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COUPLING NONLINEAR ELECTRIC FIELDS AND TEMPERATURE TO ENHANCE DRUG TRANSPORT: AN ACCURATE NUMERICAL TOOL

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ABSTRACT: The main motivation of the present work is the numerical study of a system of Partial Differential Equations that governs drug transport, through a target tissue or organ, when enhanced by the simultaneous action of an electric field and a temperature rise. The electric field, while forcing charged drug molecules through the tissue or the organ, thus creating a convection field, also leads to a rise in temperature that affects drug diffusion. The differential system is composed by a nonlinear elliptic equation, describing the potential of the electric field, and by two parabolic equations: a diffusion-reaction equation for temperature and a convection-diffusion-reaction for drug concentration. The temperature and the concentration equations are coupled with the potential equation via a reaction term and the convection and diffusion terms respectively. As the parabolic equations depend directly on the potential and its gradient, the central question is the design and mathematical study of an accurate method for the elliptic equation and its gradient. We propose a finite difference method, which is equivalent to a fully discrete piecewise linear finite element method, with superconvergent/supercloseness properties. The method is second order convergent with respect to a H^1-discrete norm for the elliptic problem, and with respect to a L^2-discrete norm for the two parabolic problems. The stability properties of the method are also analyzed. Numerical experiments illustrating the drug transport for different electrical protocols are also included.

Keywords: Finite difference methods, Piecewise linear finite element methods, Supraconvergence, Supreconvergence, Iontophoresis, Temperature, Drug delivery.

1. Introduction

In this paper our aim is to propose an accurate numerical method to compute an approximation for the system of partial differential equations

$$-\nabla \cdot (\sigma(|\nabla \phi|)\nabla \phi) = f \ \text{ in } \Omega, \tag{1}$$

$$\frac{\partial T}{\partial t} = \nabla \cdot (D_T(T)\nabla T) + G(T) + F(\nabla \phi) \ \text{ in } \Omega \times (0, T_f], \tag{2}$$

$$\frac{\partial c}{\partial t} + \nabla \cdot (v(T, \nabla \phi)c) = \nabla \cdot (D_d(T)\nabla c) + Q(c) \ \text{ in } \Omega \times (0, T_f]. \tag{3}$$

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In system (1)-(3), $\Omega = (a, b)$, $T_f > 0$ denotes a final time, σ, D_T, v, D_d, F, G and Q represent smooth functions whose regularity will be specified later. For simplicity we assume that (1)-(3) is completed with the following boundary and initial conditions

$$\phi = 0,\ T = 0,\ c = c_{\partial\Omega} \ \text{ on } \ \partial\Omega \times (0, T_f] \tag{4}$$

and

$$T(0) = T_0,\ c(0) = c_0 \ \text{ in } \Omega. \tag{5}$$

System (1)-(3) can be used to describe drug transport through a target tissue or organ, when an electric field is used as an enhancer (see for instance [4, 10, 17, 21]). Transdermal Drug Delivery (TDD) presents many advantages when compared with different routes of administration, essentially because it avoids first-pass metabolism in the liver, that is, premature metabolization of drugs. The biggest issue in TDD is the difficulty to overcome the stratum corneum barrier. Following Praunitz ([20]) we can classify transdermal delivery systems in three generations:

(1) The first generation can be identified with passive permeation;
(2) The second generation is characterized by the use of enhancers as for example chemical enhancers or electrical enhancers that provide an electrical driving force for transport across stratum corneum by applying a continuous low-voltage current (iontophoresis);
(3) The third generation enables stronger disruption of the stratum corneum barrier by applying, for example, novel chemical enhancers or short (milliseconds) high-voltage pulses (electroporation).

If we consider the effect of electric fields on TDD, in equation (1), ϕ represents the electric potential and σ denotes the electrical conductivity coefficient. Depending on the media and phenomena, σ can be assumed constant or a function of the magnitude of the gradient of the potential field.

For the transdermal electroporation case, for instance in [4] the authors propose the following expression for σ

$$\sigma(y) = \sigma_1 + (\sigma_0 - \sigma_1) \frac{e^{\frac{1}{B}(y - y_1)} - 1}{e^{\frac{1}{B}(y - y_0)} - 1}\ , \tag{6}$$

where σ_i, y_i, $i = 0, 1$, and B are suitable constants and y denotes the magnitude of the gradient of the potential field.

Equation (2) can be viewed as the Pennes' bioheat equation [18]

$$\rho k_s \frac{\partial T}{\partial t} = \nabla \cdot (D_T \nabla T) - \omega_m c_b (T - T_a) + q + F(\nabla \phi), \tag{7}$$

where T denotes the temperature, ρ represents the tissue density, k_s is the specific heat of the tissue, D_T is the thermal conductivity, T_a is the arterial blood temperature, q is the metabolic volumetric heat generation, ω_m is the nondirectional blood flow associated with perfusion and c_b is the specific heat of blood. In (7), F is given by

$$F(\nabla \phi) = \sigma(|\nabla \phi|)|\nabla \phi|^2, \tag{8}$$

which accounts for the Joule heating effect of the electric field on the medium.

In equation (3), D_d is the diffusion coefficient and v is the convective velocity that is given by the modified Nernst-Planck equation

$$v(T, \nabla \phi) = D_d \frac{zF_r}{TR} \nabla \phi + v_b, \tag{9}$$

where z is the drug valence, F_r Faraday's constant, R represents the universal gas constant and v_b denotes the electro-osmotic convective velocity.

The use of electrical fields to enhance drug transport through the skin is a usual procedure. Nowadays we witness the application of electric fields to enhance drug transport and drug absorption in contexts like pancreatic cancer [7, 8], breast cancer [15], ophthalmic applications (see [14, 16] and the references therein).

Drug release assisted by an electrical field involves different phenomena: a temperature enhanced diffusion and an electrical driven transport during the pulses. To model accurately the cascade of phenomena it is important to study how the temperature rise affects the diffusion coefficient and the convection rate of the drug molecules, and how the electric field generates a convective field. In equation (3) these three dependencies are included through $n(T, \nabla \phi)$ and $D_d(T)$ and $D_T(T)$.

From a medical point of view, the efficacy of the delivery prediction depends on the completeness of the continuous description, the accuracy of the numerical method and on the accuracy of parameters estimation. We will not address this last aspect in the present paper.

Iontophoresis and electroporation are both methods of transdermal drug delivery, based on the use of electrical fields: long low voltage (LLV) pulses and short high voltage (SHV) pulses, respectively. SHV pulses lead to a larger increase in temperature while LLV pulses create a convective field that increases the efficacy of the release. A combination of LLV pulses with SHV pulses is a promising approach that can further enhance drug transport. It is this medical problem that we address in this paper by designing different combination protocols. The novelty in our approach is the fact that the mathematical model describes not only the convection field induced by the electrical field, but also the rise of temperature observed in the targets. We believe that the approach, while being an exploratory study, can contribute to clarify TDD assisted by electrical fields.

From a mathematical point of view, the central question is the numerical solution of the initial boundary value problem (IBVP) (1)-(5). In fact, if the numerical approximation of the solution of the elliptic equation (1) is such that the numerical gradient does not converge to the corresponding continuous gradient or if it converges with a lower convergence order, then the numerical approximation for the concentration does not converge to the corresponding continuous concentration or it converges with lower convergence order, respectively. This problem was previously studied by two of the authors in [2] for the nonFickian transport in a porous medium when Darcy's law is replaced by a linear elliptic equation for the pressure. Fickian transport in porous media was considered in [12].

The main objective of the present paper is to design a numerical method for the IBVP (1)-(5) that leads to second order approximations for the numerical gradient of ϕ and for the temperature T and consequently leads to a second order approximation for the approximation of c. The main ingredients in our study are the extension of the results presented in [3] to the nonlinear elliptic equation (1) and the approach followed in [2, 12]. The numerical method introduced in what follows belongs to the class of finite difference methods (FDM) but it is equivalent to a fully discrete in space piecewise linear finite element method (PLFEM). We will show that

(1) the FD approximation for ϕ is second order convergent to ϕ with respect to a discrete H^1-norm;
(2) the numerical approximations for T and c are second order convergent to T and c, respectively, with respect to a discrete L^2-norm.

In the framework of Finite Difference Methods these results are unexpected because the truncations errors associated with the discretizations are only of first order with respect to the norm $\| \cdot \|_\infty$. If we look at the methods as a

Finite Element Methods the same argument is valid because they are based on piecewise linear finite elements.

The paper is organized as follows. In Section 2 we introduce the basic notations and definitions. In Section 3 we analyse the convergence properties of the discretization of the elliptic equation (1). The convergence properties of the semi-discrete approximations for T and c are studied in Section 4. Finally, in Section 5, we present numerical experiments illustrating the main convergence results as well as the qualitative behaviour of the solution of the IBVP (1)-(5) and some conclusions are presented in Section 6.

2. Notations and basic definitions

In what follows we assume that $c_{\partial\Omega} = 0$. Let $w : \overline{\Omega} \times [0, T_f] \longrightarrow \mathbb{R}$. For $t \in [0, T_f]$, by $w(t)$ we represent the function $w(t) : \overline{\Omega} \longrightarrow \mathbb{R}$ such that $w(t)(x, y) = w(x, y, t)$, $(x, y) \in \overline{\Omega}$. We use the notation $L^2(\Omega)$ and $H^1_0(\Omega)$ to denote the usual Sobolev spaces and, for $m \in \mathbb{N}_0$, by $H^m(0, T_f, V)$ we represent the space of functions $w : \overline{\Omega} \times [0, T_f] \to \mathbb{R}$ such that $w^{(j)}(t) \in V$, $j = 0, \ldots, m$, where $w^{(j)}(t)$ is the weak time derivative of order j.

The weak problem of the IBVP (1)-(5) reads as:

find $(\phi, T, c) \in H^1_0(\Omega) \times [L^2(0, T_f, H^1_0(\Omega)) \cap H^1(0, T_f, L^2(\Omega))]^2$ such that

$$(\sigma(|\nabla\phi|), \nabla\psi) = (f, \psi),\ \forall \psi \in H^1_0(\Omega),$$

$$(T'(t), w) + a_T(T(t), w) = (G(T(t)), w) + (F(\nabla\phi, w) \text{ a.e. in } (0, T_f), \quad (10)$$

$\forall w \in H^1_0(\Omega)$,

$$(c'(t), u) + a_c(c(t), u) = (Q(c(t)), u) \text{ a.e. in} \,(0, T_f),\ \forall u \in H^1_0(\Omega), \qquad (11)$$

and

$$(T(0), w) = (T_0, w),\ \forall w \in L^2(\Omega),\ (c(0), u) = (c_0, u),\ \forall u \in L^2(\Omega).$$

In (10) and (11) the following notations were used

$$a_T(T(t), w) = (D_T(T(t))\nabla T(t), \nabla w),$$

$$a_c(c(t), u) = (D_d(T(t))\nabla c(t), \nabla u) - (v(T(t), \nabla\phi)c(t), \nabla u).$$

To introduce the piecewise linear FE approximations for $\phi, T(t)$ and $c(t)$, we consider a sequence Λ of vectors $h = (h_1, \ldots, h_n)$, $h_i > 0$, $i = 1, \ldots, N$, and such that $\sum_{i=1}^N h_i = b - a$. and let h_{max} be defined by $h_{max} = \max_i h_i \to 0$. We assume that Λ is such that $h_{max} \to 0$. For $h \in \Lambda$, let $\overline{\Omega}_h$ be the nonuniform grid $\overline{\Omega}_h = \{x_i,\ i = 0, \ldots, N\}$ with $x_0 = a$, $x_N = b$, $x_i = x_{i-1} + h_i$, $i = 1, \ldots, N$ and let $\Omega_h = \overline{\Omega}_h - \{x_0, x_N\}$ and $I_i = (x_{i-1}, x_i)$, $i = 1, \ldots, N$. We denote by W_h the vector space of grid functions defined in $\overline{\Omega}_h$ and $W_{h,0}$ represents the subspace of W_h of zero valued functions on the boundary points $\partial\Omega_h = \{x_0, x_N\}$. For $u_h \in W_h$, we denote by $P_h u_h$ the piecewise linear interpolator of u_h.

The piecewise linear FE approximations for ϕ, $T(t)$ and $c(t)$ are then the solution of the following system

$$
\begin{aligned}
&(\sigma(|\nabla P_h\phi_h|), \nabla P_h\psi_h) = (f, \psi_h),\ \forall\psi \in W_{h,0},\\
&(P_h T_h'(t), w_h) + a_T(P_h T_h(t), P_h w_h) = (G(P_h T_h(t)), P_h w_h)\\
&\qquad + (F(\nabla P_h\phi_h, P_h w_h) \text{ a.e. in } (0, T_f),\ \forall w_h \in W_{h,0},\\
&(P_h c_h'(t), u_h) + a_c(P_h c_h(t), P_h u_h) = (Q(P_h c_h(t), P_h u_h) \text{ a.e. in } (0, T_f),\ \forall u_h \in W_{h,0},\\
&(P_h T_h(0), P_h w_h) = (P_h R_h T_0, P_h w_h),\ \forall w_h W_{h,0},\\
&(P_h c_h(0), P_h u_h) = (P_h R_h c_0, P_h u_h),\ \forall u_h \in W_{h,0}.
\end{aligned}
\tag{12}
$$

In (12), R_h denotes the restriction operator $R_h : C(\overline{\Omega}) \longrightarrow W_h$, defined by $R_h g(x_i) = g(x_i)$, $i = 0, \ldots, N$, $g \in C(\overline{\Omega})$.

