CHALMERS | UNIVERSITY OF GOTHENBURG

*PREPRINT 2012:15*

# Time-adaptive FEM for distributed parameter identification in biological models

LARISA BEILINA
IRINA GAINOVA

*Department of Mathematical Sciences*
*Division of Mathematics*
CHALMERS UNIVERSITY OF TECHNOLOGY
UNIVERSITY OF GOTHENBURG
Gothenburg Sweden 2012

Preprint 2012:15

# Time-adaptive FEM for distributed parameter identification in biological models

Larisa Beilina and Irina Gainova

Department of Mathematical Sciences
Division of Mathematics
Chalmers University of Technology and University of Gothenburg
SE-412 96 Gothenburg, Sweden

Gothenburg, September 2012

Preprint 2012:15
ISSN 1652-9715

Matematiska vetenskaper
Göteborg 2012

# Time-adaptive FEM for distributed parameter identification in biological models

Larisa Beilina* and Irina Gainova†

**Abstract** We propose a time-adaptive finite element method for the solution of a parameter identification problem for ODE which describes dynamical systems of biological models. We present framework of a posteriori error estimate in the Tikhonov functional, Lagrangian and in the reconstructed function. We also present time-mesh relaxation property in the adaptivity, formulate the time-mesh refinement recommendation and an adaptive algorithm which can be used to find optimal values of the distributed parameters in biological models.

## 1 Introduction

In the present state of the art, disease control over such hard widespread infections as HIV, hepatitis C, tuberculosis, etc. calls for interdisciplinary approaches and joint efforts of researchers and clinicians all over the world. Although a highly efficient antiretroviral therapy (HAART) was developed about 20 years ago, a number of problems still remain to be solved concerning its application in the case of HIV-1 infection caused by an etiological agent (human immunodeficiency virus type 1) [1, 2].

Study of biological systems using analysis of mathematical models of these systems is important and difficult task. These models are powerful tool to understand behavior of the complex biological systems or processes. Main challenging problem in the study of the mathematical models is estimation of the unknown parameters of ODE of these models from observed clinical data. Identifying the model parameters using solution of the corresponding inverse problem in theory enables one to eval-

Larisa Beilina*
Department of Mathematical Sciences, Chalmers University of Technology and Gothenburg University, SE-42196 Gothenburg, Sweden, e-mail: larisa.beilina@chalmers.se

Irina Gainova†
Sobolev Institute of Mathematics, 630090 Novosibirsk, Russia, e-mail: gajnova@math.nsc.ru

uate the drug efficiency, to strike a composite between a scheme and dose applied in the disease course. This also makes allowance for the individual peculiarities of a patient and eventually permits an optimum personal treatment to be developed.

In this paper we propose time-adaptive finite element method for the solution of a Parameter Identification Problem for system of ODE which arises in description of different biological processes, for example, see [3] and references therein. To do that we utilize recent results on the Adaptive Finite Element Method (adaptivity) for solution of hyperbolic coefficient inverse problem, see [4, 11, 12, 13, 14, 15, 17, 18, 19, 21] and chapter 4 of [16]. We also present relaxation property in adaptivity in time which is based on results of [21] and reformulate theorems of [21] for our specific case of system of ODE.

By the relaxation property we understand that the accuracy of the computed solution in time improves with the refinements of the initial time-mesh. Recently the relaxation property in the adaptive finite element method in space applied to the solution of CIPs was observed numerically in many publications, see, e.g. [4, 11, 12, 13, 14, 15, 17, 18, 19]. Analytically this property was proved for the first time in [21]. In the current paper we present the relaxation property on the time-dependent meshes for system of ODE.

The adaptive finite element method for CIPs was developed in [8, 11, 12, 13, 14, 15], and for the parameter identification problem, see [9] and references therein, which are different from CIPs, to some other ill-posed problems, see, e.g. [23, 25, 26].

The idea of adaptivity consists in the minimization of the Tikhonov functional on a locally refined finite element meshes using a posteriori error estimates for the finite element approximation of the problem under investigation. Since we are working with a finite number of a locally refined meshes then the corresponding finite element space is a finite dimensional one. Thus, all norms in finite dimensional spaces are equivalent, then we use the same norm in the Tikhonov regularization term as the one in the original space. Because of that we are using $L_2$-norm in the regularization term of the Tikhonov functional and derive a posteriori error estimates also in this norm. A posteriori error estimates in $L_2$-norm are more efficient from the computational point of view than the standard case of a stronger norm [7, 16, 27, 30, 31] in this term.

The proposed a posteriori error estimate for the Tikhonov functional is used in the time-adaptive algorithm of section 7. We are planning to check this estimate in numerical experiments on implementation of a parameter identification problem for the ODE system which describes the HIV infection dynamics [3] in the future research.

# 2 Forward and Parameter Identification Problems in biological models

## 2.1 *Statements of the forward and parameter identification problems with applications in biology*

Let us denote by $\Omega_T = (0,T)$ the time domain for $T > 0$, where $T$ is the final observation time in some mathematical model arisen in biology and governed by the system of ODE

$$\frac{dx}{dt} = f(x(t), q(t)), \ \ t \in (0,T) \tag{1}$$

$$x(0) = 0. \tag{2}$$

Here, $x(t) \in C^1(\Omega_T)$ is a given state variable in time $t \in \Omega_T$. Problems governed by the system of ODE (1)-(2) arises in different mathematical models for the parameter estimation $q(t)$ which depends on the time variable $t$. These mathematical models describes different biological dynamic systems, see, for example, [3] and references therein.

