] I. Arasaratnam, S. Haykin, Cubature Kalman Filters, *Automatic Control*, *IEEE Transactions on* 54 (6) (2009) 1254–1269.
- [28] The FIL Methods Group, SPM8 Manual, Available at: <http://www.fil.ion.ucl.ac.uk/spm/doc/manual.pdf>, 2013.
- [29] A. Shmuel, M. Augath, A. Oeltermann, N. K. Logothetis, Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1, *Nature Neuroscience* 9 (4) (2006) 569–577.
- [30] A. Gut, *An Intermediate Course in Probability*, Springer, second edn., 2009.
- [31] K. J. Friston, Variational filtering, *NeuroImage* 41 (3) (2008) 747–66.
- [32] H. W. Engl, M. Hanke, A. Neubauer, *Regularization of inverse problems*, Kluwer Academic Publisher, Dordrecht, 1996.
- [33] S. F. Gilyazov, N. L. Goldman, *Regularization of ill-posed problems by iteration methods*, Kluwer Academic Publishers, 2000.
- [34] R. Djellouli, *Inverse Acoustic Problems*, in: *Computational Methods for Acoustic Problems*, Saxe-Coburg Publications, 2008.
- [35] A. N. Tikhonov, Regularization of incorrectly posed problems, *Soviet Math. Doklady* 4 (1963) 1624–1627.

- [36] A. N. Tikhonov, V. Y. Arsenin, *Solutions of Ill-Posed Problems*, Winston, New York, 1977.
- [37] P. Ryan, R. Djellouli, R. Cohen, Modeling capsule tissue growth around disk-shaped implants: a numerical and in vivo study, *J. Math. Biol.* 57 (2008) 675–695.
- [38] G. Welch, G. Bishop, *An Introduction to the Kalman Filter*, SIGGRAPH, 2001.
- [39] V. A. Morozov, Choice of parameter for the solution of functional equations by the regularization method, *Dokl. Akad. Nauk. SSSR* 175 (1967) 1000–1003.
- [40] V. A. Morozov, On the solution of functional equations by the method of the regularization, *Soviet Math. Doklady* 167 (1966) 414–417.
- [41] G. Wahba, *Spline Models for Observations Data*, SIAM, 1990.
- [42] P. C. Hansen, D. O’Leary, The use of the L-curve in the regularization of discrete ill-posed problems, *SIAM J. Sci. Comput.* 14 (6) (1993) 1487–1503.
- [43] A. H. Stroud, *Approximate Calculation of Multiple Integrals*, Prentice Hall, Engle Wood Cliffs, NJ, 1971.
- [44] K. E. Atkinson, *An Introduction to Numerical Analysis*, John Wiley and sons, second edn., 1989.
- [45] N. Khoram, On the characterization of single-event related brain activity from functional Magnetic Resonance Imaging (fMRI) measurements, Master’s thesis, California State University, Northridge, Available at: <http://www.csun.edu/sites/default/files/Thesis-Manuscript-khoram.pdf>, 2013.
- [46] M. Galassi, et al, *GNU Scientific Library Reference Manual*, third edn., Available at: <http://www.gnu.org/software/gsl/>, 2013.
- [47] K. R. Colton D., *Inverse problems for partial differential equations*, Springer Verlag, 1992.