We represent by D_{-x} the usual backward finite difference operator. We introduce the finite difference operators D_x^*, D_c and D_h as follows:

$$D_x^* u_h(x_i) = \frac{u_h(x_{i+1}) - u_h(x_i)}{h_{i+1/2}},\ i = 1, \ldots, N-1,$$

$$D_h u_h(x_i) = \frac{h_{i+1} D_{-x} u_h(x_i) + h_i D_{-x} u_h(x_{i+1})}{h_{i+1} + h_i},\ i = 1, \ldots, N-1,$$

$$D_c u_h(x_i) = \frac{u_h(x_{i+1}) - u_h(x_{i-1})}{h_{i+1} + h_i},\ i = 1, \ldots, N-1,$$

where $h_{i+1/2} = \frac{h_i + h_{i+1}}{2}$. We also define M_h to be the following average operator

$$M_h u_h(x_i) = \frac{u_h(x_i) + u_h(x_{i-1})}{2},\ i = 1, \ldots, N.$$

If $g \in L^1(\Omega)$, then by $(g)_h$ we represent the following discrete function

$$
\begin{aligned}
(g)_h(x_0) &= \frac{1}{h_1}\int_{x_0}^{x_{1/2}} g(x)dx,\\
(g)_h(x_i) &= \frac{1}{h_{i+1/2}}\int_{x_{i-1/2}}^{x_{i+1/2}} g(x)dx,\ i = 1, \ldots, N-1,\\
(g)_h(x_N) &= \frac{1}{h_N}\int_{x_{N-1/2}}^{x_N} g(x)dx
\end{aligned}
$$

where $x_{i+1/2} = x_i + h_{i+1/2}$, $i = 0, \ldots, N-1$.

We now introduce some discrete inner products and norms on the previous grid function spaces. In the space $W_{h,0}$ we introduce the inner product

$$(u_h, w_h)_h = \sum_{i=1}^{N-1} h_{i+1/2} u_h(x_i) w_h(x_i),\ \forall u_h, w_h \in W_{h,0}.$$

and the corresponding norm

$$\|u_h\|_h = \sqrt{(u_h, u_h)_h}$$

that can be seen as a discrete version of the usual L^2-norm. For $u_h, w_h \in W_h$ we use the notations

$$(u_h, w_h)_+ = \sum_{i=1}^{N} h_i u_h(x_i) w_h(x_i),\ \forall u_h, w_h \in W_h,$$

and

$$\|u_h\|_+ = \sqrt{(u_h, u_h)_+}.$$

Using the previous notation, we introduce in $W_{h,0}$ the discrete H^1-norm

$$\|u_h\|_{1,h}^2 = \|u_h\|_h^2 + \|D_{-x} u_h\|_+^2,\ \forall u_h \in W_h.$$

The fully discrete FE approximations for $\phi, T(t), c(t) \in H_0^1(\Omega)$ are then defined by

$$(\sigma(|D_{-x}\phi_h|) D_{-x}\phi_h, D_{-x}\psi_h)_+ = ((f)_h, \psi_h)_h,\ \ \forall \psi_h \in W_{h,0}, \tag{13}$$

$$\begin{aligned}(T_h'(t), w_h)_h + a_{T_h}(T_h(t), w_h) &= (G(T_h(t)), w_h)_h \\ &+ (F(D_h\phi_h), w_h)_h \text{ in } (0, T_f],\ \ \forall w_h \in W_{h,0},\end{aligned} \tag{14}$$

$$(c_h'(t), u_h)_h + a_{c_h}(c_h(t), u_h) = (Q(c_h(t)), u_h)_h \text{ in } (0, T_f],\ \forall u_h \in W_{h,0}, \tag{15}$$

$$T_h(0) = R_h T_0,\ c_h(0) = R_h c_0 \text{ in } \Omega_h, \tag{16}$$

where

$$a_{T_h}(T_h(t), w_h) = (D_T(M_h T_h(t)) D_{-x} T_h(t), D_{-x} w_h)_+,$$

and

$$\begin{aligned}a_{c_h}(c_h(t), u_h) &= -(M_h(v(T_h(t), D_h\phi_h) c_h(t)), D_{-x} u_h)_+ \\ &+(D_d(M_h T_h(t)) D_{-x} c_h(t), D_{-x} u_h)_+.\end{aligned}$$

We remark that the fully discrete FE approximations defined by (13)-(16) can be obtained solving the following nonlinear finite difference system

$$-D_x^*(\sigma(|D_{-x}\phi_h|) D_{-x}\phi_h) = (f)_h \text{ in } \Omega_h, \tag{17}$$

$$T_h'(t) = D_x^*(D_T(M_h(T_h(t)))D_{-x}T_h(t)) + G(T_h(t)) + F(D_h\phi_h) \text{ in } \Omega_h \times (0, T_f], \tag{18}$$

$$\begin{aligned} c_h'(t) + D_c(v(T_h(t), D_h\phi_h)c_h(t)) = D_x^*(D_d(M_h(T_h(t)))D_{-x}c_h(t)) \\ + Q(c_h(t)) \text{ in } \Omega_h \times (0, T_f], \end{aligned} \tag{19}$$

where we take $D_h\phi_h(x_0) = D_{-x}\phi_h(x_1)$ and $D_h\phi_h(x_N) = D_{-x}\phi_h(x_N)$. System (17)-(19) is completed with the initial conditions (16) and the boundary conditions

$$T_h(t) = c_h(t) = 0 \text{ on } \partial\Omega_h \times (0, T_f].$$

3. Analysis of the FDM (FEM) for the nonlinear elliptic equation

This section aims to study the stability and convergence properties of the piecewise linear FEM (13) or equivalently the FDM (17).

3.1. Stability - a first attempt. To study the stability of the nonlinear finite difference operator defined by (17) with Dirichlet boundary conditions we consider $\tilde{\phi}_h$ as the solution of (17) with $(f)_h$ replaced by $\tilde{f}_h$. Then for $\omega_p = \phi_h - \tilde{\phi}_h$ we have

$$(\sigma(|D_{-x}\phi_h|)D_{-x}\phi_h, D_{-x}\omega_p)_+ - \sigma(|D_{-x}\tilde{\phi}_h|)D_{-x}\tilde{\phi}_h, D_{-x}\omega_p)_+ = ((f)_h - \tilde{f}_h, \omega_p)_h,$$

that leads to

$$\begin{aligned} (\sigma(|D_{-x}\tilde{\phi}_h|)D_{-x}\omega_p, D_{-x}\omega_p)_+ = ((\sigma(|D_{-x}\tilde{\phi}_h|) - \sigma(|D_{-x}\phi_h|))D_{-x}\phi_h, D_{-x}\omega_p)_+ \\ + ((f)_h - \tilde{f}_h, \omega_p)_h. \end{aligned}$$

We now impose to σ the following smoothness assumption

$\mathbf{H_1}$: $\sigma \in C_b^1(\mathbb{R}_0^+)$ and $\sigma \geq \beta_0 > 0$ in $\mathbb{R}_0^+$,

where $C_b^1(\mathbb{R}_0^+)$ denotes the space of real functions with bounded derivative in $\mathbb{R}_0^+$ and the corresponding norm is denoted by $\|\cdot\|_{C_b^1(\mathbb{R}_0^+)}$.
Under the assumption $\mathbf{H_1}$ we conclude

$$\begin{aligned} \beta_0\|D_{-x}\omega_p\|_+^2 \leq \|\sigma\|_{C_b^1(\mathbb{R}_0^+)}\|D_{-x}\phi_h\|_\infty\|D_{-x}\omega_p\|_+^2 \\ + \|(f)_h - \tilde{f}_h\|_h\|\omega_p\|_h, \end{aligned} \tag{20}$$

where

$$\|D_{-x}\phi_h\|_\infty = \max_{i=1,\ldots,N} |D_{-x}\phi_h(x_i)|.$$

Since for $u_h \in W_{h,0}$ the discrete Friedrichs-Poincaré inequality $\|u_h\|_h \leq |\Omega| \|D_{-x}u_h\|_+$ holds, where $|\Omega|$ denotes the measure of Ω, from (20) we get

$$(\beta_0 - \|\sigma\|_{C_b^1(\mathbb{R}_0^+)} \|D_{-x}\phi_h\|_\infty - \epsilon^2 |\Omega|^2) \|D_{-x}\omega_p\|_+^2 \leq \frac{1}{4\epsilon^2} \|(f)_h - \tilde{f}_h\|_h^2,$$

where $\epsilon \neq 0$. If we are able to fix ϵ such that

$$\beta_0 - \|\sigma\|_{C_b^1(\mathbb{R}_0^+)} \|D_{-x}\phi_h\|_\infty - \epsilon^2 |\Omega|^2 > 0, \; h \in \Lambda, \tag{21}$$

then we conclude the stability of (17). We remark that condition (21) is equivalent to

$$\|D_{-x}\phi_h\|_\infty < \frac{\beta_0}{\|\sigma\|_{C_b^1(\mathbb{R}_0^+)}}, \; h \in \Lambda. \tag{22}$$

In what follows we show that a uniform upper bound for $\|D_{-x}\phi_h\|_\infty$ like (22) is a consequence of the accuracy of the approximation ϕ_h.

3.2. Supraconvergence - supercloseness.

Theorem 1. *Let $E_\phi = R_h\phi - \phi_h$ where ϕ and ϕ_h are defined by* (1) *and* (17), *respectively. If $\phi \in H^3(\Omega) \cap H_0^1(\Omega)$, assumption $\mathbf{H_1}$ holds and $\beta_0 - \|\sigma\|_{C_b^1(\mathbb{R}_0^+)} \|\phi\|_{C^1(\overline{\Omega})} > 0$ then there exists a constant $C_\phi > 0$ such that*

$$\|D_{-x}E_\phi\|_+^2 \leq C_\phi \sum_{i=1}^{N} h_i^4 \|\phi\|_{H^3(I_i)}^2. \tag{23}$$

Proof: It can be shown that for the error E_ϕ holds the following

$$\begin{aligned}(\sigma(|D_{-x}\phi_h|)D_{-x}E_\phi, D_{-x}E_\phi)_+ &= (\sigma(|D_{-x}\phi_h|)D_{-x}R_h\phi, D_{-x}E_\phi)_+ \\ &\quad - ((f)_h, E_\phi)_h.\end{aligned} \tag{24}$$

For $((f)_h, E_\phi)_h$ we deduce

$$\begin{aligned}((f)_h, E_\phi)_h &= \sum_{i=1}^{N-1} \int_{x_{i-1/2}}^{x_{i+1/2}} -\nabla \cdot (\sigma(|\nabla\phi|)\nabla\phi) dx \, E_\phi(x_i) \\ &= \sum_{i=1}^{N} h_i \sigma(|\nabla\phi(x_{i-1/2})|)\nabla\phi(x_{i-1/2}) D_{-x}E_\phi(x_i) \\ &= (\hat{R}_h(\sigma(|\nabla\phi|)\nabla\phi), D_{-x}E_\phi)_+\end{aligned}$$

where $\hat{R}_h g(x_i) = g(x_{i-1/2}), i = 1, \ldots, N$.

Inserting the last representation in (24) we obtain

$$(\sigma(|D_{-x}\phi_h|)D_{-x}E_\phi, D_{-x}E_\phi)_+ = (\sigma(|D_{-x}\phi_h|)D_{-x}R_h\phi - \hat{R}_h(\sigma(|\nabla\phi|)\nabla\phi), D_{-x}E_\phi)_+. \tag{25}$$

From the representation

$$\begin{aligned}\sigma(|D_{-x}\phi_h|)D_{-x}R_h\phi - \hat{R}_h(\sigma(|\nabla\phi|)\nabla\phi) &= (\sigma(|D_{-x}\phi_h|) - \sigma(|D_{-x}R_h\phi|))D_{-x}R_h\phi \\ &+ (\sigma(|D_{-x}R_h\phi| - \hat{R}_h\sigma(|\nabla\phi|))D_{-x}R_h\phi) \\ &+ \hat{R}_h\sigma(|\nabla\phi|)(D_{-x}R_h\phi - \hat{R}_h\nabla\phi),\end{aligned}$$

equation (25) can be rewritten as

$$(\sigma(|D_{-x}\phi_h|)D_{-x}E_\phi, D_{-x}E_\phi)_+ = \tau_1 + \tau_2 + \tau_3, \tag{26}$$

where

$$\tau_1 = ((\sigma(|D_{-x}\phi_h|) - \sigma(|D_{-x}R_h\phi|))D_{-x}R_h\phi, D_{-x}E_\phi)_+,$$

$$\tau_2 = ((\sigma(|D_{-x}R_h\phi|) - \hat{R}_h\sigma(|\nabla\phi|))D_{-x}R_h\phi, D_{-x}E_\phi)_+$$

and

$$\tau_3 = (\hat{R}_h\sigma(|\nabla\phi|)(D_{-x}R_h\phi - \hat{R}_h\nabla\phi), D_{-x}E_\phi)_+.$$

We now determine upper bounds for τ_i, $i = 1, 2, 3$:

i) For τ_1 we easily establish

$$|\tau_1| \leq \|\phi\|_{C^1(\overline{\Omega})}\|\sigma\|_{C^1_b(\mathbb{R}^+_0)}\|D_{-x}E_\phi\|^2_+. \tag{27}$$

ii) To obtain an estimate for τ_2 we start by remarking that

$$|\tau_2| \leq \|D_{-x}R_h\phi\|_\infty \|\sigma\|_{C^1_b(\mathbb{R}^+_0)} \sum_{i=1}^N h_i|D_{-x}\phi(x_i) - \nabla\phi(x_{i-1/2})||D_{-x}E_\phi(x_i)|$$

and

$$h_i|D_{-x}\phi(x_i) - \nabla\phi(x_{i-1/2})| = |\lambda(1) - \lambda(0) - \lambda'(1/2)|$$

with $\lambda(\xi) = \phi(x_{i-1} + \xi h_i)$, $\xi \in [0, 1]$. Applying the Bramble-Hilbert lemma there exists a constant $C_{BH} > 0$, independent of ϕ and h, such that

$$\begin{aligned}|\lambda(1) - \lambda(0) - \lambda'(1/2)| &\leq C_{BH}\int_0^1 |\lambda^{(3)}(\xi)|d\xi \\ &\leq C_{BH}h_i^2\sqrt{h_i}\|\phi\|_{H^3(I_i)}.\end{aligned}$$

Therefore, we conclude

$$|\tau_2| \leq C_{BH}\|D_{-x}R_h\phi\|_\infty\|\sigma\|_{C_b^1(\mathbb{R}_0^+)}\Big(\sum_{i=1}^N h_i^4\|\phi\|^2_{H^3(I_i)}\Big)^{1/2}\|D_{-x}E_\phi\|_+$$

which finally leads to

$$|\tau_2| \leq \frac{C_{BH}^2}{4\epsilon^2}\|D_{-x}R_h\phi\|^2_\infty\|\sigma\|^2_{C_b^1(\mathbb{R}_0^+)}\sum_{i=1}^N h_i^4\|\phi\|^2_{H^3(I_i)} + \epsilon^2\|D_{-x}E_\phi\|_+^2 \tag{28}$$

for all $\epsilon \neq 0$.