The right hand side of equation (1) depends on the vector of parameters $q(t) \in C^1(\Omega_T)$. Further we assume that $f \in C^1(\Omega_T)$ with respect to state $x(t)$ and parameters $q(t)$. In our consideration the function $q(t) \in C\ (\mathbf{R}^1)$ belongs to the set of admissible functions $M_q$ such that

$$M_q = \{q(t) : q(t) \ \in \ (0,d) \text{ in } \Omega_T, \ q(t) = 0 \text{ outside of } \Omega_T\} \tag{3}$$

with $d > 1$ be a number. Usually, $d = 1$ and in this case function $0 \leq q(t) \leq 1$ represents the maximal efficiency of the biochemical process described by system of ODE. For example, in [3] system of ODE (1)-(2) presents the mathematical model for the progression of HIV infection and treatment, and the function $0 \leq q(t) \leq 1$ in this system represents the drug efficiency.

**Parameter Identification Problem (**PIP**)**. Let conditions (3) hold. Assume that the function $q(t)$ is unknown inside the domain $\Omega_T$. Determine this function for $t \in \Omega_T$, assuming that the following function $g(t)$ is known

$$x(t) = g(t), \ \ t \in (0,T). \tag{4}$$

The function $g(t)$ represents measurements of the function $x(t)$ inside the time interval $\Omega_T$.

## 2.2 The Tikhonov functional

Let $H$ be the Hilbert space of functions defined in $\Omega_T$. Let $\zeta \in (0,1)$ be a sufficiently small number. Consider the function $z_\zeta \in C^\infty[0,T]$ such that

$$z_\zeta(t) = \begin{cases} 1, t \in [0, T-2\zeta], \\ 0, t \in [T-\zeta, T], \\ \in [0,1], \text{ for } t \in [0, T-2\zeta, T-\zeta]. \end{cases} \tag{5}$$

The Tikhonov regularization functional for the above formulated PIP corresponding to the following state problem of system of ODE

$$\frac{du}{dt} = f(u(t), q(t)), \quad t \in (0,T) \tag{6}$$

$$u(0) = 0 \tag{7}$$

is

$$\begin{aligned} E_\alpha(q) &= \frac{1}{2}\int_{\Omega_T} (u(t)-g(t))^2 z_\zeta(t)\,dt + \frac{1}{2}\alpha\int_{\Omega_T} (q(t)-q_0)^2 dt, \\ E_\alpha &: H \to R, \quad q_0 \in H, \end{aligned} \tag{8}$$

Here, $q_0$ is the initial guess for the parameter vector $q(t)$ and $\alpha$ is the small regularization parameter.

Our goal is to find function $q(t) \in H$ which minimizes the Tikhonov functional (8). To do that we seek for a stationary point of (8) with respect to $q$ which satisfies $\forall \overline{q} \in H$

$$E'_\alpha(q)(\overline{q}) = 0. \tag{9}$$

It is well-known [5] that the functional (8) has the Fréchet derivative and it is strongly convex [21, 16] such that

$$(E'_\alpha(x) - E'_\alpha(y), x-y) \geq \alpha ||x-y||^2. \tag{10}$$

## 2.3 The Lagrangian

To find minimum of the Tikhonov regularization functional (8) we construct the corresponding Lagrangian. To do that first we introduce the following spaces,

$$\begin{aligned} H_u^1(\Omega_T) &= \{f \in H^1(\Omega_T) : f(0) = 0\}, \\ H_\lambda^1(\Omega_T) &= \{f \in H^1(\Omega_T) : f(T) = 0\}, \\ U &= H_u^1(\Omega_T) \times H_\lambda^1(\Omega_T) \times L_2(\Omega_T), \end{aligned} \tag{11}$$

where all functions are real valued. To compute the Fréchet derivative of the functional $E_\alpha(q)$, we introduce the Lagrangian $L(v) := L(\lambda, u, q)$,

$$L(v) = E_\alpha(q) + \int_{\Omega_T} \lambda \left( \frac{du}{dt} - f(u(t), q(t)) \right) dt. \tag{12}$$

where $\lambda$ is the Lagrange multiplier and $v = (\lambda(t), u(t), q(t)) \in U$. We note that if $u(t)$ is a solution of the system of ODE (6)-(7), then $L(v) = E_\alpha(q)$.

We derive the Fréchet derivative of the Lagrangian (12) by a heuristic approach where we assume that the functions $u(t), \lambda(t)$, and $q(t)$ can be varied independently. However, when the Fréchet derivative is calculated, we assume that the solutions of the forward and adjoint problems depend on $q(t)$. A rigorous derivation of the Fréchet derivative requires some smoothness assumptions for the solutions of the state and adjoint problems and will be presented in the another work.

Integration by parts in the second part of the equation (12) together with (7) and condition $\lambda(T) = 0$ leads to

$$L(v) = E_\alpha(q) - \int\limits_{\Omega_T} u \frac{d\lambda}{dt} dt - \int\limits_{\Omega_T} \lambda f(u(t), q(t)) dt. \tag{13}$$

