Time-adaptive optimization in a parameter identification problem of HIV infection

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Abstract

The paper considers a time-adaptive method for determination of drug efficacy in a parameter identification problem (PIP) for system of ordinary differential equations (ODE) which describe dynamics of the primary HIV infection. Optimization approach to solve this problem is presented and a posteriori error estimates in the Tikhonov functional and Lagrangian are formulated. Based on these estimates a time adaptive algorithm is formulated and numerically tested for different scenarios of noisy observations of virus population function. Numerical results show significant improvement of reconstruction of drug efficacy parameter when using time adaptive mesh refinement compared to usual gradient method applied on a uniform time mesh.

1 Introduction

Parameter identification problems are frequently occurring within biomedical applications. These problems are often non-linear and ill-posed, and thus challenging to solve numerically. For efficient solution of parameter identification problems a time-adaptive method was recently proposed [4]. This method uses ideas of an adaptive finite element method for solution of different coefficient inverse problems for partial differential equations (PDE) and has shown that it significantly improves reconstruction of parameters [1, 2, 3, 6, 7]. The main idea of an adaptive method is to minimize a Tikhonov functional on locally refined meshes via a posteriori error estimates for the finite element approximation of the solution of an inverse problem under investigation.

This work is a continuation of the work by authors [5] where they studied the model proposed in [16] describing the effect of the drug therapy on the dynamics of the Human Immunodeficiency Virus (HIV) infection. In [5] a time-adaptive method was formulated to determine the drug efficacy in mathematical model of HIV infection using measurements

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in time of all functions in this ODE system. Numerical simulations were not presented in [5]. In the current work we consider a more realistic case when only the virus population function is measured and present numerical results of time-adaptive reconstruction of drug efficacy from noisy measurements of virus population function on an initial non-refined mesh. New a posteriori error estimate between regularized and computed parameters is presented. Based on this estimate, a time adaptive algorithm is formulated and numerically tested on the reconstruction of drug efficacy from noisy measurements of virus population function.

The time-adaptive method proposed in this paper can eventually be used by clinicians to determine the drug-response for each treated individual. Mathematical modelling helps to understand the biological mechanisms underlying in the base of action of antiviral drugs [9]. The exact knowledge of the personal drug efficacy can aid in the determination of the most suitable drug as well as the most optimal dose to an individual, in the long run resulting in a personalized treatment with maximum efficacy and minimum adverse drug reactions.

The outline of the paper is as follows. The short biological description of the mathematical model is given in section 2. In section 3 the forward and parameter identification problems are formulated. The optimization method to solve the parameter identification problem is presented in section 4. The finite element method is formulated in section 5 and a posteriori error estimates are presented in section 6. An adaptive algorithm for solution of PIP is formulated in section 7. Finally, in section 8 numerical examples confirm the proposed time-adaptive algorithm.

2 The mathematical model and its biological description

Despite the efforts by the international community to eradicate HIV infection, the problem of its transmission, treatment and quality of life of people living with HIV remains actual. According to materials presented on the VI Eastern Europe and Central Asia AIDS Conference and the latest data on HIV (UNAIDS, 2018), there are currently more than 37 million people living with HIV globally and an estimated two million new infections were recorded every year (http://aidsinfo.unaids.org).

In general case for living organisms the genetic information goes from the storage in DNA through messenger RNA (mRNA) to protein synthesis in the ribosomes. The process of converting the genetic information from DNA to mRNA is called transcription [13]. In the case of retroviruses, such as HIV, HIV’s genetic information is encoded in form of RNA. HIV inserts its RNA into the host cell. Here viral RNA is reversely transcribed into HIV DNA, which is compatible with genetic material of the host cell (reverse transcription). This DNA is transported to the cell’s nucleus and incorporated into the DNA of the infected cell (integration). To perform the reverse transcription of RNA into DNA, HIV carries its own enzyme called reverse transcriptase, that catalyzes the reverse transcrip-
tion. Antiviral drugs inhibiting this enzyme (called Reverse Transcriptase Inhibitors) will be able to prevent the production of new viruses \[11, 15\].

Our basic mathematical model in this work is the model proposed in \[16\] which describes the effect of Reverse Transcriptase Inhibitor (RTI) on the dynamics of HIV infection. In this model the infected class of CD4+ T-cells is subdivided into two subclasses: pre-RT class and post-RT class. Pre-RT class consists of the infected CD4+ T-cells in which reverse transcription is not completed, and post-RT class consists of those infected CD4+ T-cells where the reverse transcription is completed such that they are capable to produce virus. The mathematical model is:

\[
\begin{align*}
\frac{du_1}{dt} &= f_1(u(t), \eta(t)) = s - ku_1(t)u_4(t) - \mu u_1(t) + (\eta(t)\alpha + b)u_2(t), \\
\frac{du_2}{dt} &= f_2(u(t), \eta(t)) = ku_1(t)u_4(t) - (\mu_1 + \alpha + b)u_2(t), \\
\frac{du_3}{dt} &= f_3(u(t), \eta(t)) = (1 - \eta(t))\alpha u_2(t) - \delta u_3(t), \\
\frac{du_4}{dt} &= f_4(u(t), \eta(t)) = N\delta u_3(t) - cu_4(t),
\end{align*}
\]

with initial conditions

\[
\begin{align*}
\begin{aligned}
&u_1(0) = u_0^1 = 300 \text{ mm}^{-3}, \\
&u_2(0) = u_0^2 = 10 \text{ mm}^{-3}, \\
&u_3(0) = u_0^3 = 10 \text{ mm}^{-3}, \\
&u_4(0) = u_0^4 = 10 \text{ mm}^{-3}.
\end{aligned}
\end{align*}
\]

Throughout the paper we denote by \(\Omega_T = [0, T]\) the time domain for \(T > 0\), where \(T\) is the final observation time. In system \((2.1)\) the functions \(u_i, i = 1, 2, 3, 4\) are defined as follows:

- \(u_1(t)\) – uninfected target cells population,
- \(u_2(t)\) – infected target cells from pre-RT class,
- \(u_3(t)\) – infected target cells from post-RT class,
- \(u_4(t)\) is the virus population function.