iii) Analogously, for τ_3 we have

$$|\tau_3| \leq \frac{C_{BH}^2}{4\epsilon^2}\|\sigma\|^2_{C_b^1(\mathbb{R}_0^+)}\sum_{i=1}^N h_i^4\|\phi\|^2_{H^3(I_i)} + \epsilon^2\|D_{-x}E_\phi\|_+^2. \tag{29}$$

Inserting (27)-(29) into (26) we arrive to

$$\begin{aligned}&\Big(\beta_0 - 2\epsilon^2 - \|\phi\|_{C^1(\overline{\Omega})}\|\sigma\|_{C_b^1(\mathbb{R}_0^+)}\Big)\|D_{-x}E_\phi\|_+^2\\ &\quad\leq \frac{C_{BH}^2}{4\epsilon^2}\|\sigma\|^2_{C_b^1(\mathbb{R}_0^+)}\Big(1+\|\phi\|^2_{C^1(\overline{\Omega})}\Big)\sum_{i=1}^N h_i^4\|\phi\|^2_{H^3(I_i)}.\end{aligned}$$

Finally, if $\beta_0 - \|\sigma\|_{C_b^1(\mathbb{R}_0^+)}\|\phi\|_{C^1(\overline{\Omega})} > 0$ we guarantee the existence of a positive constant C_ϕ such that (23) holds. ■

Corollary 1. *Under the assumptions of Theorem 1 there exists a positive constant C such that*

$$\|R_h\phi - \phi_h\|_{1,h} \leq Ch_{max}^2.$$

Corollary 2. *Let us suppose that the sequence of grids $\overline{\Omega}_h$, $h \in \Lambda$, are such that there exists a positive constant C_Λ such that*

$$\frac{h_{max}}{h_{min}} \leq C_\Lambda, \tag{30}$$

where $h_{min} = \min_{i=1,\dots,N} h_i$. Then under the assumptions of Theorem 1, for h_{max} sufficiently small, (22) holds.

Proof: We remark that, for $i = 1,\dots,N$, we have

$$\begin{aligned}|D_{-x}\phi_h(x_i)| &\leq \frac{1}{h_{min}}\sum_{j=1}^N h_j|D_{-x}E_\phi(x_j)| + |D_{-x}\phi(x_i)|\\ &\leq \frac{\sqrt{|\Omega|}}{h_{min}}\|D_{-x}E_\phi\|_+ + \|\phi\|_{C^1(\overline{\Omega})}.\end{aligned}$$

Using the estimate from Theorem 1 and (30), there exists a positive constant C h-independent such that

$$\|D_{-x}\phi_h\|_\infty \leq Ch_{max} + \|\phi\|_{C^1(\overline{\Omega})}$$

which concludes the proof. ∎

3.3. Stability - second attempt. As we showed in the beginning of this section, to conclude the stability of (17), with Dirichlet boundary conditions, in ϕ_h, $h \in \Lambda$, we need to impose the uniform boundness of $\|D_{-x}\phi_h\|_\infty, h \in \Lambda$. Corollary 2 establishes that, under the assumptions of Theorem 1, if the sequence of grids $\overline{\Omega}_h$, $h \in \Lambda$, satisfies condition (30) and h_{max} is sufficiently small then the boundness condition (22) holds.

Theorem 2. *Let us suppose that the sequence of grids $\overline{\Omega}_h$, $h \in \Lambda$, satisfy the condition* (30) *and the assumptions of Theorem 1 hold. Let $\tilde{\phi}_h \in W_{h,0}$, $h \in \Lambda$, be defined by* (17) *with $(f)_h$ replaced by $\tilde{f}_h$. If*

$$\beta_0 - \|\sigma\|_{C_b^1(\mathbb{R}_0^+)}\|D_{-x}\phi_h\|_\infty > 0,\ h \in \Lambda$$

then there exists a positive constant C, h-independent, such that

$$\|\phi_h - \tilde{\phi}_h\|_{1,h} \leq C\|(f)_h - \tilde{f}_h\|_h,\ h \in \Lambda.$$

Moreover, if $\tilde{f}_h \in \bar{B}_{\rho_h}((f)_h) = \{g_h \text{ is defined in } \Omega_h : \|g_h - (f)_h\|_h \leq \rho_h\}$, $h \in \Lambda$, where $\rho_h \leq \rho h_{max}$, $h \in \Lambda$, then $\|D_{-x}\tilde{\phi}_h\|$ is uniformly bounded with respect to h.

Proof: Following similar arguments as before, there exists a positive constant C, h-independent, such that it holds

$$\begin{aligned}\|D_{-x}\tilde{\phi}_h\|_\infty &\leq \|D_{-x}(\tilde{\phi}_h - \phi_h)\|_\infty + \|D_{-x}\phi_h\|_\infty \\ &\leq \frac{C}{h_{min}}\|(f)_h - \tilde{f}_h\|_h + \|D_{-x}\phi_h\|_\infty.\end{aligned}$$

We conclude the proof using the uniform bound of $\|D_{-x}\phi_h\|_\infty$, $h \in \Lambda$, and the fact that $\tilde{f}_h \in \bar{B}_{\rho_h}((f)_h)$, $h \in \Lambda$, with $\rho_h \leq \rho h_{max}$, $h \in \Lambda$. ∎

To conclude the stability analysis of our finite difference discretization of the nonlinear elliptic operator we establish the final stability result.

Corollary 3. *Under the assumptions of Theorem 2, if* $f_h^*, \tilde{f}_h \in \bar{B}_{\rho_h}((f)_h)$, $h \in \Lambda$, *with* $\rho_h \leq \rho h_{max}$, $h \in \Lambda$, *and* $\phi_h^*, \tilde{\phi}_h \in W_{h,0}$ *are solutions of the finite difference equations*

$$-D_x^*(\sigma(|D_{-x}\phi_h^*|)D_{-x}\phi_h^*) = f_h^* \text{ in } \Omega_h,$$
$$-D_x^*(\sigma(|D_{-x}\tilde{\phi}_h|)D_{-x}\tilde{\phi}_h) = \tilde{f}_h \text{ in } \Omega_h,$$

then there exists a positive constant C *h-independent such that*

$$\|D_{-x}\phi_h^*\|_\infty \leq C \text{ and } \|D_{-x}\tilde{\phi}_h\|_\infty \leq C,\ h \in \Lambda.$$

Moreover if

$$\beta_0 - \|\sigma\|_{C_b^1(\mathbb{R}_0^+)}\|D_{-x}\phi_h^*\|_\infty > 0 \text{ or } \beta_0 - \|\sigma\|_{C_b^1(\mathbb{R}_0^+)}\|D_{-x}\tilde{\phi}_h\|_\infty > 0,$$

for $h \in \Lambda$, *then there exists a positive constant* C_{stab} *(h-independent) such that*

$$\|\phi_h^* - \tilde{\phi}_h\|_{1,h} \leq C_{stab}\|f_h^* - \tilde{f}_h\|_h,\ h \in \Lambda.$$

4. Temperature analysis: second error estimates with respect to the discrete L^2-norm

4.1. Stability. We start this section by establishing energy estimates for the discrete temperature $T_h(t) \in W_{h,0}$ defined by (14) or (18) and with initial condition $T_h(0)$. We assume that the coefficient functions D_T, G and F satisfy the following assumptions:

$\mathbf{H_2}$: $D_T \in C_b^1(\mathbb{R})$, $D_T \geq \beta_1 > 0$ in $\mathbb{R}$,

$\mathbf{H_3}$: $G(0) = 0$, $(G(u_h) - G(w_h), u_h - w_h)_h \leq \beta_2\|u_h - w_h\|_h^2$, $\forall u_h, v_h \in W_{h,0}$,

$\mathbf{H_4}$: $F(0) = 0$ and F is a Lipschitz function with Lipschitz constant β_3.

The previous assumptions are considered only for theoretical purposes. For instance, if we take Pennes' equation (7), then we could consider in the stability analysis, $G(x) = -\omega_m c_b x$, which is a function that satisfies $\mathbf{H_2}$. However F defined by (8) satisfies $\mathbf{H_3}$ only locally.

Theorem 3. *Under the assumptions* $\mathbf{H_2} - \mathbf{H_4}$, *if the sequence of grids* $\overline{\Omega}_h$, $h \in \Lambda$, *satisfies condition* (30) *and* $T_h \in C^1([0, T_f], W_{h,0})$ *then*

$$\begin{aligned}\|T_h(t)\|_h^2 + 2\beta_1\int_0^t e^{(2\beta_2+1)(t-s)}\|D_{-x}T_h(s)\|_+^2 ds \leq e^{(2\beta_2+1)t}\|T_h(0)\|_h^2 \\ + \frac{2\beta_3^2 C_\Lambda}{2\beta_2+1}\left(e^{(2\beta_2+1)t} - 1\right)\|D_{-x}\phi_h\|_+^2,\end{aligned} \tag{31}$$

for $t \in [0, T_f]$.

Proof: Fixing in (14) $w_h = T_h(t)$, the assumptions $\mathbf{H_2} - \mathbf{H_4}$ and the condition (30) easily leads to

$$\begin{aligned}\frac{d}{dt}\|T_h(t)\|_h^2 + 2\beta_1\|D_{-x}T_h(t)\|_+^2 &\leq 2\beta_2\|T_h(t)\|_h^2 \\ &+2\sqrt{2}\beta_3\sqrt{C_\Lambda}\|D_{-x}\phi_h\|_+\|T_h(t)\|_h, t \in (0, T_f],\end{aligned}$$

that leads to

$$\begin{aligned}\frac{d}{dt}\Big(e^{-(2\beta_2+1)t}\|T_h(t)\|_h^2 + \beta_1\int_0^t e^{-(2\beta_2+1)s}\|D_{-x}T_h(s)\|_+^2 ds \\ - \frac{2\beta_3^2 C_\Lambda}{2\beta_2+1}\big(1 - e^{-(2\beta_2+1)t}\big)\|D_{-x}\phi_h\|_+^2\Big) \leq 0,\ t \in (0, T_f].\end{aligned}$$

Using the smoothness assumption for $T_h(t)$ we finally conclude (31). ■

The combination of Theorem 3 with Corollary 2 allow us to conclude that

$$\|T_h(t)\|_h^2 + 2\beta_1\int_0^t \|D_{-x}T_h(s)\|_+^2 ds$$

is uniformly bounded for $t \in [0, T_f]$ and for $h \in \Lambda$, provided that $2\beta_2 + 1 \geq 0$.

We now establish a first result on the stability of $T_h(t) \in W_{h,0}$ defined by (14) or (18) with respect to the initial condition.

Proposition 1. *Let* $T_h, \tilde{T}_h \in C^1([0, T_f], W_{h,0})$ *denote two solutions with initial condition* $T_h(0)$ *and* $\tilde{T}_h(0)$ *(but both computed with* $\phi_h \in W_{h,0}$ *defined by the fully discrete FEM* (13) *or equivalently the FDM* (17)*). If assumptions* $\mathbf{H_2} - \mathbf{H_3}$ *hold, there exists* $\epsilon \neq 0$ *such that*

$$\begin{aligned}\|\omega_T(t)\|_h^2 + (2\beta_1 - \epsilon^2)\int_0^t e^{\int_s^t(\frac{2}{\epsilon^2}\|D_T\|^2_{C_b^1(\mathbf{R})}\|D_{-x}\tilde{T}_h(\mu)\|_\infty^2 + 2\beta_2)d\mu}\|D_{-x}\omega_T(s)\|_+^2 ds \\ \leq e^{\int_0^t(\frac{2}{\epsilon^2}\|D_T\|^2_{C_b^1(\mathbf{R})}\|D_{-x}\tilde{T}_h(\mu)\|_\infty^2 + 2\beta_2)d\mu}\|\omega_T(0)\|_h^2,\ t \in [0, T_f]. \quad (32)\end{aligned}$$

Proof: Let $\omega_T(t)$ be defined by $\omega_T(t) = T_h(t) - \tilde{T}_h(t)$. Following [11] and using assumption $\mathbf{H_3}$, for $\omega_T(t)$ we easily get

$$\begin{aligned}&\frac{1}{2}\frac{d}{dt}\|\omega_T(t)\|_h^2 + (D_T(M_hT_h(t))D_{-x}\omega_T(t), D_{-x}\omega_T(t))_+ \\ &\quad\leq ((D_T(M_h\tilde{T}_h(t)) - D_T(M_hT_h(t)))D_{-x}\tilde{T}_h(t), D_{-x}\omega_T(t))_+ + \beta_2\|\omega_T(t)\|_h^2.\end{aligned}$$

Using assumption $\mathbf{H_2}$, we establish

$$\frac{d}{dt}\|\omega_T(t)\|_h^2 + 2\beta_1\|D_{-x}\omega_T(t)\|_+^2 \le 2\beta_2\|\omega_T(t)\|_h^2$$
$$+2\sqrt{2}\|D_T\|_{C_b^1(\mathbb{R})}\|D_{-x}\tilde{T}_h(t)\|_\infty\|\omega_T(t)\|_h\|D_{-x}\omega_T(t)\|_+,$$

and consequently we arrive at

$$\begin{aligned}&\frac{d}{dt}\|\omega_T(t)\|_h^2 + (2\beta_1-\epsilon^2)\|D_{-x}\omega_T(t)\|_+^2\\ &\le \left(\frac{2}{\epsilon^2}\|D_T\|^2_{C_b^1(\mathbb{R})}\|D_{-x}\tilde{T}_h(t)\|_\infty^2 + 2\beta_2\right)\|\omega_T(t)\|_h^2,\end{aligned} \tag{33}$$

for $t\in(0,T_f]$ and $\epsilon \neq 0$ (in fact, we can choose ϵ such that $2\beta_1-\epsilon^2>0$ to ensure the positivity of the left hand side of inequality (33)). From (33) we easily conclude (32). ■

We remark that the stability inequality (32) with $T_h(t)$ replaced by $\tilde{T}_h(t)$ can be easily established because

$$\begin{aligned}&((D_T(M_h\tilde{T}_h(t)) - D_T(M_hT_h(t)))D_{-x}\tilde{T}_h(t), D_{-x}\omega_T(t))_+\\ &\qquad = -(D_T(M_h\tilde{T}_h(t))D_{-x}\omega_T(t), D_{-x}\omega_T(t))_+\\ &\qquad + ((D_T(M_h\tilde{T}_h(t)) - D_T(M_hT_h(t)))D_{-x}T_h(t), D_{-x}\omega_T(t))_+.\end{aligned}$$

To guarantee stability from (32) we need to prove that

$$\int_0^t \|D_{-x}\tilde{T}_h(\mu)\|_\infty^2\,d\mu \ \text{ or } \int_0^t \|D_{-x}T_h(\mu)\|_\infty^2\,d\mu$$

are uniformly bounded for $h\in\Lambda$ and $t\in[0,T_f]$.