We search for a stationary point of the Lagrangian $L(v)$ which satisfies to the equation

$$L'(v)(\overline{v}) = 0, \quad \forall \overline{v} = (\overline{u}, \overline{\lambda}, \overline{q}) \in U, \tag{14}$$

where $L'(v)$ is the Fréchet derivative of the Lagrangian $L$ at $v$. Now we consider $L(v + \overline{v}) - L(v)$, $\forall \overline{v} \in U$, and single out the linear part of this expression with respect to $\overline{v}$. Hence, from equations (13) and (14) we obtain

$$\begin{aligned} L'(v)(\overline{v}) = & \int\limits_{\Omega_T} \overline{u}(u-g) z_\zeta(t)\, dt + \alpha \int\limits_{\Omega_T} \overline{q}(q - q_0) dt \\ & + \int\limits_{\Omega_T} \overline{\lambda} \left(\tfrac{du}{dt} - f(u,q)\right) dt - \int\limits_{\Omega_T} \overline{u} \tfrac{d\lambda}{dt} dt \\ & - \int\limits_{\Omega_T} \overline{u} \lambda f_1(u,q) dt - \int\limits_{\Omega_T} \overline{q} \lambda f_2(u,q) dt. \end{aligned} \tag{15}$$

Here, functions $f_1(u,q)$ and $f_2(u,q)$ are obtained after taking the Fréchet derivative of the Lagrangian $L(v)$ with respect to $u$ and $q$, correspondingly, and are derived as $f_1(u,q) = \frac{d f(u,q)}{du}$, $f_2(u,q) = \frac{d f(u,q)}{dq}$. Bringing out $\overline{v}$ we get following expression for the Fréchet derivative of the Lagrangian $L$ at $v$

$$\begin{aligned} L'(v)(\overline{v}) = & \int\limits_{\Omega_T} \overline{\lambda} \left( \tfrac{du}{dt} - f(u,q) \right) dt \\ & + \int\limits_{\Omega_T} \overline{u} \left( (u-g) z_\zeta(t) - \tfrac{d\lambda}{dt} - \lambda f_1(u,q) \right) dt \\ & + \int\limits_{\Omega_T} \overline{q} \left( \alpha (q - q_0) - \lambda f_2(u,q) \right) dt. \end{aligned} \tag{16}$$

From equations (14) and (15) we observe that every integral term in equation (16) equals zero. This means that in equation (16) the terms with $\bar{\lambda}$ correspond to the forward problem (6)- (7), the terms with $\bar{u}$ are the weak form of the following adjoint equation

$$-\frac{d\lambda}{dt} = \lambda f_1(u,q) - (u-g)z_\zeta(t),\ t \in \Omega_T, \tag{17}$$
$$\lambda(T) = 0. \tag{18}$$

The terms with $\bar{q}$ in (16) correspond to the derivative of the Lagrangian with respect to the function $q$, or to the equation $L'_q(\bar{q}) = 0$. Thus, we can find $q(t)$ from the equation

$$\alpha(q-q_0) - \lambda f_2(u,q) = 0, \tag{19}$$

or

$$q(t) = \frac{\lambda f_2(u,q)}{\alpha} + q_0,\ \ t \in \Omega_T. \tag{20}$$

To find the function $q(t)$ from (20), we need first to solve the state problem (6)-(7) to get function $u \in H_u^1$ and then, by knowing the solution of the state problem, we need to solve the adjoint problem (17)- (18) to get the function $\lambda \in H_\lambda^1$.

We note, that the adjoint problem (17)-(18) should be solved backwards in time $(T,0)$. Uniqueness and existence theorems for the equations (6)-(7) and (17)-(18), including weak solutions, can be done similarly with Chapter 4 of [29].

## 3 A Finite Element Method to solve equation (14)

For discretization of (13) we use the finite element method. We approximate solutions of state (6)-(7) and adjoint (17)- (18) problems with continuous piecewise linear basis functions in time. In $\Omega_T$ we use a partition $\mathscr{J}_\tau = J$ of the time interval $I = (0,T)$ into time intervals $J = (t_{k-1}, t_k]$ of the length $\tau_J = t_k - t_{k-1}$. We associate with the partition $\mathscr{J}_\tau$ the piecewise-constant time-mesh function $\tau$ such that

$$\tau(t) = \tau_J,\ \ \forall J \in I. \tag{21}$$

We introduce the finite element spaces $W_h^u \subset H_u^1(\Omega_T)$ and $W_h^\lambda \subset H_\lambda^1(\Omega_T)$ for $u$ and $\lambda$, respectively, as

$$\begin{aligned} W_h^u &= \{f \in H_u^1 : f|_J \in P^1(J) \forall J \in J_\tau\}, \\ W_h^\lambda &= \{f \in H_\lambda^1 : f|_J \in P^1(J) \forall J \in J_\tau\}. \end{aligned} \tag{22}$$

For the function $q(t)$ we also introduce the finite element space $V_h \subset L_2(\Omega_T)$ consisting of piecewise constant functions

$$W_h^q = \{f \in L_2(\Omega_T) : f|_J \in P^0(J) \forall J \in J_\tau\}. \tag{23}$$

Next we denote $U_h = W_h^u \times W_h^\lambda \times W_h^q$ such that $U_h \subset U$.

The finite element method for (14) now is to find $v_h \in U_h$ such that

$$L'(v_h;\overline{v}) = 0, \quad \forall \overline{v} \in U_h. \tag{24}$$

More specifically, equation (24) expresses that the finite element method for (14) is to find $v_h = (u_h, \lambda_h, q_h) \in U_h$ such that $\forall \overline{v} = (\overline{u}, \overline{\lambda}, \overline{q}) \in U_h$

$$\int_{\Omega_T} \frac{du_h}{dt} \cdot \overline{u} dt = \int_{\Omega_T} f_h(u_h, q_h) \cdot \overline{u} dt, \tag{25}$$

$$-\int_{\Omega_T} \frac{d\lambda_h}{dt} \cdot \overline{\lambda} dt = \int_{\Omega_T} \lambda_h f_{1h}(u_h, q_h) \cdot \overline{\lambda} dt - \int_{\Omega_T} (u_h - g) z_\zeta(t) \cdot \overline{\lambda} dt, \tag{26}$$

$$\int_{\Omega_T} q_h \cdot \overline{q} dt = \int_{\Omega_T} \left( \frac{\lambda_h f_{2h}(u_h, q_h)}{\alpha} + q_0 \right) \overline{q} dt. \tag{27}$$

## 4 An a Posteriori Error Estimate for the Lagrangian

In this section we briefly present main steps in the derivation of a posteriori error estimate in the Lagrangian (13).