The initial data \((2.2)\) are chosen such that they satisfy two steady states (see details in \[16\]). The system \((2.1)\) can be presented in the following compact form:

\[
\begin{align*}
\frac{du}{dt} &= f(u(t), \eta(t)) \quad t \in [0, T], \\
u(0) &= u^0,
\end{align*}
\]

with

\[
\begin{align*}
&u = u(t) = (u_1(t), u_2(t), u_3(t), u_4(t))^T, \\
&u^0 = (u_1(0), u_2(0), u_3(0), u_4(0))^T, \\
&\frac{du}{dt} = \left( \frac{\partial u_1}{\partial t}, \frac{\partial u_2}{\partial t}, \frac{\partial u_3}{\partial t}, \frac{\partial u_4}{\partial t} \right)^T, \\
f(u(t), \eta(t)) = (f_1(t), f_2(t), f_3(t), f_4(t))^T = (f_1(u_1, \ldots, u_4, \eta(t)), \ldots, f_4(u_1, \ldots, \eta(t)))^T.
\end{align*}
\]
### Table 1

| Parameter | Value | Units      | Description                                      |
|-----------|-------|------------|--------------------------------------------------|
| $s$       | 10    | $mm^{-3} day^{-1}$ | inflow rate of T cells                           |
| $\mu$    | 0.01  | $day^{-1}$ | natural death rate of T cells                     |
| $k$       | 2.4E-5| $mm^3 day^{-1}$ | interaction-infection rate of T cells            |
| $\mu_1$  | 0.015 | $day^{-1}$ | death rate of infected cells                     |
| $\alpha$ | 0.4   | $day^{-1}$ | transition rate from pre-RT infected T cells class to post-RT class |
| $b$       | 0.05  | $day^{-1}$ | reverting rate of infected cells return to uninfected class |
| $\delta$ | 0.26  | $day^{-1}$ | death rate of actively infected cells            |
| $c$       | 2.4   | $day^{-1}$ | clearance rate of virus                          |
| $N$       | 1000  | virr/cell  | total number of viral particles produced by an infected cell |

#### 3 The mathematical model and parameter identification problem

In the model (2.1) we assume that $f \in C^1(\Omega_T)$ is Lipschitz continuous and the function $\eta(t) \in C(\Omega_T)$ represents the unknown drug efficacy which belongs to the set of admissible functions $M_\eta$:

$$M_\eta = \{ \eta(t) : \eta(t) \in [0, 1] \text{ in } \Omega_T, \eta(t) = 0 \text{ outside of } \Omega_T \}.$$  

(3.1)

To formulate the parameter identification problem we assume that all parameters in system (2.1) are known except the parameter $\eta(t)$ which describes efficacy of the drug. The typical values of parameters $\{s, \mu, k, \mu_1, \alpha, b, \delta, c, N\}$ in (2.1) are taken from [16], see Table 1.

**Parameter Identification Problem (PIP).** Assume that conditions (3.1) hold and parameters $\{s, \mu, k, \mu_1, \alpha, b, \delta, c, N\}$ in system (2.1) are known. Assume further that the function $\eta(t)$ is unknown inside the domain $\Omega_T$. The PIP is: determine $\eta(t)$ for $t \in \Omega_T$, under the condition that the virus population function $g(t)$ is known

$$u_4(t) = g(t), \quad t \in [T_1, T_2], 0 \leq T_1 < T_2 \leq T.$$  

(3.2)

Here, the function $g(t)$ presents observations of the function $u_4(t)$ inside the observation interval $[T_1, T_2]$.

Note, that we solve the PIP on the time interval $[0, T]$ and assume that observations of $g(t)$ can even be on the more narrow interval $[T_1, T_2] \subset [0, T]$. Numerical results of section
show that reconstruction of the parameter \( \eta(t) \) is not very good on the time interval where observations are not available and thus, observations of the virus population function \( u_4(t) \) should be taken as early as possible from the date when the virus started to be reproduced in the body of the host.

4 Optimization method

Let \( H \) be a Hilbert space of functions defined in \( \Omega_T \). To determine \( \eta(t), t \in [0, T] \) in PIP we minimize the following Tikhonov functional

\[
J(\eta) = \frac{1}{2} \int_{T_1}^{T_2} (u_4(t) - g(t))^2 \varsigma_\zeta(t) \, dt + \frac{1}{2} \gamma \int_0^T (\eta - \eta^0)^2 \, dt. \tag{4.1}
\]

Here, the solution \( u_4(t) \) of the system (2.1) with parameter \( \eta(t) \), \( g(t) \) is the observed virus population function, \( \eta^0 \) is the initial guess for the parameter \( \eta(t) \) and \( \gamma \in (0, 1) \) is the regularization parameter, \( \varsigma_\zeta(t), \zeta \in (0, 1) \) is smoothness function which can be defined similarly to [5].

To find the function \( \eta(t) \in H \) which minimizes the Tikhonov functional (4.1) we seek for a stationary point of (4.1) with respect to \( \eta \) which satisfies

\[
J'(\eta)(\bar{\eta}) = 0, \quad \forall \bar{\eta} \in H. \tag{4.2}
\]

To find minimum of (4.1) we use the Lagrangian approach and introduce the Lagrangian

\[
L(v) = J(\eta) + \sum_{i=1}^4 \int_0^T \lambda_i \left( \frac{du_i}{dt} - f_i \right) \, dt, \tag{4.3}
\]

where \( u(t) = (u_1(t), u_2(t), u_3(t), u_4(t)) \) is the solution of the system (2.1), \( \lambda(t) \) is the Lagrange multiplier \( \lambda(t) = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t)) \) and \( v = (\lambda, u, \eta) \).

Let us introduce following spaces needed for further analysis

\[
H^1_u(\Omega_T) = \{ f \in H^1(\Omega_T) : f(0) = 0 \}, \quad H^1_\lambda(\Omega_T) = \{ f \in H^1(\Omega_T) : f(T) = 0 \}, \quad U = H^1_u(\Omega_T) \times H^1_\lambda(\Omega_T) \times C(\Omega_T), \tag{4.4}
\]

where all functions are real valued.

To derive the Fréchet derivative of the Lagrangian (4.3) we assume that functions \( v = (\lambda, u, \eta) \) can be varied independently of each other in the sense that

\[
L'(v)(\bar{v}) = 0, \quad \forall \bar{v} = (\bar{\lambda}, \bar{u}, \bar{\eta}) \in U. \tag{4.5}
\]
Thus, we consider \( L(v + \tilde{v}) - L(v) \), single out the linear part with respect to \( v \) of the obtained expression and neglect all nonlinear terms. The optimality condition (4.5) means that for all \( \tilde{v} \in U \) we have

\[
L'(v; \tilde{v}) = \frac{\partial L}{\partial \lambda}(v)(\tilde{\lambda}) + \frac{\partial L}{\partial \bar{u}}(v)(\bar{\tilde{u}}) + \frac{\partial L}{\partial \eta}(v)(\bar{\eta}) = 0,
\]

(4.6)
i.e., every component of (4.6) should be zero out. Thus, the optimality conditions (4.5) yields

\[
0 = \frac{\partial L}{\partial \lambda}(v)(\tilde{\lambda}) = -\alpha \int_0^T u_2(\lambda_1 - \lambda_3)\bar{\eta}dt
\]
\[
+ \int_0^T (\dot{u}_1 - s + ku_1u_4 + \mu u_1 - (\eta\alpha + b)u_2)\tilde{\lambda}_1dt
\]
\[
+ \int_0^T (\dot{u}_2 - ku_1u_4 + (\mu_1 + \alpha + b)u_2)\tilde{\lambda}_2dt
\]
\[
+ \int_0^T (\dot{u}_3 - (1 - \eta)\alpha u_2 + \delta u_3)\tilde{\lambda}_3dt
\]
\[
+ \int_0^T (\dot{u}_4 - N\delta u_3 + cu_4)\tilde{\lambda}_4dt \quad \forall \tilde{\lambda} \in H^1_\lambda(\Omega_T),
\]