4.2. Convergence analysis. Let $E_T(t) = R_hT(t) - T_h(t)$, $t\in[0,T_f]$ and

$$H_{\epsilon,\delta}(s,t) = e^{\int_s^t(\frac{1}{\epsilon^2}\|D_T\|^2_{C_b^1(\mathbb{R})}\|T(\mu)\|^2_{C^1(\overline{\Omega})}+2\beta_2+2\beta_3^2\delta^2)d\mu},\ s,t\in[0,T_f]$$

where $\epsilon,\delta\in\mathbb{R}-\{0\}$. An estimate for $\|E_T(t)\|_h$ is established in the next result whose proof follows the one of Theorem 1 of [11].

Theorem 4. *Let T and T_h be solutions of the IBVP* (2) *and* (18)*, with homogeneous Dirichlet boundary conditions and initial values $T(0)$ and $T_h(0)$, respectively. Let ϕ and ϕ_h be solutions of the elliptic equations* (1) *and* (13)*, with homogeneous Dirichlet boundary conditions, respectively. We suppose that*

$$T\in H^1(0,T_f,H^2(\Omega))\cap L^2(0,T_f,H^3(\Omega)\cap H_0^1(\Omega)),\ \phi\in H^3(\Omega)\cap H_0^1(\Omega),$$

$$R_hT,\, T_h \in C^1([0,T_f], W_{h,0}),\ \ G(T(t)) \in H^2(\Omega).$$

If the assumptions $\mathbf{H_2} - \mathbf{H_4}$ *hold and the sequence of grids* $\overline{\Omega}_h$, $h \in \Lambda$, *satisfies condition* (30), *then the following estimate holds*

$$\begin{aligned}\|E_T(t)\|_h^2 + 2(\beta_1 - 5\epsilon^2)\|D_{-x}E_T(s)\|_+^2 ds \leq \|E_T(0)\|_h^2\, H_{\epsilon,\delta}(0,t)\\ + \int_0^t H_{\epsilon,\delta}(s,t)\left(\frac{1}{\delta^2}C_\Lambda\|D_{-x}E_\phi\|_+^2 + \Gamma(s)\right) ds,\end{aligned} \tag{34}$$

where $E_\phi = R_h\phi - \phi_h$, $\epsilon \neq 0$, $\delta \neq 0$, *are constants, and, for* $t \in [0, T_f]$,

$$\begin{aligned}|\Gamma(t)| \leq \frac{C}{\epsilon^2}\Big(1 + \|D_T\|^2_{C_b^1(\mathbb{R})}(1 + \|T(t)\|^2_{C^1(\overline{\Omega})})\Big)\\ \Big(\sum_{i=1}^N h_i^4\Big(\|T'(t)\|^2_{H^2(I_i)} + \|T(t)\|^2_{H^3(I_i)} + \|G(T(t))\|^2_{H^2(I_i)} + \|\phi\|^2_{H^3(I_i)}\Big)\\ + \sum_{i=1}^{N-1}(h_i^4 + h_{i+1}^4)\|\phi\|^2_{H^3(I_i\cap I_{i+1})}\Big)\end{aligned} \tag{35}$$

where C *is a positive constant,* h*-independent.*

Proof: It can be shown that

$$\begin{aligned}&(E_T'(t), E_T(t))_h = (R_hG(T(t)) - G(T_h(t)), E_T(t))_h\\ &\quad -(D_T(M_h(R_hT(t)))D_{-x}R_hT(t) - D_T(M_h(T_h(t)))D_{-x}T_h(t), D_{-x}E_T(t))_+\\ &\quad +(F(D_hR_h\phi) - F(D_h\phi_h), E_T(t))_h\\ &\quad +\tau_d(E_T(t)) + \tau_{D_T}(E_T(t)) + \tau_G(E_T(t)) + \tau_F(E_T(t)),\end{aligned} \tag{36}$$

where

$$\begin{aligned}\tau_d(E_T(t)) &= (R_hT'(t) - (T'(t))_h, E_T(t))_h,\\ \tau_{D_T}(E_T(t)) &= ((\nabla\cdot(D_T(T(t))\nabla T(t)))_h, E_T(t))_h\\ &\quad + (D_T(M_h(R_hT(t)))D_{-x}R_hT(t), D_{-x}E_T(t))_+\\ \tau_G(E_T(t)) &= ((G(T(t)))_h, E_T(t))_h - (R_hG(T(t)), E_T(t))_h\\ \tau_F(E_T(t)) &= ((F(\nabla\phi))_h, E_T(t))_h - (F(D_hR_h\phi), E_T(t))_h.\end{aligned}$$

We establish a convenient representation of the three first terms of the right-hand side of (36). For the first term we have

$$
\begin{aligned}
-&(D_T(M_h(R_hT(t)))D_{-x}R_hT(t) - D_T(M_h(T_h(t)))D_{-x}T_h(t), D_{-x}E_T(t))_+ \\
&= -(D_T(M_hT_h(t))D_{-x}E_T(t), D_{-x}E_T(t))_+ \\
&\quad + ((D_T(M_hT_h(t)) - D_T(M_hR_hT(t)))D_{-x}R_hT(t), D_{-x}E_T(t))_+
\end{aligned}
$$

and considering assumption $\mathbf{H_2}$ we deduce

$$
\begin{aligned}
&-(D_T(M_h(R_hT(t)))D_{-x}R_hT(t) - D_T(M_h(T_h(t)))D_{-x}T_h(t), D_{-x}E_T(t))_+ \\
&\le -\beta_1\|D_{-x}E_T(t)\|_+^2 + \sqrt{2}\|D_T\|_{C_b^1(\mathbb{R})}\|T(t)\|_{C^1(\overline{\Omega})}\|E_T(t)\|_h\|D_{-x}E_T(t)\|_+.
\end{aligned}
\tag{37}
$$

Using assumption $\mathbf{H_3}$, we easily get for the second term the estimate

$$
(R_hG(T(t)) - G(T_h(t)), E_T(t))_h \le \beta_2\|E_T(t)\|_h^2.
$$

For the third term of, a direct application of assumption $\mathbf{H_4}$ and under the hypothesis that the sequence of spatial grids $\overline{\Omega}_h$, $h \in \Lambda$, satisfies condition (30), it can be shown that the following holds

$$
(F(D_hR_h\phi) - F(D_h\phi_h), E_T(t))_h \le \sqrt{2}\beta_3\sqrt{C_\Lambda}\|D_{-x}E_\phi\|_+\|E_T(t)\|_h. \tag{38}
$$

Estimates for $\tau_d(E_T(t))$, $\tau_{D_T}(E_T(t))$, and $\tau_G(E_T(t))$ in (36) were obtained in the proof of Theorem 1 of [11].

(1) For $\tau_d(E_T(t))$, there exists a positive constant C_d, h-independent such that

$$
|\tau_d(E_T(t))| \le C_d\left(\sum_{i=1}^{N} h_i^4\|T'(t)\|_{H^2(I_i)}^2\right)^{1/2}\|D_{-x}E_T(t)\|_+. \tag{39}
$$

provided that $T'(t) \in H^2(\Omega)$.

(2) For $\tau_{D_T}(E_T(t))$ it can be shown that there exists a positive constant, h-independent, C_{D_T} such that

$$
\begin{aligned}
|\tau_{D_T}(E_T(t))| &\le C_{D_T}\|D_T\|_{C_b^1(\mathbb{R})}\left(1 + \|T(t)\|_{C^1(\overline{\Omega})}\right) \\
&\quad \cdot \left(\sum_{i=1}^{N} h_i^4\|T(t)\|_{H^3(I_i)}^2\right)^{1/2}\|D_{-x}E_T(t)\|_+,
\end{aligned}
\tag{40}
$$

provided that $T(t) \in H^3(\Omega) \cap H_0^1(\Omega)$.

(3) For $\tau_G(E_T(t))$ holds a similar result. In fact, there exists a positive constant C_G, h-independent, such that the following holds

$$|\tau_G(E_T(t))| \leq C_G \left(\sum_{i=1}^{N} h_i^4 \|G(T(t))\|^2_{H^2(I_i)} \right)^{1/2} \|D_{-x}E_T(t)\|_+. \tag{41}$$

provided that $G(T(t)) \in H^2(\Omega)$.

(4) To estimate the error term $\tau_F(E_T(t))$ we observe that this error term admits the representation

$$\tau_F(E_T(t)) = \tau_1(t) + \tau_2(t),$$

where

$$\tau_1(t) = ((F(\nabla\phi))_h, E_T(t))_h - (R_hF(\nabla\phi), E_T(t))_h,$$

and

$$\tau_2(t) = (R_hF(\nabla\phi), E_T(t))_h - (F(D_hR_h\phi), E_T(t))_h.$$

Using the same type of approach followed for $\tau_G(E_T(t))$, for the term $\tau_1(t)$, there exists a positive constant $C_{F,1}$, h-independent, such that

$$|\tau_1(t)| \leq C_{F,1}\beta_3 \left(\sum_{i=1}^{N} h_i^4 \|\phi\|^2_{H^3(I_i)} \right)^{1/2} \|D_{-x}E_T(t)\|_+,$$

provided that $\phi \in H^3(\Omega)$. To arrive to an estimate for $\tau_2(t)$ we remark that using the Lipschitz condition for F we have

$$\begin{aligned} |\tau_2(t)| &\leq \beta_3 \sum_{i=1}^{N-1} h_{i+1/2} |\nabla\phi(x_i) - D_h\phi(x_i)||E_T(x_i,t)| \\ &\leq \beta_3 \sum_{i=1}^{N-1} |\lambda(g)||E_T(x_i,t)| \end{aligned} \tag{42}$$

where

$$g(\mu) = \frac{\phi(x_i + \mu h_{i+1}) - \phi(x_i - \mu h_i)}{2}, \forall \mu \in [0,1]$$

and $\lambda(\xi) = \xi'(0) - \xi(1) + \xi(0) + \frac{\xi''(0)}{2}$, $\xi \in H^3(0,1)$. The Bramble-Hilbert lemma guarantees the existence of a positive constant $C_{BH,2}$

such that

$$|\lambda(g)| \leq \frac{C_{BH,2}}{2} \int_0^1 |g^{(3)}(\mu)| d\mu$$
$$\leq \frac{C_{BH,2}}{2} h_i h_{i+1} \int_{x_{i-1}}^{x_{i+1}} |\phi^{(3)}(x)|\, dx.$$

Inserting the last upper bound in (42) we easily get that there exists a positive constant $C_{F,2}$, h-independent, such that

$$|\tau_2(t)| \leq C_{F,2} \left(\sum_{i=1}^{N-1} (h_i^4 + h_{i+1}^4) \|\phi\|^2_{H^3(I_i \cup I_{i+1})} \right)^{1/2} \|D_{-x} E_T(t)\|_+$$

provided that $\phi \in H^3(\Omega) \cap H_0^1(\Omega)$.
Consequently, for $\tau_F(E_T(t))$ we conclude the existence of a positive constant C_F, h-independent, such that

$$|\tau_F(E_T(t))| \leq C_F \left(\left(\sum_{i=1}^{N-1} (h_i^4 + h_{i+1}^4) \|\phi\|^2_{H^3(I_i \cup I_{i+1})} \right)^{1/2} + \left(\sum_{i=1}^{N} h_i^4 \|\phi\|^2_{H^3(I_i)} \right)^{1/2} \right) \|D_{-x} E_T(t)\|_+. \tag{43}$$

Taking into account the upper bounds (37)-(38) and the error estimates (39), (40), (41), (43) in (36) we arrive to

$$\frac{d}{dt} \|E_T(t)\|_h^2 + 2(\beta_1 - 5\epsilon^2) \|D_{-x} E_T(t)\|_+^2$$
$$\leq \left(\frac{2}{\epsilon^2} \|D_T\|^2_{C_b^1(\mathbb{R})} \|T(t)\|^2_{C^1(\overline{\Omega})} + 2\beta_2 + 2\beta_3^2 \delta^2 \right) \|E_T(t)\|_h^2 + \frac{C_\Lambda}{\delta^2} \|D_{-x} E_\phi\|_+^2 + \Gamma(t), \tag{44}$$

where $\epsilon \neq 0$, $\delta \neq 0$, and $|\Gamma(t)|$ is bounded by (35). Finally, inequality (44) leads to (34). ■

Corollary 4. *Under the assumptions of Theorems 1 and 4, there exists a positive constant C_T, h-independent, such that*

$$\|E_T(t)\|_h^2 + \int_0^t \|D_{-x} E_T(s)\|_+^2 ds \leq C_T \left(\|E_T(0)\|_h^2 + h_{max}^4 \right), \; t \in [0, T_f]. \tag{45}$$

Proof: It is enough to fix in (34) ϵ and δ such that

$$\beta_1 - 5\epsilon^2 > 0$$

and

$$\frac{1}{\epsilon^2}\|D_T\|^2_{C^1_b(\mathbb{R})}\|T(\mu)\|^2_{C^1(\overline{\Omega})} + 2\beta_2 + 2\beta_3^2\delta^2 > 0.$$

■

4.3. Again stability. Let us revisit (32). To conclude stability we need to guarantee that

$$\int_0^t \|D_{-x}\tilde{T}_h(s)\|^2_\infty\, ds \text{ or } \int_0^t \|D_{-x}T_h(s)\|^2_\infty\, ds$$

are uniformly bounded in $t \in [0, T_f]$ and $h \in \Lambda$. From Corollary 4, if $\tilde{T}_h(0) \in \overline{B}_r(R_hT(0))$ or $T_h(0) \in \overline{B}_r(R_hT(0))$, with $r = \sqrt{h_{max}}$, then, from (45), for $u_h(t) = T_h(t)$ or $u_h(t) = \tilde{T}_h(t)$, we obtain

$$\|R_hT(t) - u_h(t)\|^2_h + \int_0^t \|D_{-x}(R_hT(s) - u_h(s))\|^2_+ ds \le C\, h_{max},\, t \in [0, T_f]$$

where C is a positive constant, h-independent. Then

$$\begin{aligned}\int_0^t \|D_{-x}u_h(s)\|^2_\infty\, ds &\le \frac{\sqrt{\Omega}}{h_{min}}\int_0^t \|D_{-x}(R_hT(s) - u_h(s))\|^2_+ ds + \int_0^t \|T(s)\|^2_{C^1(\overline{\Omega})} ds\\ &\le \sqrt{\Omega}\frac{h_{max}}{h_{min}} + \int_0^t \|T(s)\|^2_{C^1(\overline{\Omega})} ds\\ &\le \sqrt{\Omega}C_\Lambda + \int_0^t \|T(s)\|^2_{C^1(\overline{\Omega})} ds,\end{aligned}$$

for $t \in [0, T_f]$ and $h \in \Lambda$.