We consider the function $v \in U$ as a minimizer of the Lagrangian $L$, and $v_h \in U_h$ and a minimizer of this functional on $U_h$. In this consideration the function $v$ is a solution of (14) and $v_h$ is a solution of (24).

We assume that we know good approximation to the exact solution $v^* \in U$. Since measurements $g(t)$ in (4) are always given with some noise level (small) $\sigma$ we assume that

$$g(t) = g^*(t) + g_\delta(t); \, g^*, g_\delta \in L_2(\Omega_T), \|g_\delta\|_{L_2(\Omega_T)} \leq \delta. \tag{28}$$

where $g^*(t)$ is the exact data and the function $g_\delta(t)$ represents the error in these data.

The *a posteriori* error estimate $e := L(v) - L(v_h)$ for the Lagrangian is based on the consideration

$$\begin{aligned} L(v) - L(v_h) &= \int_0^1 \frac{\mathrm{d}}{\mathrm{d}s} L(sv + (1-s)v_h) \mathrm{d}s \\ &= \int_0^1 L'(sv + (1-s)v_h)(v - v_h) \mathrm{d}s = L'(v_h)(v - v_h) + R, \end{aligned} \tag{29}$$

where $R = \mathscr{O}\left(\sigma^2\right)$. We assume that $\sigma$ is small and then we can ignore $R$ in (29). We refer to [21] and [7] for similar results in the case of a general nonlinear operator equation.

Using Galerkin orthogonality (24) together with the splitting $v - v_h = (v - v_h^I) + (v_h^I - v_h)$, where $v_h^I$ is an interpolant of $v \in V$, see section 76.4 of [22]. It can be easily derived from formula (76.3) of [22] that

$$\left\| v - v_h^I \right\|_{L_2(\Omega_T)} \leq C_I \left\| \tau \frac{dv}{dt} \right\|_{L_2(\Omega_T)}, \forall v \in V, \tag{30}$$

where $C_I = C_I(\Omega_T) = const > 0$ is the interpolation constant. By one of well known properties of orthogonal projection operators,

$$\|v - P_n v\| \leq \left\|v - v_h^I\right\|, \ \forall v \in V. \tag{31}$$

Hence, from (30) and (31) follows that

$$\|v - P_n v\|_{L_2(\Omega)} \leq C_I \left\|\tau \frac{dv}{dt}\right\|_{L_2(\Omega)}, \forall v \in V. \tag{32}$$

Recalling (29) we obtain the following error representation for the Lagrangian

$$L(v) - L(v_h) \approx L'(v_h)(v - v_h^I). \tag{33}$$

In (33) terms $L'(v_h)$ represents residuals and $(v - v_h^I)$ - interpolation errors. Next, $v - v_h^I$ can be estimated in terms of derivatives of $v$ and the mesh parameter $\tau$ using formulas (31)-(32). Finally, we approximate the derivatives of $v$ by the corresponding derivatives of $v_h$, similarly with [11, 14].

The dominating contribution to the error in the Lagrangian occurs in the residuals of the reconstruction of $q(t)$, which can be estimated by

$$A(t) = |\alpha(q - q_0) - \lambda f_2(u,q)|. \tag{34}$$

Thus, the error in the Lagrangian may be decreased by refining the time mesh locally in the regions where the absolute value of the $L_q'(t)$ attains its maximum.

Theorem 4.1 can be easily derived from a combination of Theorems 4.7.1, 4.7.2 and 4.8 of [16] as well as from Theorems 3.1, 3.2 of [18].

**Theorem 4.1**. *Let $\Omega_T \subset \mathbf{R}^1$. For every function $q \in M_q$ functions $v, \lambda \in H^1(Q_T)$, where $u, \lambda$ are solutions of state and adjoint problems (6)-(7) and (17)-(18). Next, for every $q \in M_q$ there exists Fréchet derivative $E_\alpha'(q)$ of the Tikhonov functional $E_\alpha(q)$ in (8) and*

$$E_\alpha'(q)(t) = \alpha(q(t) - q_0) - \lambda f_2(u(t), q(t)). \tag{35}$$

*The functional of the Fréchet derivative $E_\alpha'(q)$ acts on any function $b \in H^1(\Omega_T)$ as $E_\alpha'(q)(b) = \int\limits_{\Omega_T} E_\alpha'(q)(t)\, b(t)\, dt$.*

## 5 An a posteriori error estimate for the Tikhonov functional

In the Theorem 5 we derive an a posteriori error estimate for the error in the Tikhonov functional (8) on the finite element time-mesh $J$.