(4.7)

\[
0 = \frac{\partial L}{\partial \bar{u}}(v)(\bar{\tilde{u}}) = -\int_0^T (\lambda_1 - \lambda_1 ku_4 - \lambda_1\mu + \lambda_2 ku_4)\bar{\tilde{u}}_1dt
\]
\[
- \int_0^T (\dot{\lambda}_2 - \lambda_1 ku_4)(\bar{\tilde{u}}_2 + \bar{\lambda}_1\mu)dt
\]
\[
- \int_0^T (\dot{\lambda}_3 - \lambda_3\delta + \lambda_4 N\delta)\bar{\tilde{u}}_3dt
\]
\[
- \int_0^T (\dot{\lambda}_4 - \lambda_4 c - \lambda_1 ku_4 + \lambda_2 ku_4)\bar{\tilde{u}}_4dt + \int_{T_2}^{T_3} (u_4 - g)z_4\bar{\tilde{u}}_4dt \quad \forall \bar{\tilde{u}} \in H^1_\lambda(\Omega_T),
\]

(4.8)
\[ 0 = \frac{\partial L}{\partial \eta}(v(\eta)) = \gamma \int_0^T (\eta - \eta^0) \tilde{\eta} dt + \alpha \int_0^T u_2(\lambda_3 - \lambda_1) \tilde{\eta} dt \quad \forall \eta \in C(\Omega_T). \quad (4.9) \]

The equation (4.7) corresponds to the forward problem (2.1)-(2.2), the equation (4.8) — to the following adjoint problem

\[
\begin{align*}
\frac{\partial \lambda_1}{\partial t} &= \lambda_1 k u_4 + \lambda_1 \mu - \lambda_2 k u_4, \\
\frac{\partial \lambda_2}{\partial t} &= \lambda_2 (\mu_1 + \alpha + b) - \lambda_1 (\eta \alpha + b) - (1 - \eta) \alpha \lambda_3, \\
\frac{\partial \lambda_3}{\partial t} &= \lambda_3 \delta - \lambda_4 N \delta, \\
\frac{\partial \lambda_4}{\partial t} &= \lambda_4 c + \lambda_1 k u_4 - \lambda_2 k u_4 + (u_4 - g) z_\zeta, \\
\lambda_i(T) &= 0, \quad i = 1, \ldots, 4. \quad (4.10)
\end{align*}
\]

which can be rewritten in the compact form as

\[
\frac{\partial \lambda}{\partial t} = \hat{f}(\lambda(t)),
\]

\[
\lambda_i(T) = 0, \quad i = 1, \ldots, 4
\]

(4.11)

with

\[
\begin{align*}
\lambda &= \lambda(t) = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t))^T, \\
0 &= (\lambda_1(T), \lambda_2(T), \lambda_3(T), \lambda_4(T))^T, \\
d\lambda &= \begin{pmatrix} \frac{\partial \lambda_1}{\partial t} \\ \frac{\partial \lambda_2}{\partial t} \\ \frac{\partial \lambda_3}{\partial t} \\ \frac{\partial \lambda_4}{\partial t} \end{pmatrix}^T, \\
\hat{f}(\lambda(t)) &= (\hat{f}_1, \hat{f}_2, \hat{f}_3, \hat{f}_4)(\lambda(t))^T. 
\end{align*}
\]

(4.12)

The adjoint system should be solved backwards in time with already known solution \(u(t)\) to the forward problem (2.1)-(2.2) and a given measurement function \(g(t)\).

For the case when \(u\) and \(\lambda\) are exact solutions of the forward (2.1)-(2.2) and adjoint (4.11) problems, respectively, to the known function \(\eta\), we get from (4.3) that

\[ L(v(\eta)) = J(\eta), \quad (4.13) \]

and thus the Fréchet derivative of the Tikhonov functional can be written as

\[ J'(\eta) := J_\eta(u(\eta), \eta) = \frac{\partial J}{\partial \eta}(u(\eta), \eta) = \frac{\partial L}{\partial \eta}(v(\eta)). \quad (4.14) \]

Using (4.9) in (4.14), we get the following expression for the Fréchet derivative of the Tikhonov functional

\[ J'(\eta)(t) = \gamma(\eta - \eta^0)(t) + \alpha u_2(\lambda_3 - \lambda_1)(t) = 0, \quad (4.15) \]
Thus, to find the unknown parameter $\eta$ which minimizes the Tikhonov functional (4.1) we can use the following expression

$$\eta = \frac{1}{\gamma} \alpha u_2 (\lambda_1 - \lambda_3) + \eta^0. \quad (4.16)$$

## 5 Finite Element Discretization

For solution of (4.5) we will use the finite element discretization and consider a partition $J = \{ J \}$ of the time domain $\Omega_T = [0, T]$ into time subintervals $J = (t_{k-1}, t_k]$ of the time step $\tau_k = t_k - t_{k-1}$. We define also the piecewise-constant time-mesh function $\tau$ such that

$$\tau(t) = \tau_k, \quad \forall J \in J_r. \quad (5.1)$$

For discretization of the state and adjoint problems we define the finite element spaces $W^u_\tau \subset H^1_u(\Omega_T)$ and $W^\lambda_\tau \subset H^1_\lambda(\Omega_T)$ for $u$ and $\lambda$, respectively, as

$$W^u_\tau = \{ f \in H^1_u : f|_J \in P^1(J) \quad \forall J \in J \},$$
$$W^\lambda_\tau = \{ f \in H^1_\lambda : f|_J \in P^1(J) \quad \forall J \in J \}. \quad (5.2)$$

For the function $\eta(t)$ we also introduce the finite element space $W_\eta \subset L^2(\Omega_T)$ consisting of piecewise constant functions

$$W_\eta = \{ f \in L^2(\Omega_T) : f|_J \in P^0(J) \quad \forall J \in J \}. \quad (5.3)$$

We use different finite element spaces since we are working in a finite dimensional space and all norms in finite dimensional spaces are equivalent. Next we denote $U_r = W^u_\tau \times W^\lambda_\tau \times W_\eta$ such that $U_r \subset U$.