From (32), if $\tilde{T}_h(0) \in \overline{B}_r(R_hT(0))$ or $T_h(0) \in \overline{B}_r(R_hT(0))$, with $r = \sqrt{h_{max}}$, we conclude that for $\omega_T(t) = T_h(t) - \tilde{T}_h(t)$, where $T_h(t)$ and $\tilde{T}_h(t)$ are defined by (18) with ϕ_h given by the fully discrete FEM (13), or equivalently the FDM (17),

$$\|\omega_T(t)\|^2_h + \int_0^t \|D_{-x}\omega_T(s)\|^2_+ ds \le Const\|\omega_T(0)\|^2_h,\ t \in [0, T_f],\ h \in \Lambda, \quad (46)$$

provided that

$$\frac{2}{\epsilon^2}\|D_T\|^2_{C^1_b(\mathbb{R})}\|D_{-x}\tilde{T}_h(t)\|^2_\infty + 2\beta_2 \ge 0, t \in [0, T_f].$$

Inequality (46) shows the stability of (18) under Dirichlet boundary conditions.

5. Concentration - second error estimates with respect the discrete L^2-norm

5.1. Stability. In this section we impose for D_d, v and Q in (3) the following assumptions:

$$\mathbf{H_5}: \ D_d \in C_b^1(\mathbb{R}),\ D_d \geq \beta_4 > 0 \text{ in } \mathbb{R},$$

$$\mathbf{H_6}: \ v(0,0)=0,\ |v(x,y)-v(\tilde{x},\tilde{y})| \leq \beta_5(|x-\tilde{x}|+|y-\tilde{y}|), x, \tilde{x}, y, \tilde{y} \in \mathbb{R},,$$

$$\mathbf{H_7}: \ Q(0)=0, (Q(u_h)-Q(w_h), u_h-v_h)_h \leq \beta_6\|u_h-w_h\|_h^2,\ u_h, w_h \in W_{h,0}.$$

The assumptions $\mathbf{H_5}-\mathbf{H_7}$ are introduced only for the theoretical analysis. In fact, we highlight that the convective velocity v given by (9) does not satisfy assumption $\mathbf{H_5}$. This function is not defined at $x=0$ and is a Lipschitz function only on a bounded set of $\mathbb{R}^2$.

We start by establishing energy estimates for $c_h(t)$ defined by (17), (18), (19) with homogeneous Dirichlet boundary conditions (or by (13), (14), (15)) and initial conditions $T_h(0), c_h(0)$ for the temperature and concentration, respectively.

Theorem 5. *Let us suppose that the assumptions* $\mathbf{H_5}-\mathbf{H_7}$ *hold,* $c_h \in C^1([0,T_f], W_{h,0})$ *and let* ϕ_h, $T_h(t)$, $c_h(t) \in W_{h,0}$ *be defined by* (17)-(19) *with homogeneous Dirichlet boundary conditions (or by* (13)-(15)*) and initial conditions* $T_h(0)$, $c_h(0)$ *for the temperature and concentration, respectively. There exists a nonzero* ϵ *such that we have*

$$\begin{aligned}\|c_h(t)\|_h^2 + 2(\beta_4-\epsilon^2)\int_0^t e^{\int_s^t\left(\frac{\beta_5^2}{\epsilon^2}\left(\sqrt{2}\|T_h(\mu)\|_\infty^2+4\|D_{-x}\phi_h\|_\infty^2\right)+2\beta_6\right)d\mu}\|D_{-x}c_h(s)\|_+^2 ds \\ \leq \|c_h(0)\|_h^2 e^{\int_0^t\left(\frac{\beta_5^2}{\epsilon^2}\left(\sqrt{2}\|T_h(\mu)\|_\infty^2+4\|D_{-x}\phi_h\|_\infty^2\right)+2\beta_6\right)d\mu},\ t\in[0,T_f].\end{aligned} \tag{47}$$

Proof: Taking $u_h = c_h(t)$ in (15) and considering assumptions $\mathbf{H_5}-\mathbf{H_7}$ we deduce

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|c_h(t)\|_h^2 + \beta_4\|D_{-x}c_h(t)\|_+^2 \leq \beta_6\|c_h(t)\|_h^2 \\ \sqrt{2}\beta_5\big(\|T_h(t)\|_\infty + \sqrt{2}\|D_{-x}\phi_h\|_\infty\big)\|c_h(t)\|_h\|D_{-x}c_h(t)\|_+,\ t\in(0,T_f].\end{aligned}$$

Then we arrive to

$$\frac{d}{dt}\|c_h(t)\|_h^2 + 2(\beta_4-\epsilon^2)\|D_{-x}c_h(t)\|_+^2$$
$$\leq \Big(\frac{\beta_5^2}{\epsilon^2}\big(\sqrt{2}\|T_h(t)\|_\infty^2 + 4\|D_{-x}\phi_h\|_\infty^2\big) + 2\beta_6)\|c_h(t)\|_h^2,\ t\in(0,T_f],$$

which leads to (47). ■

From Corollary 2 we know that under suitable assumptions, $\|D_{-x}\phi_h\|_\infty$, $h\in\Lambda$, is bounded. Moreover, under the assumptions of Theorem 3, as $\|T_h(t)\|_\infty \leq \sqrt{|\Omega|}\|D_{-x}T_h(t)\|_+$, if $2\beta_2+1\geq 0$, and $\|T_h(0)\|_h$ is uniformelly bounded with respect to $h\in\Lambda$, then there exists a positive constant C (h and t independent) such that

$$\int_0^t \|T_h(s)\|_\infty^2\,ds \leq C,\ t\in[0,T_f],\ h\in\Lambda,$$

Furthermore, if

$$\frac{\beta_5^2}{\epsilon^2}\left(\sqrt{2}\|T_h(t)\|_\infty^2 + 4\|D_{-x}\phi_h\|_\infty^2\right) + 2\beta_6 \geq 0, t\in[0,T_f], h\in\Lambda,$$

with ϵ such that $\beta_4-\epsilon^2>0$, then

$$\|c_h(t)\|_h^2 + \int_0^t \|D_{-x}c_h(s)\|_+^2 ds,\ t\in[0,T_f], h\in\Lambda,$$

is uniformelly bounded, provided that $\|c_h(0)\|_h$, $h\in\Lambda$, is bounded. Consequently

$$\int_0^t \|c_h(s)\|_\infty^2 ds,\ t\in[0,T_f],$$

is uniformelly bounded with respect to $h\in\Lambda$.

Theorem 6. *Let $T_h, \tilde{T}_h, c_h, \tilde{c}_h \in C^1([0,T_f], W_{h,0})$ be defined by* (18)-(19) *with homogeneous Dirichlet boundary conditions (or by* (14)-(15)*) and initial conditions $T_h(0), \tilde{T}_h(0), c_h(0), \tilde{c}_h(0)$, where $\phi_h\in W_{h,0}$ is defined by* (17) *or* (13)*. Under the assumptions* $\mathbf{H_5}-\mathbf{H_7}$*, for $\omega_c = c_h(t)-\tilde{c}_h(t)$, $\omega_T(t) = T_h(t)-\tilde{T}_h(t)$ we have*

$$\|\omega_c(t)\|_h^2 + (2\beta_4 - 3\epsilon^2)\int_0^t e^{\int_s^t g_h(\mu)d\mu}\|D_{-x}\omega_c(s)\|_+^2 ds \leq \|\omega_c(0)\|_h^2 e^{\int_0^t g_h(\mu)d\mu}$$
$$+\frac{|\Omega|}{\epsilon^2}\int_0^t e^{\int_s^t g_h(\mu)d\mu}\Big(\|D_d\|_{C_b^1(\mathbb{R})}^2\|D_{-x}c_h(s)\|_+^2 + 2\beta_5^2\|\tilde{c}_h(s)\|_h^2\Big)\|D_{-x}\omega_T(s)\|_+^2 ds,$$
(48)

for $t \in [0, T_f]$ and with

$$g_h(\mu) = \left(\frac{2\beta_5^2}{\epsilon^2}(\|T_h(\mu)\|_\infty + \|D_{-x}\phi_h\|_\infty)^2 + 2\beta_6\right), \mu \in [0, T_f].$$

Proof: It can be shown that

$$\begin{aligned} &\frac{1}{2}\frac{d}{dt}\|\omega_c(t)\|_h^2 + (D_d(M_h\tilde{T}_h(t))D_{-x}\omega_c(t), D_{-x}\omega_c(t))_+ \\ &\le ((D_d(M_h\tilde{T}_h(t)) - D_d(M_hT_h(t)))D_{-x}c_h(t), D_{-x}\omega_c(t))_+ \\ &\quad +(M_h(v_h(t)c_h(t) - \tilde{v}_h(t)\tilde{c}_h(t)), D_{-x}\omega_c(t))_+ + \beta_6\|\omega_c(t)\|_h^2, \end{aligned} \tag{49}$$

where $v_h(t) = v(T_h(t), D_h\phi_h)$ and $\tilde{v}_h(t) = v(\tilde{T}_h(t), D_h\phi_h)$.

For the term $(M_h(v_h(t)c_h(t) - \tilde{v}_h(t)\tilde{c}_h(t)), D_{-x}\omega_c(t))_+$, using assumption $\mathbf{H_6}$, it is a straightforward task to show that

$$\begin{aligned} &(M_h(v_h(t)c_h(t) - \tilde{v}_h(t)\tilde{c}_h(t)), D_{-x}\omega_c(t))_+ \\ &\le \sqrt{2}\beta_5\left((\|T_h(t)\|_\infty + 2\|D_{-x}\phi_h\|_\infty)\|\omega_c(t)\|_h + \|\tilde{c}_h(t)\|_h\|\omega_T(t)\|_\infty\right)\|D_{-x}\omega_c(t)\|_+. \end{aligned} \tag{50}$$

As for $((D_d(M_hT_h(t)) - D_d(M_h\tilde{T}_h(t)))D_{-x}c_h(t), D_{-x}\omega_c(t))_+$ we have

$$\begin{aligned} &((D_d(M_hT_h(t)) - D_d(M_h\tilde{T}_h(t)))D_{-x}c_h(t), D_{-x}\omega_c(t))_+ \\ &\le \|D_d\|_{C_b^1(\mathbb{R})}\|D_{-x}c_h(t)\|_+\|\omega_T(t)\|_\infty\|D_{-x}\omega_c(t)\|_+ \end{aligned} \tag{51}$$

Finally, from (49), taking (50)-(51) and $\|\omega_T(t)\|_\infty \le \sqrt{|\Omega|}\|D_{-x}\omega_T(t)\|_+$ we deduce

$$\begin{aligned} &\frac{d}{dt}\|\omega_c(t)\|_h^2 + (2\beta_4 - 3\epsilon^2)\|D_{-x}\omega_c(t)\|_+^2 \\ &\le \left(\frac{2\beta_5^2}{\epsilon^2}(\|T_h(t)\|_\infty + \|D_{-x}\phi_h\|_\infty)^2 + 2\beta_6\right)\|\omega_c(t)\|_h^2 \\ &+\frac{|\Omega|}{\epsilon^2}\Big(\|D_d\|_{C_b^1(\mathbb{R})}^2\|D_{-x}c_h(t)\|_+^2 + 2\beta_5^2\|\tilde{c}_h(t)\|_h^2\Big)\|D_{-x}\omega_T(t)\|_+^2,\ t \in (0, T_f], \end{aligned}$$

that leads to (48).

■

From (48), to conclude the stability result, we need only to notice that

$$\|D_{-x}c_h(t)\|_+,\ \|D_{-x}\omega_T(t)\|_+,\ \|\tilde{c}_h(t)\|_h$$

are uniformly bounded in Λ, a.e. in $[0, T_f]$. In fact, this is a consequence of Theorem 2.14 from [1] and it holds for $\|D_{-x}c_h(t)\|_+$ and $\|\tilde{c}_h(t)\|_h$ due to Theorem 5 provided that $\|c_h(0)\|_h$ and $\|\tilde{c}_h(0)\|_h$ are uniformelly bounded with respect to $h \in \Lambda$. Inequality (46) leads to the same conclusion for $\|D_{-x}\omega_T(t)\|_+$ provided a uniform bound exists for $\|\omega_T(0)\|_h$, $h \in \Lambda$.

5.2. Convergence analysis. We establish in what follows an estimate for the error $E_c(t) = R_h c(t) - c_h(t)$. We follow the proof of the Theorem 2 of [11]. The novelty of the new result lies on the fact that the behaviour of $E_c(t)$ is not only determined by the error $E_T(t) = R_h T(t) - T_h(t)$, as in the Theorem 2 of [11], but also by the error $E_\phi = R_h\phi - \phi_h$.