**Theorem 5**

*Suppose that there exists minimizer $q_\alpha \in H^1(\Omega_T)$ of the functional $E_\alpha(q)$. Suppose also that there exists finite element approximation of a minimizer $q_h \in W_h^q$*

*of $E_\alpha$. Then the following approximate a posteriori error estimate for the error $e = |E_\alpha(q_\alpha) - E_\alpha(q_h)|$ in the Tikhonov functional (8) holds*

$$e = |E_\alpha(q_\alpha) - E_\alpha(q_h)| \leq C_I C \left\| E'_\alpha(q_h) \right\|_{L^2(\Omega_T)} \max_{\tau_J} \tau_J^{-1} ||[q_h]||_{L_2(\Omega_T)} \tag{36}$$

with positive constants $C_I, C > 0$ and where

$$E'_\alpha(q_h)(t) = \alpha(q_h(t) - q_0) - \lambda_h f_2(u_h(t), q_h(t)). \tag{37}$$

**Proof**

By definition of the Frechét derivative we can write that on the mesh $J$ we have

$$E_\alpha(q_\alpha) - E_\alpha(q_h) = E'_\alpha(q_h)(q_\alpha - q_h) + R(q_\alpha, q_h), \tag{38}$$

where $R(q_\alpha, q_h) = O((q_\alpha - q_h)^2),\ (q_\alpha - q_h) \to 0\ \forall q_\alpha, q_h \in W_h^q$. The term $R(q_\alpha, q_h)$ is small since we assume that $q_h$ is the minimizer of the Tikhonov functional on the mesh $J$ and this minimizer is located in a small neighborhood of the regularized solution $q_\alpha$. Because of that we neglect $R$ in (38). Next, we use the splitting

$$q_\alpha - q_h = q_\alpha - q_\alpha^I + q_\alpha^I - q_h \tag{39}$$

and the Galerkin orthogonality

$$E'_\alpha(q_h)(q_\alpha^I - q_h) = 0\ \forall q_\alpha^I, q_h \in W_h^q \tag{40}$$

to get

$$E_\alpha(q_\alpha) - E_\alpha(q_h) \leq E'_\alpha(q_h)(q_\alpha - q_\alpha^I), \tag{41}$$

where $q_\alpha^I$ is a standard interpolant of $q_\alpha$ on the mesh $J$ [22]. We have that

$$|E_\alpha(q_\alpha) - E_\alpha(q_h)| \leq ||E'_\alpha(q_h)||_{L^2(\Omega_T)} ||q_\alpha - q_\alpha^I||_{L^2(\Omega_T)}, \tag{42}$$

where the term $||q_\alpha - q_\alpha^I||_{L^2(\Omega_T)}$ can be estimated via the interpolation estimate with the constant $C_I$

$$||q_\alpha - q_\alpha^I||_{L^2(\Omega_T)} \leq C_I ||\tau \, \frac{\partial q_\alpha}{\partial t}||_{L^2(\Omega_T)}.$$

Now we substitude above estimate into (42) to get

$$|E_\alpha(q_\alpha) - E_\alpha(q_h)| \leq C_I \left\| E'_\alpha(q_h) \right\|_{L^2(\Omega_T)} ||\tau \, \frac{\partial q_\alpha}{\partial t}||_{L^2(\Omega_T)}. \tag{43}$$

Using that

$$|\frac{\partial q_\alpha}{\partial t}| \leq \frac{|[q_h]|}{\tau_J}, \tag{44}$$

where $[q_h]$ is the jump of the function $q_h$ over the time intervals $[t_{k-1}, t_k]$ and $[t_k, t_{k+1}]$ defined as

$$[q_h] = q_h^+ - q_h^-$$

with functions $q_h^-, q_h^+$ computed on $[t_{k-1}, t_k]$ and $[t_k, t_{k+1}]$, respectively, we can get from (45) with a constant $C > 0$ (see details in [28] for a similar derivation on the space mesh)

$$|E_\alpha(q_\alpha) - E_\alpha(q_h)| \leq C_I C \left\| E'_\alpha(q_h) \right\|_{L^2(\Omega_T)} \max_{\tau_J} \tau_J^{-1} ||[q_h]||_{L^2(\Omega_T)}. \tag{45}$$

## 6 Relaxation property for the functional $E_\alpha(q)$

In this section we specify the relaxation property of [21] for the functional $E_\alpha(q)$ defined in (8). Let $M_q$ be the set of admissible parameters defined in (3) and $U_h$ be the finite dimensional space of finite elements. We define the set $G$ as $G := M_q \cap U_h$. We consider the set $G$ as the subset of the space $U_h$ with the same norm as in $U_h$. We define the operator $F$ as

$$F : \overline{G} \to L_2(\Omega_T), F(q)(t) = z_\zeta(t)\left[g(t) - u(t,q)\right],\ t \in \Omega_T, \tag{46}$$

where the function $u := u(t,q)$ is the weak solution of the state problem (6)-(7), $g$ is the function in (4) and $z_\zeta(t)$ is the function defined in (5).

To make sure that the operator $F$ is one-to-one, we need assume that there exists unique solution of our PIP. Therefore, we introduce Assumption 6.1.

**Assumption 6.1.** *The operator $F(c)$ defined in (46) is one-to-one.*

Theorem 6.3 follows from Theorems 3.3 of [20], 4.1 and 6.2.

**Theorem 6.3.** *Let $\Omega_T \subset \mathbf{R}^1$. Let Assumption 6.1 and condition (28) hold. Let the function $u = u(t,q) \in H^1(\Omega_T)$ in (8) be the solution of the state problem (6)-(7) for the function $q \in G$. Assume that there exists the exact solution $q^* \in G, q^*(t) \in [1,d]$ of the equation $F(q^*) = 0$ for the case when in (28) the function $g$ is replaced with the function $g^*$. Let in (28) $\alpha = \alpha(\delta) = \delta^{2\mu}, \mu = const. \in (0,1/4)$. Let in (8) the function $q_0 \in G$ be such that $\|q_0 - q^*\| < \frac{\delta^{3\mu}}{3}$. Then there exists a sufficiently small number $\delta_0 = \delta_0\left(\Omega_T, d, z_\zeta, \mu\right) \in (0,1)$ such that for all $\delta \in (0,\delta_0)$ the neighborhood $V_{\delta^{3\mu}}(c^*)$ of the function $q^*$ is such that $V_{\delta^{3\mu}}(q^*) \subset G$ and the functional $E_\alpha(q)$ is strongly convex in $V_{\delta^{3\mu}}(q^*)$ with the strong convexity constant $\alpha/4$:*

$$\|q_1 - q_2\|^2 \leq \frac{2}{\delta^{2\mu}}\left(E'_\alpha(q_1) - E'_\alpha(q_2), q_1 - q_2\right),\ \forall q_1, q_2 \in G, \tag{47}$$