Now the finite element method for (4.5) is: find $v_r \in U_r$ such that

$$L'(v_r; \tilde{v}) = 0, \quad \forall \tilde{v} \in U_r. \quad (5.4)$$

Since the forward (2.1) - (2.2) and adjoint (4.8) problems are nonlinear their solutions can be found by Newton’s method. For the discretization

$$\frac{\partial u}{\partial t} = \frac{u^{k+1} - u^k}{\tau_k}$$

the variational formulation of the forward problem (2.1) - (2.2) for all $\tilde{u} \in H^1_u(\Omega_T)$ is:

$$(u^{k+1}, \tilde{u}) - (u^k, \tilde{u}) - \tau_k f(u^{k+1}, \tilde{u}) = 0. \quad (5.5)$$

Denoting

$$\tilde{u} = u^{k+1},$$
$$F(\tilde{u}) = \tilde{u} - \tau_k f(\tilde{u}) - u^k \quad (5.6)$$
we can rewrite (5.5) as
\[ (F(\tilde{u}), \tilde{u}) = 0. \]  
(5.7)

For solution \( F(\tilde{u}) = 0 \) the Newton’s method can be used for the iterations \( n = 1, 2, \ldots \)
\[ \tilde{u}^{n+1} = \tilde{u}^n - [F'(\tilde{u}^n)]^{-1} \cdot F(\tilde{u}^n). \]  
(5.8)

Here, we can determine \( F'(\tilde{u}^n) \) via definition of \( F(\tilde{u}) \) in (5.6) as
\[ F'(\tilde{u}^n) = I - \tau_k f'(\tilde{u}^n), \]  
where \( I \) is the identity matrix, \( f'(\tilde{u}^n) \) is the Jacobian of \( f \) (the right hand side of the forward problem (2.1)) at \( \tilde{u}^n \) and \( n \) is the iteration number in Newton’s method. We note that the finite element method (5.4) will work even in this case, see details in [12].

In a similar way the Newton’s method can be derived for the solution the adjoint problem (4.11). Since we solve the adjoint problem backwards in time, we discretize time derivative as
\[ \frac{\partial \lambda}{\partial t} = \lambda^{k+1} - \lambda^k \]  
(5.9)

for the already known \( \lambda^{k+1} \) values, and write the variational formulation of the adjoint problem for all \( \bar{\lambda} \in H^1_\lambda(\Omega_T) \)
\[ (\lambda^k - \lambda^{k+1} + \tau_k \tilde{f}(\lambda^k), \bar{\lambda}) = 0. \]  
(5.10)

Denoting
\[ \bar{\lambda} = \lambda^k, \]  
\[ \tilde{F}(\bar{\lambda}) = \bar{\lambda} + \tau_k \tilde{f}(\bar{\lambda}) - \lambda^{k+1}, \]  
(5.11)

we can rewrite (5.10) for all \( \bar{\lambda} \in H^1_\lambda(\Omega_T) \) as
\[ (\tilde{F}(\bar{\lambda}), \bar{\lambda}) = 0. \]  
(5.12)

For solution \( \tilde{F}(\bar{\lambda}) = 0 \) we use again Newton’s method for iterations \( n = 1, 2, \ldots \)
\[ \bar{\lambda}^{n+1} = \bar{\lambda}^n - [\tilde{F}'(\bar{\lambda}^n)]^{-1} \cdot \tilde{F}(\bar{\lambda}^n). \]  
(5.13)

We compute \( \tilde{F}'(\bar{\lambda}^n) \) using the definition of \( \tilde{F}(\bar{\lambda}) \) in (5.11) as
\[ \tilde{F}'(\bar{\lambda}^n) = I + \tau_k \tilde{f}'(\bar{\lambda}^n), \]  
where \( I \) is the identity matrix, \( \tilde{f}'(\bar{\lambda}^n) \) is the Jacobian of \( \tilde{f} \) (the right hand side of the adjoint problem (4.11)) at \( \bar{\lambda}^n \) and \( n \) is the iteration number in Newton’s method.
6 A Posteriori Error Estimates

We consider the function \( \eta \in C(\Omega_T) \) as a minimizer of the Lagrangian \((4.3)\), and \( \eta_\tau \in W^\tau_\eta \) its finite element approximation. Let us assume that we know good approximation to the exact solution \( \eta^* \in C(\Omega_T) \). Let \( g^*(t) \) be the exact data and the function \( g_\sigma(t) \) represents the error level in these data. We assume that measurements \( g(t) \) in \((3.2)\) are given with some noise level \( \sigma \) such that

\[
g(t) = g^*(t) + g_\sigma(t); \quad g^*, g_\sigma \in L_2(\Omega_T), \quad \| g_\sigma \|_{L_2(\Omega_T)} \leq \sigma. \tag{6.1}
\]

Accordingly \[8\] we assume that \( \gamma = \gamma(\sigma) = \sigma^2 \mu, \quad \mu \in (0, 1/4), \quad \sigma \in (0, 1) \) \((6.2)\)

and

\[
\| \eta_0 - \eta^* \| \leq \frac{\sigma^{3\mu}}{3}, \tag{6.3}
\]

where \( \eta^* \) is the exact solution of PIP with the exact data \( g^*(t) \). Let

\[
V_\varepsilon(\eta) = \{ x \in C(\Omega_T) : \| \eta - x \| < \varepsilon \quad \forall \eta \in C(\Omega_T) \}. \tag{6.4}
\]

Assume that for all \( \eta \in V_1(\eta^*) \) the operator

\[
F(\eta) = \frac{1}{2} \int_{T_1}^{T_2} (u_4(\eta, t) - g(t))^2 z_\varepsilon(t) \, dt \tag{6.5}
\]

has the Fréchet derivative \( F'(\eta) \) which is bounded and Lipschitz continuous in \( V_1(\eta^*) \) for \( D_1, D_2 = \text{const.} > 0 \)

\[
\| F'(\eta) \| \leq D_1, \quad \forall \eta \in V_1(\eta^*),
\]

\[
\| F'(\eta_1) - F'(\eta_2) \| \leq D_2 \| \eta_1 - \eta_2 \|, \quad \forall \eta_1, \eta_2 \in V_1(\eta^*). \tag{6.6}
\]

6.1 An a posteriori error estimate for the Tikhonov functional

In the Theorem 1 we derive an a posteriori error estimate for the error in the Tikhonov functional \((4.1)\) on the finite element time partition \( \mathcal{J}_\tau \).

**Theorem 1.** We assume that there exists minimizer \( \eta \in C(\Omega_T) \) of the functional \( J(\eta) \) defined by \((4.1)\). We assume also that there exists finite element approximation of a minimizer \( \eta_\tau \in W^\tau_\eta \) of \( J(\eta) \). Then the following approximate a posteriori error estimate for the error \( e = \| J(\eta) - J(\eta_\tau) \|_{L^2(\Omega_T)} \) in the Tikhonov functional \((4.1)\) holds true

\[
e = \| J(\eta) - J(\eta_\tau) \|_{L^2(\Omega_T)} \leq C \| J'(\eta_\tau) \|_{L^2(\Omega_T)} \| \tau \eta_\tau \|_{L^2(\Omega_T)} \tag{6.7}
\]
with positive constants $C_I, C > 0$ and where

$$J'(\eta) = \gamma(\eta - \eta^0) - \alpha u_{2\tau}(\lambda_{1\tau} - \lambda_{3\tau}). \quad (6.8)$$

**Proof**

Proof follows from the Theorem 5 of [4]. □

### 6.2 A posteriori error estimate of the minimizer on refined meshes

Theorems 2 and 3 present two a posteriori error estimates for a minimizer $\eta$ of the functional (4.1).