Theorem 7. *Let*

$$T, c \in L^2(0, T_f, H^3(\Omega) \cap H_0^1(\Omega)),\ c \in H^1(0, T_f, H^2(\Omega)),$$

$$\phi \in H^3(\Omega) \cap H_0^1(\Omega),$$

be solutions of the IBVP (1)-(5). *Let ϕ_h, T_h and c_h be the corresponding approximations defined by* (17)-(19) *with homogeneous Dirichlet boundary conditions and initial conditions $T_h(0)$ and $c_h(0)$. If*

$$R_h c, c_h \in C^1([0, T_f], W_{h,0}),$$

assumptions $\mathbf{H_5} - \mathbf{H_7}$ hold and $Q(c(t)) \in H^2(\Omega)$, then for $E_c(t) = R_h c(t) - c_h(t), E_T(t) = R_h T(t) - T_h(t)$ and $E_\phi = R_h\phi - \phi_h$, there exists a positive constant C, h and t independent, such that

$$\begin{aligned}
&\|E_h(t)\|_h^2 + 2(\beta_4 - 6\epsilon^2)\int_0^t e^{\int_s^t g_h(\mu)d\mu}\|D_{-x}E_c(s)\|_+^2 ds \\
&\quad \le \|E_c(0)\|_h^2 e^{\int_0^t g_h(\mu)d\mu} + \int_0^t e^{\int_s^t g_h(\mu)d\mu}\Gamma(s)ds \\
&\quad +4\frac{\beta_5^2}{\epsilon^2}\int_0^t e^{\int_s^t g_h(\mu)d\mu}\Big(\|E_T(s)\|_h^2 + \|D_{-x}E_\phi\|_+^2\Big)\|c(s)\|_{C^1(\overline{\Omega})}^2 ds,\ t \in (0, T_f],
\end{aligned} \tag{52}$$

where $\epsilon \neq 0$,

$$g_h(\mu) = 4\frac{\beta_5^2}{\epsilon^2}\big(\|T_h(\mu)\|_\infty^2 + \|D_{-x}\phi_h\|_\infty^2\big)\|c(\mu)\|_{C^1(\overline{\Omega})}^2 + 2\beta_6,$$

$$
\begin{aligned}
|\Gamma(t)| \ &\leq \frac{1}{\epsilon^2} C\Big(\sum_{i=1}^N h_i^4 \|c'(t)\|^2_{H^2(I_i)} \\
&\quad +(\|D_d\|^2_{C_b^1(\mathbb{R})}+1)(\|c(t)\|^2_{C^1(\overline{\Omega})}+1) \\
&\qquad \sum_{i=1}^N h_i^4\big(\|T(t)\|^2_{H^2(I_i)}+\|c(t)\|^2_{H^3(I_i)}+\|\phi(t)\|^2_{H^3(I_i)}\big) \\
&\quad +\sum_{i=1}^{N-1}(h_i^4+h_{i+1}^4)\|\phi(t)\|^2_{H^3(I_i\cup I_{i+1})}+\sum_{i=1}^N h_i^4\|Q(c(t))\|^2_{H^2(I_i)}\Big).
\end{aligned} \tag{53}
$$

Proof: Following the proof of Theorem 2 of [11], it can be shown that $E_c(t)$ is solution of the following differential problem

$$
\begin{aligned}
(E_c'(t), E_c(t))_h \ &= -(D_d(M_h(R_hT(t)))D_{-x}R_hc(t) \\
&\quad -D_d(M_h(T_h(t)))D_{-x}c_h(t), D_{-x}E_c(t))_+ \\
&\quad +(M_h(R_h(v(T(t),D_hR_h\phi))c(t))), D_{-x}E_c(t))_+ \\
&\quad -(M_h(v(T_h(t),D_h\phi_h)c_h(t)), D_{-x}E_c(t))_+ \\
&\quad +(R_hQ(c(t))-Q(c_h(t)), E_c(t))_h \\
&\quad +\tau_d(E_c(t))+\tau_{D_d}(E_c(t))+\tau_v(E_c(t))+\tau_Q(E_c(t)),
\end{aligned} \tag{54}
$$

where

$$
\begin{aligned}
|\tau_d(E_c(t))| &= |(R_hc'(t)-(c'(t))_h, E_c(t))_h| \\
&\leq C_1\left(\sum_{i=1}^N h_i^4\|c'(t)\|^2_{H^2(I_i)}\right)^{1/2}\|D_{-x}E_c(t)\|_+,
\end{aligned}
$$

provided that $c'(t)\in H^2(\Omega)$,

$$
\begin{aligned}
|\tau_{D_d}(E_c(t))| \ &= |(D_d(M_hR_hT(t))D_{-x}R_hc(t), D_{-x}E_c(t))_+ \\
&\quad -(D_d(\hat{R}_hT(t))\hat{R}_h\nabla c(t), D_{-x}E_c(t))_+| \\
&\leq C_2\|D_d\|_{C_b^1(\mathbb{R})}\left(\|c(t)\|_{C^1(\overline{\Omega})}+1\right) \\
&\qquad \left(\sum_{i=1}^N h_i^4\left(\|T(t)\|^2_{H^2(I_i)}+\|c(t)\|^2_{H^3(I_i)}\right)\right)^{1/2}\|D_{-x}E_c(t)\|_+,
\end{aligned}
$$

provided that $T(t) \in H^2(\Omega), c(t) \in H^3(\Omega)$,

$$\begin{aligned}
|\tau_v(E_c(t))| &= |(v(\hat{R}_h T(t), \hat{R}_h \nabla\phi)\hat{R}_h c(t), D_{-x}E_c(t))_+ \\
&\qquad - (M_h(v(R_hT(t), D_hR_h\phi)R_hc(t)), D_{-x}E_c(t))_+| \\
&\le |(v(\hat{R}_h T(t), \hat{R}_h \nabla\phi)\hat{R}_h c(t), D_{-x}E_c(t))_+ \\
&\qquad - (M_h(v(R_hT(t), R_h\nabla\phi)R_hc(t)), D_{-x}E_c(t))_+| \\
&\quad + |(M_hv(R_hT(t), R_h\nabla\phi)R_hc(t), D_{-x}E_c(t))_+ \\
&\qquad - (M_h(v(R_hT(t), D_hR_h\phi)R_hc(t)), D_{-x}E_c(t))_+| \\
&\le C_3\Big(\Big(\sum_{i=1}^{N} h_i^4 \|v(T(t),\nabla\phi)c(t)\|^2_{H^2(I_i)}\Big)^{1/2} \\
&\qquad + \|c(t)\|_{C^1(\overline{\Omega})}\Big(\sum_{i=1}^{N-1}(h_i^4 + h_{i+1}^4)\|\phi\|^2_{H^3(I_i\cup I_{i+1})}\Big)^{1/2}\Big)\|D_{-x}E_c(t)\|_+,
\end{aligned}$$

provided that and $v(T(t), \nabla\phi)c(t) \in H^2(\Omega)$ and $\phi \in H^3(\Omega)$,

$$\begin{aligned}
|\tau_Q(E_c(t))| &= |((Q(c(t)))_h - R_hQ(c(t)), E_c(t))_h| \\
&\le C_4\left(\sum_{i=1}^{N} h_i^4 \|Q(c(t))\|^2_{H^2(I_i)}\right)^{1/2} \|D_{-x}E_c(t)\|_+,
\end{aligned}$$

provided that $Q(c(t)) \in H^2(\Omega)$, for suitable positive constants C_i, $i = 1\ldots,4$, h and t independent. Analogously to (50) and (51), we have

$$\begin{aligned}
&((D_d(M_hR_hT(t)) - D_d(M_hT_h(t)))D_{-x}R_hc(t), D_{-x}E_c(t))_+ \\
&\quad \le \sqrt{2}\|D_d\|_{C_b^1(\mathbb{R})}\|c(t)\|_{C^1(\overline{\Omega})}\|D_{-x}E_T(t)\|_+\|D_{-x}E_c(t)\|_+
\end{aligned} \tag{55}$$

and

$$\begin{aligned}
&(M_h(v(R_hT(t), D_hR_h\phi)R_hc(t)) - M_h(v(T_h(t), D_h\phi_h)c_h(t)), D_{-x}E_c(t))_+ \\
&\quad \le \sqrt{2}\beta_5\Big(\Big(\|E_T(t)\|_h + \|D_{-x}E_\phi\|_+\Big)\|c(t)\|_{C^1(\overline{\Omega})} \\
&\quad +\Big(\|T_h(t)\|_\infty + \|D_{-x}\phi_h\|_\infty\Big)\|E_c(t)\|_h\Big)\|D_{-x}E_c(t)\|_+,
\end{aligned} \tag{56}$$

respectively. As

$$|(R_hQ(c(t)) - Q(c_h(t)), E_c(t))_h| \le \beta_6\|E_c(t)\|_h^2, \tag{57}$$

taking (55)-(57) in (54) we arrive to

$$
\begin{aligned}
&\tfrac{d}{dt}\|E_h(t)\|_h^2 + 2(\beta_4 - 6\epsilon^2)\|D_{-x}E_c(t)\|_+^2 \\
&\quad \leq +\Big(4\tfrac{\beta_5^2}{\epsilon^2}\big(\|T_h(t)\|_\infty^2 + \|D_{-x}\phi_h\|_\infty^2\big)\|c(t)\|_{C^1(\overline{\Omega})}^2 + 2\beta_6\Big)\|E_c(t)\|_h^2 \\
&\quad +4\tfrac{\beta_5^2}{\epsilon^2}\Big(\|E_T(t)\|_h^2 + \|D_{-x}E_\phi\|_+^2\Big)\|c(t)\|_{C^1(\overline{\Omega})}^2 \\
&\quad +\Gamma(t),\ t \in (0, T_f],
\end{aligned}
\tag{58}
$$

where Γ is bounded in (53). Finally, inequality (58) leads to (52). ■

Corollary 5. *Under the assumptions of the Theorems 1, 4 and 7, with* $T_h(0) = R_hT(0), c_h(0) = R_hc(0)$, *the error* $E_c(t) = R_hc(t) - c_h(t)$ *satisfies*

$$
\|E_c(t)\|_h^2 + \int_0^t \|D_{-x}E_c(s)\|_+^2 ds \leq Consth_{max}^4, t \in [0, T_f], h \in \Lambda. \tag{59}
$$

The estimate (59) shows that the errors E_ϕ and $E_T(t)$ do not deteriorates de quality of the semi-discrete approximation $c_h(t)$. We notice that (59) is a supraconvergence result in the finite difference community but it can be seen also as a supercloseness result in the finite element community because our finite difference discretization (17)-(19) is equivalent to the fully discrete finite element discretization (13)-(15).

6. Numerical experiments

In what follows we illustrate the qualitative behaviour of the IBVP (1)-(5) using the finite difference method (17)-(19) with the boundary and initial conditions (4)-(5). The accuracy of the method was established in the Theorems 1, 4 and 7. These theoretical results are illustrated in Section 6.1. The medical outcomes of our results are illustrated in Section 6.2.

In $[0, T_f]$ we introduce the uniform grid $\{t_m,\ m = 0, \dots, M\}$, $t_0 = 0, t_M = T_f, \Delta t = t_m - t_{m-1},\ m = 1, \dots, M\}$. We integrate in time (18)-(19) using the IMEX (implicit-explicit) approach

$$
\begin{cases}
T_h^{m+1} = T_h^m + \Delta t D_x^*(D_T(M_h(T_h^m))D_{-x}T_h^{m+1}) + \Delta t G(T_h^m) \\
\qquad\qquad +F(D_h\phi_h) + f_{1,h}^m \ \text{ in } \Omega_h, m = 0, \dots, M-1, \\
T_h^0 = R_hT_0 \ \text{ in } \ \Omega_h, \\
T_h^m = 0 \ \text{ on } \ \partial\Omega_h, m = 1, \dots, M,
\end{cases}
\tag{60}
$$

where $G(T_h^m)(x_i) = G(T_h^m(x_i))$, $F(D_h\phi_h)(x_i) = F(D_h\phi_h(x_i)), i = 1, \ldots, N-1$, and ϕ_h is defined by (17),

$$\begin{cases} c_h^{m+1} + \Delta t D_c(v(T_h^{m+1}, D_h\phi_h)c_h^{m+1}) = \Delta t D_x^*(D_d(M_h(T_h^{m+1}))D_{-x}c_h^{m+1}) \\ \qquad\qquad\qquad\qquad\qquad\qquad +\Delta t Q(c_h^m) + f_{2,h}^m \ \text{ in } \Omega_h, m = 0, \ldots, M-1, \\ c_h^0 = R_h c_0 \ \text{ in } \ \Omega_h, \\ c_h^m = 0 \ \text{ on } \ \partial\Omega_h, m = 1, \ldots, M, \end{cases} \tag{61}$$

where $Q(c_h^m)(x_i) = Q(c_h^m(x_i)), i = 1, \ldots, N-1$. The grid function $f_{\ell,h}^m$, $\ell = 1, 2$, in (60), (61) are introduced only to illustrate the convergence results. In this case, these functions are such that the corresponding continuous problems have known solutions.

6.1. Convergence results. In this section we illustrate the error results obtained in this work - Theorems 1, 4 and 7. We use the following notations:

$$Error_\phi = \|D_{-x}E_\phi\|_+^2,$$

$$Error_T = \|E_T^0\|_h^2 + \Delta t \sum_{i=1}^{M} \|D_{-x}E_T^i\|_+^2,$$

where $E_T^i(x_\ell) = R_h T(x_\ell, t_i) - T_h^i(x_\ell)$, $\ell = 0, \ldots, N$,

$$Error_c = \|E_c^0\|_h^2 + \Delta t \sum_{i=1}^{M} \|D_{-x}E_c^i\|_+^2.$$

with $E_c^i(x_\ell) = R_h c(x_\ell, t_i) - c_h^i(x_\ell)$, $\ell = 0, \ldots, N$. The convergence rates $Rate_\ell$ are computed by

$$Rate_\ell = \frac{\log\left(\dfrac{Error_\ell, h_{max,i}}{Error_\ell, h_{max,i+1}}\right)}{\log\left(\dfrac{h_{max,i}}{h_{max,i+1}}\right)}, \ell = \phi, T, c,$$

where $h_{max,i}, h_{max,i+1}$ are the maximum stepsizes of the grids $\overline{\Omega}_h^{(i)}, \overline{\Omega}_h^{(i+1)}$, respectively, being the last two grids defined by the vectors $h^{(i)}, h^{(i+1)}$, where $h^{(i+1)}$ is obtained from $h^{(i)}$ introducing the middle point of each interval $[x_j, x_{j+1}]$.