*where $(\cdot,\cdot)$ is the scalar product in $L_2(\Omega_T)$ and the Fréchet derivative $E'_\alpha$ is calculated using (35). Next, there exists the unique regularized solution $q_{\alpha(\delta)}$, and $q_{\alpha(\delta)} \in V_{\delta^{3\mu}/3}(q^*)$. In addition, the gradient method of the minimization of the functional $E_\alpha(q)$, converges to $q_{\alpha(\delta)}$. Let $\xi \in (0,1)$ be an arbitrary number. Then there exists a number $\delta_1 = \delta_1\left(\Omega_T, d, z_\zeta, \mu, \xi\right) \in (0,\delta_0)$ such that $\left\|q_{\alpha(\delta)} - q^*\right\| \leq \xi\|q_0 - q^*\|, \forall \delta \in (0,\delta_1)$. Next, ( 47) implies that*

$$\left\|q - q_{\alpha(\delta)}\right\|_{L_2(\Omega_T)} \leq \frac{2}{\delta^{2\mu}} \left\|E'_\alpha(q)\right\|_{L_2(\Omega_T)}. \tag{48}$$

Theorem 6.4 presents *a posteriori* error estimate between the computed function $q_n$ obtained on the mesh after $n$ mesh refinements and the regularized solution $q_\alpha$. Theorem 6.4 follows from Theorems 5.1 of [20] and 6.3 as well as from Theorem 4.11.3 of [16].

**Theorem 6.4.** *Let conditions of Theorem 6.3 hold. Let $\|q^*\| \leq A$, where the constant $A$ is given. Let $M_n \subset U_h$ be the subspace obtained after $n$ mesh refinements. Let $h\tau_n$ be the maximal time step of the subspace $M_n$. Let $C_I$ be the constant in (32). Then there exists a constant $\overline{N}_2$ such that if $\tau_n \leq \frac{\delta^{4\mu}}{A\overline{N}_2 C_I}$, then there exists the unique minimizer $q_n$ of the functional (8) on the set $G \cap M_n$, $q_n \in V_{\delta^{3\mu}}(q^*) \cap M_n$ and the following a posteriori error estimate holds*

$$\left\|q_n - q_{\alpha(\delta)}\right\| \leq \frac{2}{\delta^{2\mu}} \left\|E'_{\alpha(\delta)}(q_n)\right\|_{L_2(\Omega)}. \tag{49}$$

Theorem 6.5 presents relaxation property of the adaptivity in time. It follows from Theorems 5.2, 5.3, 6.4 as well as from Theorem 4.11.4 of [16].

**Theorem 6.5** (relaxation property of the adaptivity in time)**.** *Assume that conditions of Theorem 6.4 hold. Let $q_n \in V_{\delta^{3\mu}}(x^*) \cap M_n$ be the unique minimizer of the Tikhonov functional (8) on the set $G \cap M_n$ (Theorem 6.4). Assume that the regularized solution $q_{\alpha(\delta)} \neq q_n$, i.e. $q_{\alpha(\delta)} \notin M_n$. Let $\eta \in (0,1)$ be an arbitrary number. Then one can choose the maximal time step $\tau_{n+1} = \tau_{n+1}\left(A, \overline{N}_2, C_I, \delta, z_\zeta, \mu, \eta\right) \in (0, \tau_n]$ of the mesh refinement number $(n+1)$ so small that*

$$\left\|q_{n+1} - q_{\alpha(\delta)}\right\| \leq \eta \left\|q_n - q_{\alpha(\delta)}\right\| \leq \frac{2\eta}{\delta^{2\mu}} \left\|E'_{\alpha(\delta)}(q_n)\right\|_{L_2(\Omega_T)}. \tag{50}$$

*Let $\xi \in (0,1)$ be an arbitrary number. Then there exists a sufficiently small number $\delta_0 = \delta_0\left(A, \overline{N}_2, C_I, \delta, z_\zeta, \xi, \mu, \eta\right) \in (0,1)$ and a decreasing sequence of maximal time steps $\{\tau_k\}_{k=1}^{n+1}, \tau_k = \tau_k\left(A, \overline{N}_2, C_I, \delta, z_\zeta, \xi, \mu.\eta\right)$ such that if $\delta \in (0, \delta_0)$, then*

$$\|q_{k+1} - q^*\| \leq \eta^k \left\|q_1 - q_{\alpha(\delta)}\right\| + \xi \|q_0 - q^*\|, k = 1, ..., n. \tag{51}$$

Theorem 6.6 follows from Theorems 5.4 of [20] and 6.5 and presents relaxation property of the adaptivity for local mesh refinements.