**Theorem 2**

Let $\eta_{\tau} \in W^\eta$ be a finite element approximation on the finite element mesh $J_{\tau}$ of the minimizer $\eta \in L^2(\Omega_T)$ of the functional (4.1) with the mesh function $\tau(t)$. Then there exists a Lipschitz constant $D = \text{const.} > 0$ defined by

$$\|J'(\eta_1) - J'(\eta_2)\| \leq D \|\eta_1 - \eta_2\|, \forall \eta_1, \eta_2 \in L^2(\Omega_T), \quad (6.9)$$

and interpolation constant $C_I$ independent on $\tau$ such that the following a posteriori error estimate for the minimizer $\eta$ holds true

$$\|\eta - \eta\|_{L^2(\Omega_T)} \leq \frac{D}{\gamma} C_I \|\tau \eta\|_{L^2(\Omega_T)} \forall \eta \in W^\eta. \quad (6.10)$$

**Proof.**

Proof follows from the Theorem 5.1 of [14]. □

**Theorem 3**

Let $\eta_{\tau} \in W^\eta$ be a finite element approximation on the finite element mesh $J_{\tau}$ of the minimizer $\eta \in L^2(\Omega_T)$ of the functional (4.1) with the mesh function $\tau(t)$. Then there exists an interpolation constant $C_I$ independent on $\tau$ such that the following a posteriori error estimate for the minimizer $\eta$ holds

$$\|\eta - \eta\|_{L^2(\Omega_T)} \leq \frac{R(\eta_{\tau})}{\gamma} C_I \|\tau \eta_{\tau}\|_{L^2(\Omega_T)} \forall \eta \in W^\eta, \quad (6.11)$$

where $R(\eta_{\tau})$ is the residual defined as

$$R(\eta_{\tau})(t) = \gamma(\eta_{\tau} - \eta^0)(t) + \alpha u_{2\tau}(\lambda_{3\tau} - \lambda_{1\tau})(t). \quad (6.12)$$

**Proof.**

Proof follows from Theorems 1 and 2. □
7 Algorithms for solution of PIP

Here we present two algorithms for solution of PIP:

- CGA - usual conjugate gradient algorithm (CGA) on a coarse time partition,
- ACGA - time-adaptive conjugate gradient algorithm which minimized the Tikhonov functional \( (4.1) \) on a locally refined meshes in time.

We denote the nodal value of the gradient at the observation points \( \{t_i\} \) by \( G^m(t_i) \) and compute it accordingly to (4.15) as

\[
G^m(t_i) = \gamma (\eta^m_1(t_i) - \eta^0_1(t_i)) + \alpha u^m_2(t_i)(\lambda^m_3(t_i) - \lambda^m_1(t_i)).
\]  

The approximate computed solutions \( u^m_2(t_i) \) and \( \lambda^m_1, \lambda^m_3(t_i) \) are obtained computationally by Newton’s method with \( \eta := \eta^m_1 \). A sequence \( \{\eta^m_1\}_{m=1,\ldots,M} \) of approximations to \( \eta \) is computed as follows

\[
\eta^{m+1}_1(t_i) = \eta^m_1(t_i) + r^m d^m(t_i),
\]

with

\[
d^m(t_i) = -G^m(t_i) + \beta^m d^{m-1}(t_i),
\]

and

\[
\beta^m = \frac{||G^m(t_i)||^2}{||G^{m-1}(t_i)||^2},
\]

where \( d^0(t_i) = -G^0(t_i) \) and \( G^m(t_i) \) is the gradient vector which is computed by (7.1) in time moments \( t_i \). In (7.2) the parameter \( r^m \) is the step-size in the gradient update at the iteration \( m \) which is computed as

\[
r^m = -\frac{(G^m, d^m)}{\gamma \|d^m\|^2}.
\]

In the adaptive algorithm ACGA we have used Theorem 3 for the error \( e = ||\eta_1 - \eta||_{L^2(\Omega_T)} \) on locally refined meshes. More precisely, first we choose tolerance \( 0 < \theta < 1 \) and run adaptive algorithm until

\[
e = ||\eta_1 - \eta||_{L^2(\Omega_T)} \leq \theta.
\]

For the time-mesh refinements we propose following refinement procedure based on the Theorem 3.
Algorithm 1 Conjugate Gradient Algorithm (CGA).

1: Choose time partition \( J_\tau \) of the time interval \((0, T)\). Start with the initial approximations \( \eta_{\tau}^0 \) and compute the sequence of \( \eta_{\tau}^m \) for all \( m > 0 \) in the following steps.

2: Compute solutions \( u_{\tau}^m = u_\tau(t, \eta_{\tau}^m) \), \( \lambda_{\tau}^m = \lambda_\tau(t, \eta_{\tau}^m) \) of the state (2.1) and adjoint (4.11) problems via (5.8), (5.13), respectively, using Newton’s method on the time partition \( J_\tau \).

3: Compute gradient \( G^m(t_i) \) on the time partition \( I_\tau \) by (7.1).

4: Update the unknown parameter \( \eta := \eta_{\tau}^{m+1} \) using (7.2) as

\[
\eta_{\tau}^{m+1}(t_i) = \eta_{\tau}^m(t_i) + r^m d^m(t_i).
\]

5: Compute residual \( R(\eta_{\tau}^m) \) using (6.12) with solutions \( u_\tau(t, \eta_{\tau}^m) \), \( \lambda_\tau(t, \eta_{\tau}^m) \) of the state (2.1) and adjoint (4.11) problems.

6: For the tolerance \( 0 < \theta < 1 \) chosen by the user, stop computing the functions \( \eta_{\tau}^m \) if either \( ||R(\eta_{\tau}^m)||_{L^2(\Omega_T)} \leq \theta \), or norms of residuals \( ||R(\eta_{\tau}^m)||_{L^2(\Omega_T)} \) abruptly grow, or norms of computed \( ||\eta_{\tau}^m||_{L^2(\Omega_T)} \) are stabilized. Otherwise, set \( m := m + 1 \) and go to Step 2.