- Smooth solutions: We start by considering the differential problems (1)-(3) with $T_f = 1$, σ defined by (6), $\sigma_0 = 2 \times 10^{-3}$, $\sigma_1 = 1.6 \times 10^{-1}$, $E_0 = 40000$, $E_1 = 90000$, $B = 30$ (see [4] and $D_T(T) = 1$, $G(T) = 0$,

$F(y) = \sigma(|y|)y$, $v(x,y) = 10^{-5}ye^{-x}$, $D_d(T) = 1$ and $Q(c) = 0$, f_1 and f_2 that are such that these problems have the following solutions

$$\begin{aligned} \phi(x) &= sin(\pi x)|2x-1|^{\alpha}, \\ T(x,t) &= e^{2t+x}|2x-1|^{\beta} + 1, \\ c(x,t) &= e^{t+x}|2x-1|^{\gamma}, \end{aligned} \tag{62}$$

for $(x,t) \in [0,1]^2$ and suitable values of $\alpha, \beta, \gamma \in \mathbb{R}^+$. We remark that the coefficient functions introduced before do not satisfy all of the assumptions $\mathbf{H_1} - \mathbf{H_6}$. However, we will show that, even in this case, the convergence orders stated in Theorems 1, 4 and 7 are observed. To ensure $\phi, T(t), c(t) \in H^3(0,1) \cap H_0^1(0,1)$ we take $\alpha = 3.1$, $\beta = 3.1$, $\gamma = 3.1$. In Table 1 we present the obtained numerical results with $\Delta t = 10^{-4}$. From these results, we notice that the convergence rates $Rate_\ell$, $\ell = \phi, T, c$ are approximately 2 which is in agreement with the error estimates stated in Theorems 1, 4 and 7.

N	h_{max}	E_ϕ	R_ϕ	E_T	R_T	E_c	R_c
50	7.3569×10^{-2}	1.5656×10^{-2}	——	5.1084×10^{-2}	——	5.1206×10^{-2}	——
100	3.6785×10^{-2}	3.9062×10^{-3}	2.0029	1.27121×10^{-2}	2.0067	1.2842×10^{-2}	1.9954
200	1.8392×10^{-2}	9.7615×10^{-4}	2.0006	3.0864×10^{-3}	2.0422	3.2168×10^{-3}	1.9972
400	9.1962×10^{-3}	2.4404×10^{-4}	1.9999	6.8725×10^{-4}	2.1669	8.0849×10^{-4}	1.9923
800	4.5981×10^{-3}	6.1006×10^{-5}	2.0001	1.49730×10^{-4}	2.1985	2.0642×10^{-4}	1.9696

TABLE 1. Convergence rates for smooth solutions ($\alpha = \beta = \gamma = 3.1$).

- Nonsmooth solutions: To show the sharpness of the smoothness assumptions in the Theorems 1, 4 and 7 we consider now the solutions (62) with $\alpha = 1.6$, $\beta = 1.6$, $\gamma = 1.6$. In this case $\phi, T(t), c(t) \in H^2(0,1) \cap H_0^1(0,1)$. In Table 2 we present the numerical results obtained in this case that illustrate that $Rate_\ell, \ell = \phi, T, c$ are approximately 1. This result illustrates the sharpness of our smoothness assumptions in the convergence results.

6.2. Qualitative behaviour. In this section our aim is to illustrate the behaviour of the system of partial differential equations, studied in this paper, in the context of transdermal iontophoresis. To simplify, we take skin as a single layer defined by $[0,L]$, $L = 1.1515 \times 10^{-3}m$ ([4]), the applied potential ϕ is defined with $f = 0$ and the boundary conditions $\phi(0) = 0$ and $\phi(L) = \phi_L$, where ϕ_L depends on the application protocol that we intend to illustrate.

N	h_{max}	E_ϕ	R_ϕ	E_T	R_T	E_c	R_c
25	1.3768×10^{-1}	3.0229×10^{-2}	——	1.3906×10^{-2}	——	5.3434×10^{-2}	——
50	6.8842×10^{-2}	7.7112×10^{-3}	1.9709	4.9451×10^{-3}	1.4916	2.1863×10^{-2}	1.2892
100	3.4421×10^{-2}	4.7356×10^{-3}	0.7034	2.4472×10^{-3}	1.0149	1.3877×10^{-2}	0.6557
200	1.7211×10^{-2}	2.2403×10^{-3}	1.0798	1.2192×10^{-3}	1.0052	6.5674×10^{-3}	1.0794
400	8.6053×10^{-3}	7.3566×10^{-4}	1.6066	6.5727×10^{-4}	0.8914	2.1729×10^{-3}	1.5956

TABLE 2. Convergence rates in the nonsmooth solutions ($\alpha = \beta = \gamma = 1.6$).

The boundary conditions for the concentration are defined by $c(0) = c_{ext}$ and $c(L) = 0$ which means that at the skin surface we have a known concentration of drug and all the drug that arrives at $x = L$ is immediately removed by the blood stream. In this case our coefficient functions are defined as follows: the electrical conductivity σ is defined by (6) with $\sigma_0 = 2 \times 10^{-3} S/m$, $\sigma_1 = 1.6 \times 10^{-1} S/m$, $y_0 = 40000 V/m$, $y_1 = 90000 V/m$ and $B = 30$,

$$D_T(T(t)) = \frac{k}{\rho k_s}, \ \ G(T(t)) = -\frac{1}{\rho k_s} \omega_m c_b (T(t) - T_a), \ \ F(\nabla \phi) = \frac{1}{\rho k_s} \sigma(|\nabla \phi|) |\nabla \phi|^2,$$

$D_d(T) = D$, v is defined by (9) with $v_b = 0$, and $Q(c) = 0$. The parameter values are included in Table 3 (see [4, 5]).

Symbol	Definition	Value	Units
ρ	Density	1116	kg/m^3
k_s	Heat capacity (specific)	3800	J/kgK
k	Thermal conductivity	0.293	W/mK
ω_m	Perfusion	2.33	$kg/m^3 s$
c_b	Perfusion of blood	3800	J/kgK
T_a	Arterial Blood Temperature	310.15	K
D	Drug diffusivity	10^{-12}	m^2/s
F_r	Faraday constant	9.6485×10^4	C/mol
R	Gas constant	8.3144	$J/Kmol$
z	Valence	± 1	-

TABLE 3. Parameters: values and units.

The behaviour of the drug transport enhanced by the electric field is illustrated in what follows considering different combinations of the protocols presented in Table 4. These combinations are presented in Table 5.

Protocol	$\phi(L)$	Pulse duration	Pause
LLV (Low Long Voltage)	$45V$	$240ms$	$100ms$
SHV (Short High Voltage)	$500V$	$500\mu s$	$500\mu s$

TABLE 4. Protocols: potential, duration and pause.

Notation	Characterization	Total duration
3LLV	3 times LLV	$1.02s$
3SHV	3 times SHV	$3 \times 10^{-3}s$
3SHV+3LLV	3 times SHV followed by 3 times LLV	$1.053s$.

TABLE 5. Different protocols combinations and total time of action of the electric field.

The results are compared with the drug transport through the skin without the effect of the electric field which defines the control scenario.

In Figure 1 we plot the temperature and drug concentration for $t \in [0, 2s]$ when the first protocol 3LLV is applied. The time axis is the vertical axis while space axis is the horizontal axis. The effect of the three impulses applied at $x = L$ on the temperature distribution is well illustrated by this picture as well as on the drug distribution. While the effect of the applied potential on the temperature is felt in all space domain, the corresponding effect on the drug distribution is felt only in the first part of the skin. To clarify these conclusions, in Figures 2 and 3 we plot the temperature and drug concentration evolution in several points of the spatial domain.

To compare the different protocols we compute the absorbed drug mass at $x = L$,

$$M_\ell(t) = \int_0^t J_{d,\ell}(s)ds,$$

for $\ell = control$, 3LLV, 3SHV, 3SHV+3LLV, where $J_{d,\ell}(t)$ is the drug flux at $x = L$,

$$J_{d,\ell}(t) = -(D_d(T(L,t))\nabla c(L,t) + v(T(L,t), \nabla\phi(L,t))c(L,t),$$

with the potential ϕ depending on time because the potential at $x = L$ is a time dependent function. In what follows the behaviour of the protocols

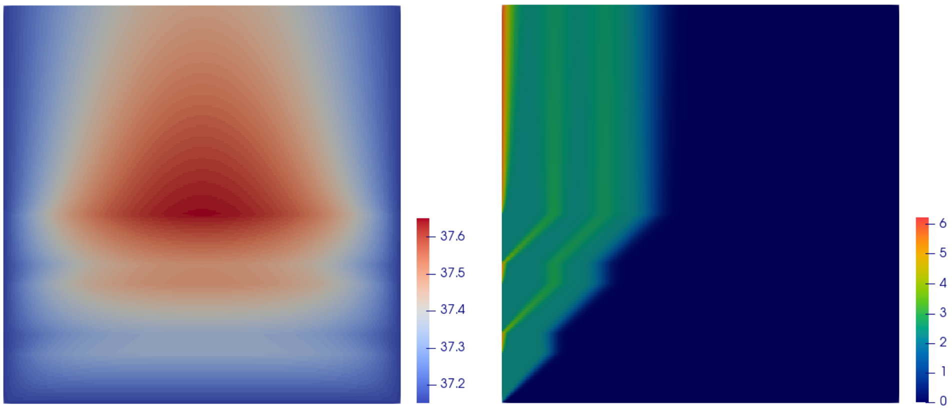

FIGURE 1. Temperature (left) and drug distributions (right) for $t \in [0, 2s]$ enhanced by the electric field defined by the 3LLV protocol.

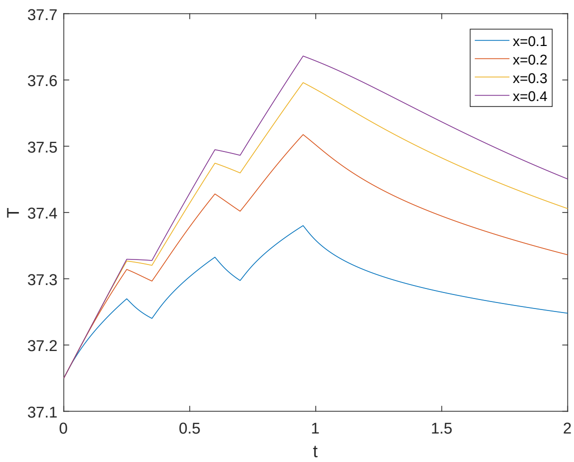

FIGURE 2. Evolution of the temperature at $x = 0.1, 0.2, 0.3, 0.4$ for $t \in [0, 2s]$ for the 3LLV protocol.

defined in Table 5 are illustrated considering very short times, short times and large times.

- **Very short times**

  In Figure 4 we observe that for very short times ($t \in [0, 4 \times 10^{-5}s]$) the protocols 3SHV+3LLV e 3SHV lead to similar results. Moreover

$$M_{control}(t) \leq M_{3LLV}(t) \leq M_{\ell}(t),\ \ell = 3SHV, 3SHV + 3LLV.$$

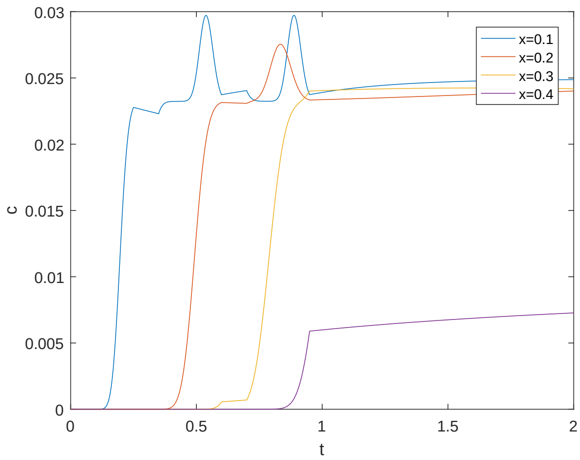

FIGURE 3. Evolution of the concentration at $x = 0.1, 0.2, 0.3, 0.4$ for $t \in [0, 2s]$ for the 3LLV protocol.

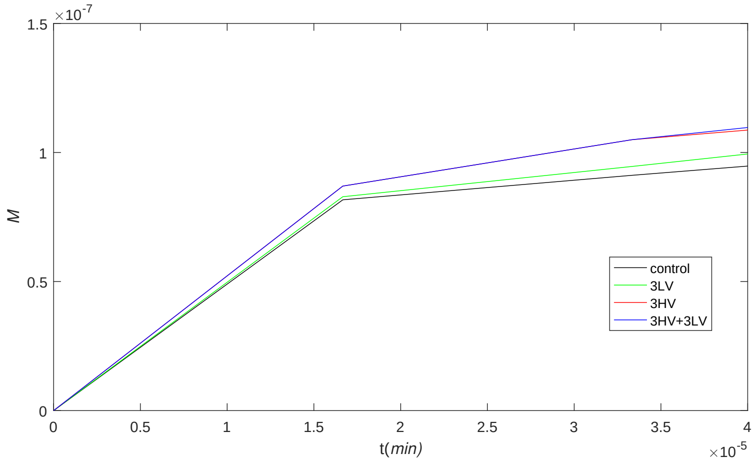

FIGURE 4. Plot of $M_\ell(t), \ell = control$, 3LLV, 3SHV, 3SHV+3LLV, for $t \in [0, 4 \times 10^{-5}s]$.

The plot highlights the effect of the SHV pulses in the combination protocol $3SHV + 3LLV$.

- **Short times**

  From Figure 5 where the plots are exhibited for $t \in [0, 10^{-3}s]$, protocol 3SHV+3LLV still dominates de delivery of drug, however protocol 3LLV leads to a larger release of drug than protocol 3SHV. This means that, comparing Figures 4 and 5, there is an inversion in the amount of drug released with protocols 3SHV and 3LLV. We could explain such inversion by the fact the high pulses are more active and their intensity was not high enough to induce a steadier transport. In Figure 6 such inversion is captured.