**Theorem 6.6**. *Assume that conditions of Theorem 6.5 hold. Let $\Omega = \Omega_{T1} \cup \Omega_{T2}$. Suppose that mesh refinements in time are performed only in the subdomain $\Omega_{T2}$. Let $\tau^{(1)}$ be the maximal grid step size in $\Omega_{T1}$. Then there exists a sufficiently small number $\delta_0 = \delta_0\left(A, \overline{N}_2, C_I, \delta, z_\zeta, \xi, \mu, \eta\right) \in (0,1)$ and a decreasing sequence of maximal time steps $\{\widetilde{\tau}_k\}_{k=1}^{n+1}, \widetilde{\tau}_k = \widetilde{\tau}_k\left(A, \overline{N}_2, C_I, \delta, z_\zeta, \xi, \mu, \eta\right)$ of time-meshes in $\Omega_{T2}$ such that if*

$$\frac{2C_I\overline{N}_3}{\delta^{2\mu}} \left\|\frac{dq_{\alpha(\delta)}}{dt}\right\|_{L_\infty(\Omega_{T1})} \tau^{(1)} \leq \frac{\eta}{2} \left\|q_k - q_{\alpha(\delta)}\right\|, k = 1, ..., n \text{ and } \delta \in (0, \delta_0), \tag{52}$$

*then (51) holds with the replacement of* $\{\tau_k\}_{k=1}^{n+1}$ *with local time steps in the refined meshes* $\{\widetilde{\tau}_k\}_{k=1}^{n+1}$.

## 7 The Time-Mesh Refinement Recommendation and the Adaptive Algorithm

We now present recommendation for mesh refinement in time which is based on the Theorem 5.

**The Time Mesh Refinement Recommendation.**

*Refine the time-mesh $J$ in neighborhoods of those time-mesh points $t \in \Omega_{T2}$ where the function $|E'_\alpha(q_h)(t)|$ attains its maximal values. Here, the function $E'_\alpha(q_h)(t)$ is given by formula (38). More precisely, let $\beta_1 \in (0,1)$ be the tolerance number. Refine the time-mesh in such subdomains of $\Omega_{T2}$ where*

$$\left|E'_\alpha(q_h)(t)\right| \geq \beta_1 \max_{\overline{\Omega_{T2}}} \left|E'_\alpha(q_h)(t)\right|. \tag{53}$$

Now we will present our adaptive algorithm which uses above time-mesh refinement recommendation. On every time-mesh $J$ we find an approximate solution of the equation $E'_\alpha(q) = 0$. Hence, on every mesh we should find an approximate solution of the equation (19).

For each newly refined time-mesh we first linearly interpolate the initial guess-function $q_0(t)$ on it and iteratively update approximations $q_h^m$ of the function $q_h$, where $m$ is the number of iteration in optimization procedure. Let us denote the gradient with respect to the function $q$ on the iteration $m$ in the gradient method by $g^m(t) = \alpha(q_h^m - q_0)(t) - \lambda_h^m(t) f_{2h}(u_h^m, q_h^m)$ where functions $u_h\left(t, q_h^m\right), \lambda_h\left(t, q_h^m\right)$ are calculated finite element solutions of state and adjoint problems with the computed already $q_h^m$, and $f_{2h}$ is the computed approximation of the function $f_2(u,h) = \frac{df}{dq}$.

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

**Time-Adaptive algorithm**

- Step 0. Choose an initial time partition $J_k, k = 0$ of the time interval $(0,T)$. Start with the known initial approximation $q_h^0$ and compute the sequence of $q_h^m$ via the following steps:
- Step 1. Compute solutions $u_h = u_h\left(t, q_h^m\right)$ and $\lambda_h = \lambda_h\left(t, q_h^m\right)$ of state (6)- (7) and adjoint (17)- (18) problems, respectively, on the time-mesh $J_k$.
- Step 2. Update the function $q_h := q_h^{m+1}$ on $J_k$ using the gradient method as $q_h^{m+1} = q_h^m + \gamma g^m(t)$, where $\gamma$ is the step-size in the gradient update given by one-dimensional search algorithm [24].
- Step 3. Stop computing $q_h^m$ and obtain the function $q_h$ if either $||g^m||_{L_2(\Omega_T)} \leq \theta$ or norms $||g^m||_{L_2(\Omega_T)}$ are stabilized. Otherwise set $m := m+1$ and go to step 1. Here $\theta$ is the tolerance in gradient method.

- Step 4. Compute the function $B_h(t)$, $B_h(t) = \left| \alpha \, (q_h - q_0)(t) - \lambda_h f_2(u_h, q_h)(t) \right|$. Next, refine the mesh at all points where

$$B_h(x) \geq \beta_1 \max_{\overline{\Omega_2}} B_h(x). \tag{54}$$

Here the tolerance number $\beta_1 \in (0,1)$ is chosen by the user.
- Step 5. Construct a new time partition $J_k$ of the time interval $(0,T)$. Interpolate the initial approximation $q_0$ from the previous time-mesh to the new time-mesh. Next, return to step 1 and perform all above steps on the new time-mesh.
- Step 6. Stop time-mesh refinements if norms defined in step 3 either increase or stabilize, compared with the previous mesh.

**Acknowledgements** This research was supported by the Swedish Research Council, the Swedish Foundation for Strategic Research (SSF) in Gothenburg Mathematical Modelling Centre (GMMC), the Swedish Institute, Visby Program, the program of the Russian Academy of Sciences Basic Research for Medicine and the Russian Foundation for Basic Research (Grant 11-01-00117).