The Time Mesh Refinements Criterion
Refine the time-mesh \( J_\tau \) in neighborhoods of those time-mesh points \( t \in \Omega_T \) where the residual \( |R(\eta_\tau)(t)| \) defined in (6.12) attains its maximal values. More precisely, let \( \beta_1 \in (0, 1) \) be the tolerance number. Refine the time-mesh in such subdomains of \( \Omega_T \) where

\[
|R(\eta_\tau)(t)| \geq \beta_1 \max_{\Omega_T} |R(\eta_\tau)(t)|.
\]

Using the above mesh refinement recommendation we propose the following time-adaptive algorithm in computations:

8 Numerical results

In this section we present several numerical results which show performance and effectiveness of the time-adaptive reconstruction of unknown parameter \( \eta(t), t \in [0, T] \) in PIP using ACGA algorithm. Numerical results of reconstruction of function \( \eta(t) \) using usual conjugate gradient Algorithm 1 on the nonrefined time-meshes are presented in [13]. We note that observations of all \( u_i, i = 1, 2, 3, 4 \) functions in system (2.1) were used in [13].

The goal of numerical tests of this note is to determine the unknown function \( \eta(t) \) from observation of the virus population function \( u_4(t) \) in (2.1) on the interval \([T_1, T_2] \subset \)
Algorithm 2 Adaptive Conjugate Gradient Algorithm (ACGA).

1: Perform steps 1-6 in CGA algorithm. Let $M$ be the final iteration in CGA algorithm.
2: Refine the time mesh $\mathcal{J}_\tau$ at all points where

$$\left| R(\eta^M_\tau)(t) \right| \geq \beta_1 \max_{\Omega_T} \left| R(\eta^M_\tau)(t) \right|. \quad (7.4)$$

Here the tolerance number $\beta_1 \in (0, 1)$ is chosen by the user.
3: Construct a new time partition $\mathcal{J}_\tau$ of the time interval $(0, T)$. Interpolate the initial approximation $\eta_0$ from the previous time partition to the new time partition. Next, perform steps 1-6 in CGA algorithm on the new time partition.
4: Stop time partition refinements if norms of residuals $\left| R(\eta^M_\tau) \right|_{L^2(\Omega_T)}$ either increase or stabilize, compared with the previous time partition.

$[0, T], 0 \leq T_1 < T_2 \leq T$. In all numerical tests assumed that parameter $\eta(t)$ satisfy conditions (3.1) and is unknown in the system (2.1), but all other parameters \{s, $\mu$, $k$, $\mu_1$, $\alpha$, $b$, $\delta$, $c$, $N$\} of this system are known and their values are chosen as in the Table 1. The observation interval $[T_1, T_2]$ is such that $T_2 = T = 300$, but $T_1$ is taken differently in different tests since observations of the virus population function $u_4(t)$ can be taken after the first 3 – 9 weeks since the virus started to be reproduced in the body of host.

For generation of data $u_4(t) = g(t)$ the problem (2.1)-(2.2) was solved numerically with exact values of the test model function $\eta(t)$. For solution of problem (2.1)-(2.2) was used Newton’s method presented in section 4.

Next, the random noise was added to the observed solution $u_4(t)$ as

$$u_{4\sigma}(t) = u_{4\sigma}(t)(1 + \sigma \alpha), \quad (8.1)$$

where $\sigma \in [0, 1]$ is noise level and $\alpha \in [-1, 1]$ is random number.

In Algorithms 1, 2 it is of vital importance to take initial guess $\eta^0(t)$ such that it satisfy condition (6.3) which means that $\eta^0$ is located in the close neighborhood of the exact solution. This condition is fulfilled in our PIP since we can compute explicitly values of the parameter $\eta(t)$ on the initial non-refined time mesh using, for example, the third equation of system (2.1) as

$$\eta(t) = 1 - \frac{\partial u_3(t)}{\alpha u_2(t)} + \delta u_3(t). \quad (8.2)$$

We used following discretised version of this equation to get initial guess $\eta^0_\tau$

$$\eta^0_\tau(t) \approx 1 - \frac{u_{3k}^{k+1} - u_{3k}^k}{\frac{\tau}{\alpha} u_{2k}^k} + \delta u_{3k}^k. \quad (8.3)$$

Here, $u_{3k+1}^k, u_{3k}^k, u_{2k}^k$ are known computed approximations of functions $u_3, u_2$ at time iterations $k + 1$ and $k$, respectively. We note that denominator is not approaching zero because
\( \alpha = 0.4 \) and \( u_{2,\tau}(t) > 0 \ \forall t \in [0, T] \). To get reasonable approximation \( \eta_\tau^0 \) for the initial guess \( \eta^0 \) in Algorithm 2 we assume that noisy functions \( u_{3,\sigma}, u_{2,\sigma} \) are known on the initial non-refined mesh, apply (8.3) and then use polynomial fitting to obtained noisy data \( \eta_\tau^0 \). Finally, the condition (3.1) was applied for the computed \( \eta_\tau^0 \) in order to ensure that \( \eta^0(t) \) belongs to the set of admissible parameters \( M_\eta \).

All tests are performed with tolerance \( \Theta = 10^{-7} \) in ACGA algorithm and \( \beta_1 = 0.1 \) in (7.4). The value of \( \beta_1 \) is chosen such that it allows local refinements and avoids refinement of the very large time region in the time mesh. All tests are performed for different \( T_1 = 25, 50, 100 \) for the time interval \( [T_1, T_2] = [T_1, 300] \) which corresponds to the fact that HIV virus can be detected in the first 3-9 weeks after infection.

Relative errors in the reconstructed parameters \( \eta(t) \) presented in the Tables are measured in \( L_2 \)-norm and are computed as

\[
e_\eta = \frac{\| \eta - \eta_\tau \|_{L_2(\Omega_T)}}{\| \eta \|_{L_2(\Omega_T)}}. \tag{8.4}
\]

### 8.1 Test 1

In this test we present results of reconstruction of a smooth function \( \eta(t) = 0.7e^{-t} + 0.05, t \in [0, 300] \) for \( T_1 = 25, 50, 100 \) and number of observation points 15. The initial time partition \( \mathcal{J}_\tau \) is generated with equidistant time step \( \tau = 300/14 \). Results of reconstruction of the model function \( \eta(t) = 0.7e^{-t} + 0.05 \) for noise levels \( \sigma = 5\%, 10\%, 20\%, 40\% \) in data \( u_4(t) \) are presented Table 1. Figures 1-4 show results of reconstruction of the function \( \eta(t) = 0.7e^{-t} + 0.05 \) for noise levels \( \sigma = 5\%, 10\%, 20\%, 40\% \) in data \( u_4(t) \) for \( T_1 = 50 \), respectively. Figure 5 shows results of reconstruction of this function for noise level \( \sigma = 40\% \) in data \( u_4(t) \) and for \( T_1 = 100 \).