## References

1. V.A. Chereshnev, S.I. Bazhan, B.A. Bakhmetev, I.A. Gainova, G.A. Bocharov, Systems Analysis of HIV Infection Pathogenesis, *Biology Bulletin Reviews*, 132(2), 115-140, 2012.
2. R. Medzhitov and D. Littman, HIV immunology needs a new direction: Commentary, *Nature*, 455(7213), 591, 2008.
3. B.M. Adams, H.T. Banks, M. Davidian, H.-D. Kwon, H.T. Tran, S.N. Wynne, E.S. Rosenberg, HIV dynamics: Modeling, data analysis, and optimal treatment protocols, *JCAM*, 184, 10-49, 2005.
4. M. Asadzadeh and L. Beilina, *A posteriori* error analysis in a globally convergent numerical method for a hyperbolic coefficient inverse problem, *Inverse Problems*, 26, 115007, 2010.
5. A. B. Bakushinsky, M. Y. Kokurin, A. Smirnova, *Iterative methods for ill-posed problems*, Walter de Gruyter GmbH&Co., 2011.
6. A.B. Bakushinsky, *A posteriori* error estimates for approximate solutions of irregular operator equations, *Doklady Mathematics*, 83, 1-2, 2011.
7. A.B. Bakushinskii and M.Yu. Kokurin, *Iterative Methods for Approximate Solution of Inverse Problems*, Springer, New York, 2004.
8. W. Bangerth and A. Joshi, Adaptive finite element methods for the solution of inverse problems in optical tomography, *Inverse Problems* 24, 034011, 2008.
9. R. Becker and R. Rannacher, An optimal control approach to *a posteriori* error estimation in finite element method, *Acta Numerica*, 10, 1-102, 2001.
10. L. Beilina, K. Samuelsson and K. Åhlander, Efficiency of a hybrid method for the wave equation. In *International Conference on Finite Element Methods*, Gakuto International Series Mathematical Sciences and Applications. Gakkotosho CO., LTD, 2001.
11. L. Beilina and C. Johnson, A hybrid FEM/FDM method for an inverse scattering problem. In *Numerical Mathematics and Advanced Applications - ENUMATH 2001*, Springer-Verlag, Berlin, 2001.
12. L. Beilina, Adaptive finite element/difference method for inverse elastic scattering waves, *Applied and Computational Mathematics*, 1, 158-174, 2002.
13. L. Beilina and C. Johnson, *A posteriori* error estimation in computational inverse scattering, *Mathematical Models and Methods in Applied Sciences*, 15, 23-37, 2005.

14. L. Beilina and C. Clason, An adaptive hybrid FEM/FDM method for an inverse scattering problem in scanning acoustic microscopy, *SIAM J. Sci. Comp.*, 28, 382-402, 2006.
15. L. Beilina, Adaptive finite element method for a coefficient inverse problem for the Maxwell's system, *Applicable Analysis*, 90, 1461-1479, 2011.
16. L. Beilina and M.V. Klibanov, *Approximate Global Convergence and Adaptivity for Coefficient Inverse Problems*, Springer, New York, 2012.
17. L. Beilina and M.V. Klibanov, Synthesis of global convergence and adaptivity for a hyperbolic coefficient inverse problem in 3D, *J. Inverse and Ill-posed Problems*, 18**,** 85-132, 2010.
18. L. Beilina and M.V. Klibanov, *A posteriori* error estimates for the adaptivity technique for the Tikhonov functional and global convergence for a coefficient inverse problem, *Inverse Problems*, 26**,** 045012, 2010.
19. L. Beilina and M.V.Klibanov, Reconstruction of dielectrics from experimental data via a hybrid globally convergent/adaptive inverse algorithm, *Inverse Problems*, 26, 125009, 2010.
20. L. Beilina and M.V.Klibanov, Relaxation property of the adaptivity technique for some ill-posed problems, preprint, Department of Mathematical Sciences, Chalmers University of Technology and Göteborg University, ISSN 1652-9715; nr 2012:4.
21. L. Beilina, M.V. Klibanov and M.Yu Kokurin, Adaptivity with relaxation for ill-posed problems and global convergence for a coefficient inverse problem, *Journal of Mathematical Sciences*, 167, 279-325, 2010.
22. K. Eriksson, D. Estep and C. Johnson, *Calculus in Several Dimensions*, Springer, Berlin, 2004.
23. T. Feng, N. Yan and W. Liu, Adaptive finite element methods for the identification of distributed parameters in elliptic equation, *Advances in Computational Mathematics*, 29, 27-53, 2008.
24. R. Fletcher, *Practical methods of optimization*, John Wiley and Soms, Ltd, 1986.
25. A. Griesbaum, B. Kaltenbacher and B. Vexler, Efficient computation of the Tikhonov regularization parameter by goal-oriented adaptive discretization, *Inverse Problems*, 24, 025025, 2008.
26. B. Kaltenbacher, A. Krichner and B. Vexler, Adaptive discretizations for the choice of a Tikhonov regularization parameter in nonlinear inverse problems, *Inverse Problems*, 27, 125008, 2011.
27. B. Kaltenbacher, A. Neubauer and O. Scherzer, *Iterative Regularization Methods for Nonlinear Ill-Posed Problems*, de Gruyter, New York, 2008.
28. N.A. Koshev, L. Beilina, A posteriori error estimates for the Fredholm integral equation of the first kind, accepted to book series *Springer Proceedings in Mathematics*, 2012.
29. O. A. Ladyzhenskaya, *Boundary Value Problems of Mathematical Physics*, Springer Verlag, Berlin, 1985.
30. A. N. Tikhonov and V. Ya. Arsenin, *Solutions of Ill-Posed Problems*, Winston and Sons, Washington, DC, 1977.
31. A.N. Tikhonov, A.V. Goncharsky, V.V. Stepanov and A.G. Yagola, *Numerical Methods for the Solution of Ill-Posed Problems*, London: Kluwer, London, 1995.