Table 1 and Figures 1-5 confirm that with local time-mesh refinements the reconstruction of the drug efficacy function \( \eta_\tau \) is significantly improved compared to the reconstruction of \( \eta_\tau \) obtained on initial non-refined time-mesh.
\[ T_1 = 25 \]

| \(|\sigma| 5 \%\) | \(10\%\) | \(20\%\) | \(40\%\) |
|---|---|---|---|
| nr.of ref. | | | |
| 0 | 0.1893 | 0.2022 | 0.2129 | 0.2203 |
| 1 | 0.1151 | 0.1223 | 0.1391 | 0.1279 |
| 2 | 0.0470 | 0.0354 | 0.0242 | 0.0208 |
| 3 | 0.0354 | 0.0394 | 0.0657 | 0.1677 |
| 4 | 0.0242 | 0.0217 | | |

\[ T_1 = 50 \]

| \(|\sigma| 5 \%\) | \(10\%\) | \(20\%\) | \(40\%\) |
|---|---|---|---|
| nr.of ref. | | | |
| 0 | 0.1917 | 0.1933 | 0.1639 | 0.3498 |
| 1 | 0.1194 | 0.1267 | 0.1027 | 0.2990 |
| 2 | 0.0684 | 0.0550 | 0.1002 | 0.1755 |
| 3 | 0.0337 | 0.0394 | 0.0657 | 0.1677 |
| 4 | 0.0217 | | | |

\[ T_1 = 100 \]

| \(|\sigma| 5 \%\) | \(10\%\) | \(20\%\) | \(40\%\) |
|---|---|---|---|
| nr.of ref. | | | |
| 0 | 0.1560 | 0.1851 | 0.2494 | 0.3229 |
| 1 | 0.1106 | 0.1275 | 0.1442 | 0.2035 |
| 2 | 0.0775 | 0.0810 | 0.1132 | 0.1038 |
| 3 | 0.0354 | 0.0403 | | |
| 4 | 0.0193 | | | |

Table 1: Test 1. Relative errors \(e_\eta\) computed for reconstruction of the function \(\eta(t) = 0.7e^{-t} + 0.05, t \in [0, 300]\) for \(T_1 = 25, 50, 100\) on different locally adaptively refined time-meshes.

### 8.2 Test 2

In this test we present numerical results of reconstruction of the model function \(\eta(t) = 0.7\) from noisy observations of the function \(u_4(t)\) at the observation interval \([T_1, T_2]\). We again took \(T_1 = 25, 50, 100\), but number of observation points were 20 at the time interval \([T_1, T_2] = [T_1, 300]\). We generate initial time partition \(J_\tau\) with equidistant time step \(\tau = 300/19\). Results of reconstruction of the model function \(\eta(t) = 0.7\) for noise levels \(|\sigma| = 5\%, 10\%, 20\%, 40\%\) in data \(u_4(t)\) are presented in Table 2. Figures 6 and 10-13 show results of reconstruction of the function \(\eta(t) = 0.7\) for noise levels \(|\sigma| = 5\%, 10\%, 20\%, 40\%\) in data \(u_4(t)\) for \(T_1 = 50\) and \(T_1 = 100\), respectively.
$T_1 = 25$

| $\sigma$ nr.of ref. | 5%  | 10%  | 20%  | 40%  |
|---------------------|-----|------|------|------|
| 0                   | 0.0718 | 0.0802 | 0.0834 | 0.0617 |
| 1                   | 0.0592 | 0.0315 | 0.0290 | 0.0493 |
| 2                   | 0.0403 | 0.0091 | 0.0301 | 0.0240 |
| 3                   | 0.0272 | 0.0050 | 0.0064 | 0.0050 |
| 4                   | 0.0191 | 0.0064 | 0.0040 | 0.0024 |
| 5                   | 0.0170 | 0.0117 | 0.0085 | 0.0064 |
| 6                   | 0.0117 | 0.0064 | 0.0040 | 0.0024 |

$T_1 = 50$

| $\sigma$ nr.of ref. | 5%  | 10%  | 20%  | 40%  |
|---------------------|-----|------|------|------|
| 0                   | 0.0725 | 0.0758 | 0.0720 | 0.1026 |
| 1                   | 0.0656 | 0.0572 | 0.0694 | 0.0730 |
| 2                   | 0.0459 | 0.0414 | 0.0505 | 0.0571 |
| 3                   | 0.0273 | 0.0239 | 0.0179 | 0.0236 |
| 4                   | 0.0111 | 0.0183 | 0.0130 | 0.0183 |
| 5                   | 0.0066 | 0.0099 | 0.0070 | 0.0099 |

$T_1 = 100$

| $\sigma$ nr.of ref. | 5%  | 10%  | 20%  | 40%  |
|---------------------|-----|------|------|------|
| 0                   | 0.0801 | 0.0676 | 0.0535 | 0.0852 |
| 1                   | 0.0568 | 0.0547 | 0.0547 | 0.0487 |
| 2                   | 0.0351 | 0.0481 | 0.0481 | 0.0208 |
| 3                   | 0.0265 | 0.0265 | 0.0265 | 0.0208 |
| 4                   | 0.0212 | 0.0130 | 0.0130 | 0.0130 |
| 5                   | 0.0095 | 0.0090 | 0.0090 | 0.0090 |
| 6                   | 0.0084 | 0.0084 | 0.0084 | 0.0084 |

Table 2: Test 2. Relative errors $e_\eta$ computed for reconstruction of the function $\eta(t) = 0.7, t \in [0,300]$ for $T_1 = 25, 50, 100$ on different locally adaptively refined time-meshes.

We again observe from the results of Table 2 and Figures 6-13 that with local time-mesh refinements the reconstruction of the drug efficacy $\eta_T$ is significantly improved compared to the reconstruction of $\eta_T$ obtained on initial non-refined time-mesh.
9 Conclusion

The time-adaptive optimization method for determination of drug efficacy in the mathematical model of HIV infection is presented. More precisely, first the time-dependent drug efficacy is determined at known coarse time partition using several known values of observed functions (usually 15-20 observations). Then the time-mesh is locally refined at points where the residual $|R(\eta_\tau)|$ attains its maximal values and the drug efficacy is computed on a new refined time-mesh until the error in the reconstructed parameter $\eta$ is reduced to the desired accuracy. Numerical experiments show efficiency and reliability of proposed adaptive method on reconstruction of different model functions $\eta$ from noisy observed virus population function.

The proposed new time-adaptive method can eventually be used by clinicians to determine the drug-response for each treated individual. The exact knowledge of the personal drug efficacy can aid in the determination of the most suitable drug as well as the most optimal dose for each person, in the long run resulting in a personalized treatment with maximum efficacy and minimum adverse drug reactions.

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nr.ref. = 0

Figure 1: Test 1. Left figures: simulated $u_{4\tau}$ vs. noisy $u_{4\tau}$ on different adaptively refined time meshes. Here, noisy observed data are presented by circles. Middle figures: least squares fitting to noisy data for $\eta_{\tau}(t)$. Right figures: results of ACGA on adaptively refined meshes. Computations are done for noise level $\sigma = 5\%$ in $u_{4\tau}$ and for $T_1 = 50$. 


nr.ref. = 1


nr.ref. = 2


nr.ref. = 3
Figure 2: Test 1. Left figures: simulated $u_{4,\tau}$ vs. noisy $u_{4,\tau}$ on different adaptively refined time meshes. Here, noisy observed data are presented by circles. Middle figures: least squares fitting to noisy data for $\eta_{\tau}(t)$. Right figures: results of ACGA on adaptively refined meshes. Computations are done for noise level $\sigma = 10\%$ in $u_4$ and for $T_1 = 50$. 

$nr.ref. = 0$

$u_{4,\tau}$

LS fitting to $\eta_{\tau}(t)$

$\eta_{\tau}(t)$

$nr.ref. = 1$

$u_{4,\tau}$

LS fitting to $\eta_{\tau}(t)$

$\eta_{\tau}(t)$

$nr.ref. = 2$

$u_{4,\tau}$

LS fitting to $\eta_{\tau}(t)$

$\eta_{\tau}(t)$

$nr.ref. = 3$

$u_{4,\tau}$

LS fitting to $\eta_{\tau}(t)$

$\eta_{\tau}(t)$
nr.ref. = 0

\[ u_4 \tau \]

\[ \eta_\tau(t) \]

nr.ref. = 1

\[ u_4 \tau \]

\[ \eta_\tau(t) \]

nr.ref. = 2

\[ u_4 \tau \]

\[ \eta_\tau(t) \]

nr.ref. = 3

\[ u_4 \tau \]

\[ \eta_\tau(t) \]

Figure 3: Test 1. Left figures: simulated \( u_4 \tau \) vs. noisy \( u_4 \tau \) on different adaptively refined time meshes. Here, noisy observed data are presented by circles. Middle figures: least squares fitting to noisy data for \( \eta_\tau \). Right figures: results of ACGA on adaptively refined meshes. Computations are done for noise level \( \sigma = 20\% \) in \( u_4 \) and for \( T_1 = 50 \).
Figure 4: Test 1. Left figures: simulated $u_{4\tau}$ vs. noisy $u_{4\tau}$ on different adaptively refined time meshes. Here, noisy observed data are presented by circles. Middle figures: least squares fitting to noisy data for $\eta_{\tau}$. Right figures: results of ACGA on adaptively refined meshes. Computations are done for noise level $\sigma = 40\%$ in $u_4$ and for $T_1 = 50$. 
Figure 5: Test 1. Left figures: simulated \( u_{4r} \) vs. noisy \( u_{4r} \) on different adaptively refined time meshes. Here, noisy observed data are presented by circles. Middle figures: least squares fitting to noisy data for \( \eta_r(t) \). Right figures: results of ACGA on adaptively refined meshes. Computations are done for noise level \( \sigma = 40\% \) in \( u_4 \) and for \( T_1 = 100 \).
Figure 6: Test 2. Left figures: simulated $u_4$ vs. noisy $u_4$ on different adaptively refined time meshes. Here, noisy observed data are presented by circles. Middle figures: least squares fitting to noisy data for $\eta$. Right figures: results of ACGA on adaptively refined meshes. Computations are done for noise level $\sigma = 5\%$ in $u_4$ and for $T_1 = 50$. 

nr.ref. = 0

$u_4$ vs. $\eta$

nr.ref. = 1

$u_4$ vs. $\eta$

nr.ref. = 2

$u_4$ vs. $\eta$

nr.ref. = 3

$u_4$ vs. $\eta$
Figure 7: Test 2. Left figures: simulated $u_{4,T}$ vs. noisy $u_{4,T}$ on different adaptively refined time meshes. Here, noisy observed data are presented by circles. Middle figures: least squares fitting to noisy data for $\eta_T$. Right figures: results of ACGA on adaptively refined meshes. Computations are done for noise level $\sigma = 10\%$ in $u_4$ and for $T_1 = 50$.
Figure 8: Test 2. Left figures: simulated $u_{4,\tau}$ vs. noisy $u_{4,\tau}$ on different adaptively refined time meshes. Here, noisy observed data are presented by circles. Middle figures: least squares fitting to noisy data for $\eta_{\tau}$. Right figures: results of ACGA on adaptively refined meshes. Computations are done for noise level $\sigma = 20\%$ in $u_4$ and for $T_1 = 50$. 

nr.ref. = 0

$u_{4,\tau}$ - LS fitting to $\eta_{\tau}(t)$ - $\eta_{\tau}(t)$

nr.ref. = 1

$u_{4,\tau}$ - LS fitting to $\eta_{\tau}(t)$ - $\eta_{\tau}(t)$

nr.ref. = 2

$u_{4,\tau}$ - LS fitting to $\eta_{\tau}(t)$ - $\eta_{\tau}(t)$

nr.ref. = 3

$u_{4,\tau}$ - LS fitting to $\eta_{\tau}(t)$ - $\eta_{\tau}(t)$
Figure 9: Test 2. Left figures: simulated $u_{4\tau}$ vs. noisy $u_{4\tau}$ on different adaptively refined time meshes. Here, noisy observed data are presented by circles. Middle figures: least squares fitting to noisy data for $\eta_{\tau}$. Right figures: results of ACGA on adaptively refined meshes. Computations are done for noise level $\sigma = 40\%$ in $u_4$ and for $T_1 = 50$. 

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Figure 10: Test 2. Left figures: simulated $u_{4\tau}$ vs. noisy $u_{4\tau}$ on different adaptively refined time meshes. Here, noisy observed data are presented by circles. Middle figures: least squares fitting to noisy data for $\eta_{\tau}$. Right figures: results of ACGA on adaptively refined meshes. Computations are done for noise level $\sigma = 5\%$ in $u_4$ and for $T_1 = 100$. 
Figure 11: Test 2. Left figures: simulated $u_{4,\tau}$ vs. noisy $u_{4,\tau}$ on different adaptively refined time meshes. Here, noisy observed data are presented by circles. Middle figures: least squares fitting to noisy data for $\eta_{\tau}(t)$. Right figures: results of ACGA on adaptively refined meshes. Computations are done for noise level $\sigma = 10\%$ in $u_4$ and for $T_1 = 100$. 
Figure 12: Test 2. Left figures: simulated $u_{4,r}$ vs. noisy $u_{4,r}$ on different adaptively refined time meshes. Here, noisy observed data are presented by circles. Middle figures: least squares fitting to noisy data for $\eta_{r}(t)$. Right figures: results of ACGA on adaptively refined meshes. Computations are done for noise level $\sigma = 20\%$ in $u_4$ and for $T_1 = 100$. 
Figure 13: Test 2. Left figures: simulated $u_{4\tau}$ vs. noisy $u_{4\tau}$ on different adaptively refined time meshes. Here, noisy observed data are presented by circles. Middle figures: least squares fitting to noisy data for $\eta_{\tau}$. Right figures: results of ACGA on adaptively refined meshes. Computations are done for noise level $\sigma = 40\%$ in $u_4$ and for $T_1 = 100$. 