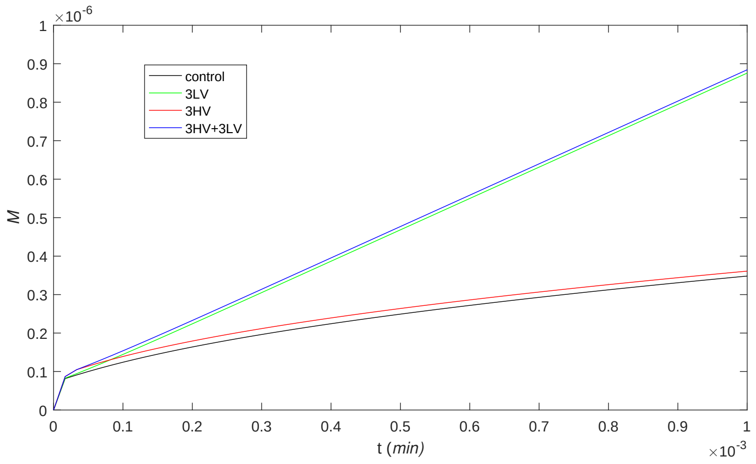

FIGURE 5. Plots of $M_\ell(t), \ell = control, 3LLV, 3HV, 3SHV + 3LLV$, $t \in [0, 10^{-3}s]$.

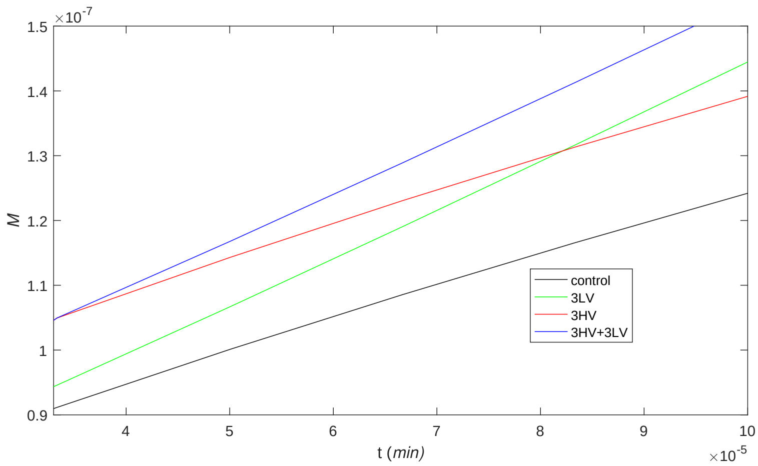

FIGURE 6. Plots of $M_\ell(t), \ell = control, 3LLV, 3HV, 3SHV + 3LLV$, for $t \in [3 \times 10^{-5}, 10^{-4}]$.

- **Large times**

  The results presented in Figure 7 and 8 show that as time increases, the protocols 3LLV and 3SHV+3LLV lead to similar results, while the mass obtained with the protocol 3SHV is similar to the control

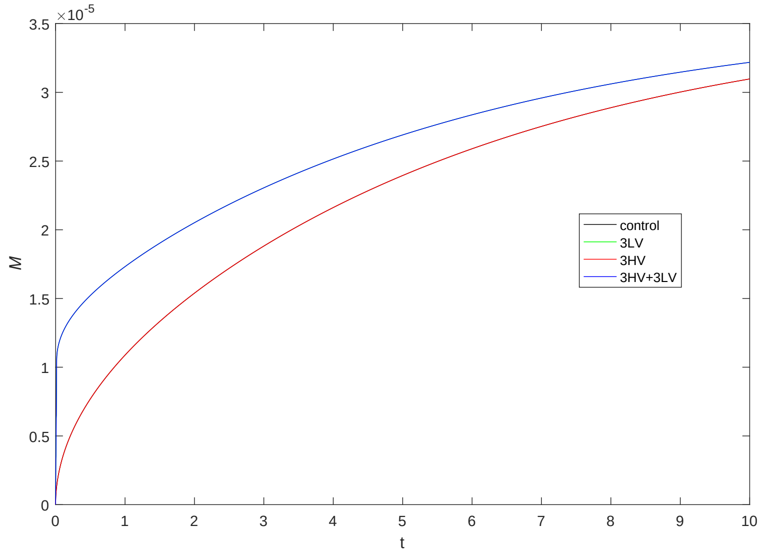

FIGURE 7. Plots of $M_\ell(t)$, $\ell = control, 3LLV, 3SHV, 3SHV + 3LLV$, for $t \in [0, 10min]$.

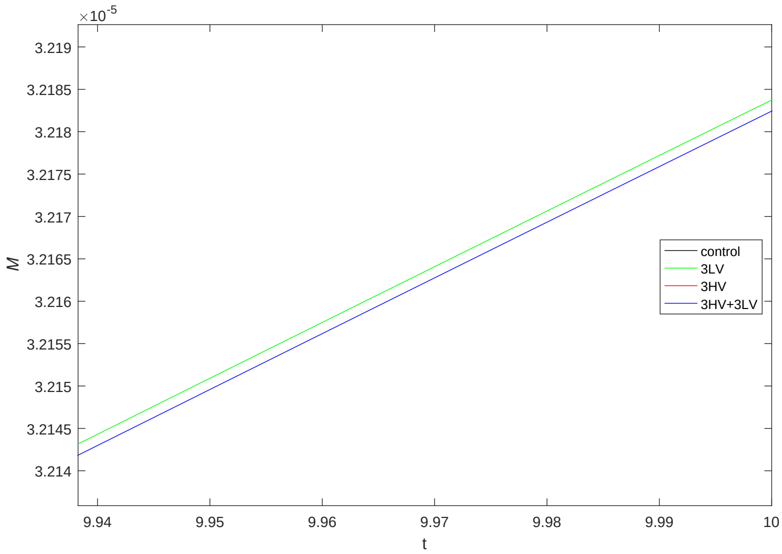

FIGURE 8. Zoom of the plots of $M_\ell(t)$, $\ell = 3LLV, 3SHV + 3LLV$.

protocol. Moreover, the drug mass transported through the skin is larger for the first set of protocols (3LLV, 3SHV+3LLV). When we look at the zooms of the plots of Figure 7, that is Figures 8 and 9,

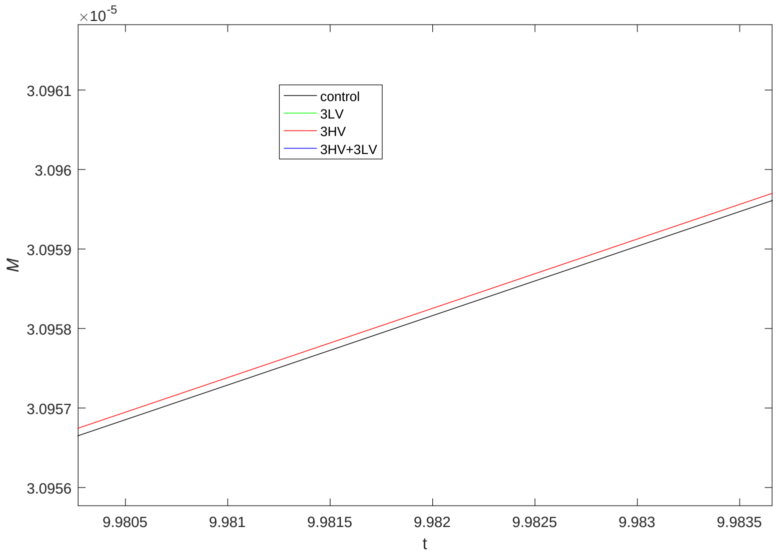

FIGURE 9. Zoom of the plots of $M_\ell(t)$, $\ell = control, 3SHV$.

we observe that for large times the dominance of 3SHV+3LLV is lost. This result suggests that SHV pulses were not high enough.

7. Conclusions

In this paper a differential model composed of a nonlinear elliptic equation (1) and two parabolic equations (2)-(3) is presented. These equations, a diffusion-reaction equation and a convection-diffusion-reaction equation, are coupled with the elliptic equation via the reaction term and the convection term respectively. The system can be used to describe drug transport through a target organ or tissue when an electric field is used as an enhancer.

From a numerical point of view the main problem when solving the system (1)-(3) is the computation of the numerical approximation for the elliptic problem. In fact if its numerical gradient does not have the right convergence order then the numerical approximation for the convection-diffusion will lack accuracy.

To circumvent this difficulty we propose a finite difference discretization (17)-(19), that can be seen as a fully finite element method (13)-(15), that leads to accurate second order approximations. More exactly a second order approximation for the solution of the nonlinear elliptic equation, with respect to a discrete version of the usual H^1-norm, and second order approximations for the solutions of the two parabolic equations with respect to a discrete version of the usual L^2-norm. The error estimates are established in the main results of this paper: Theorems 1, 4 and 7. The estimates in these theorems can be seen as supraconvergence results if we look to the discretizations as finite differences; the same estimates can be viewed as supercloseness results if the discretization is considered a fully discrete piecewise linear finite element method. In Theorem 1 we extend the results included in [3] to nonlinear problems. The convergence results were established assuming that the solution of the elliptic equation is in $H^3(\Omega)$ and the solutions of the parabolic equations, for each time t, are also in $H^3(\Omega)$. Numerical results illustrating the convergence results and showing the sharpness of the smoothness assumptions are also include in this paper. To the best of our knowledge these convergence results are original.

The stability of the coupled problem (17)-(19) was also studied. As we were dealing with nonlinear problems, for stationary problem (17) or for the evolution problems (18)-(19), the stability analysis is a difficult question because the uniform boundness of the numerical approximations is required. As in [6], we are able to retrieve the desired result using the convergence results.

From a medical point of view, the paper contains an exploratory study that can assist in the definition of protocols for electrically enhanced drug delivery. The completeness of the model lies on the accurate description of electric effects: while in previous papers [13, 19], only the effect on the convective field of the permeant was considered, in the present paper the effect of the electric field on the rise of temperature is also taken into account. The results obtained with different protocols are in agreement with the physics of the problem: short high voltage pulses have short time effects; long time low voltage has long time effects.

We summarize in what follows some conclusions that can be established from the illustrations in this paper.

- Electric fields enhance drug transport through target organs or tissues;
- For small times, protocols defined by short high intensity pulses followed by long lower intensity pulses are more effective than the protocols defined only by one of the type of pulses (see Figures 4 and 5);
- For large times the combination protocol, 3SHV+3LLV, leads to a similar amount of released drug than the 3LLV (see Figure 7). A closer observation of Figure 8 shows that 3SHV+3LLV slightly lost its dominance. This finding is in agreement with experimental results (see

for example [9]) where transport increase over iontophoresis depends on the SHV protocol adopted.

- For large times, protocols based on long lower intensity pulses are more effective than protocols based on short high intensity pulses (see Figures 7 and 8). The rationale underlying this observation is a consequence of the fact that after an initial increase on the temperature, the distribution of drug depends on the convective field mainly created by the long low intensity pulses.

We are aware that, from a medical point of view, our simulations have an academic character. In fact we considered protocols used in an abstract target. However the application of electric fields in Transdermal Drug Delivery depends on the type of therapeutic use and target organ or tissue. The use of the model in this paper, must take these aspects into account by adopting experimental parameter values.

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References

[1] R. A. Adams. *Sobolev spaces / Robert A. Adams*. Academic Press New York, 1975.

[2] S. Barbeiro, S. Bardeji, J. A. Ferreira, and L. Pinto. Non-fickian convection–diffusion models in porous media. *Numerische Mathematik*, 138(4):869–904, 2018.

[3] S. Barbeiro, J. A. Ferreira, and R. D. Grigorieff. Supraconvergence of a finite difference scheme for solutions in $H^s(0,l)$. *IMA Journal of Numerical Analysis*, 25(4):797–811, 2005.

[4] S. Becker. Skin electroporation with passive transdermal transport theory: a review and a suggestion for future numerical model development. *Journal of Heat Transfer*, 133(1):011011, 2011.

[5] S. Becker, B. Zorec, D. Miklavčič, and N. Pavšelj. Transdermal transport pathway creation: electroporation pulse order. *Mathematical Biosciences*, 257:60–68, 2014.

[6] J. Borges, J. A. Ferreira, G. Romanazzi, and E. Abreu. Drug release from viscoelastic polymeric matrices - a stable and supraconvergent FDM. Technical report, Department of Mathematics of the University of Coimbra, 2019. 19–20 Preprint.

[7] J. Byrne, J. Yeh, and J. DeSimone. Use of iontophoresis for the treatment of cancer. *Journal of Controlled Release*, 284:144–151, 2018.

[8] J. D. Byrne, M. Jajja, A. O'Neill, A. Schorzman, A. Keeler, J. Luft, W. Zamboni, J. DeSimone, and J. Yeh. Impact of formulation on the iontophoretic delivery of the FOLFIRINOX regimen for the treatment of pancreatic cancer. *Cancer Chemotherapy and Pharmacology*, 81(6):991–998, 2018.

[9] S-L. Chang, G. Hofmann, L. Zhang, L. Deftos, and A. Banga. The effect of electroporation on iontophoretic transdermal delivery of calcium regulating hormones. *Journal of Controlled Release*, 66:127–133, 2000.

[10] J. Edd and R. Davalos. Mathematical modeling of irreversible electroporation for treatment planning. *Technology in Cancer Research & Treatment*, 6(4):275–286, 2007.

[11] J. A. Ferreira, P. de Oliveira, and E. Silveira. Drug release enhanced by temperature: An accurate discrete model for solutions in H^3. *To appear in Computers & Mathematics with Applications*, 2019.

[12] J. A. Ferreira and L. Pinto. Supraconvergence and supercloseness in quasilinear coupled problems. *Journal of Computational and Applied Mathematics*, 252:120–131, 2013.

[13] J.A. Ferreira, P. Oliveira, and G. Pena. Transdermal iontophoresis-a quatitative and qualitative study. *Computers and Mathematics with Applications*, 74(10):2231–2242, 2017.

[14] T. Gratieri, V. Santer, and Y. Kalia. Basic principles and current status of transcorneal and transscleral iontophoresis. *Expert Opinion on Drug Delivery*, 14(9):1091–1102, 2017.

[15] M. Komuro, K. Suzuki, M. Kanebako, T. Kawahara, T. Otoi, K. Kitazato, T. Inagi, K. Makino, M. Toi, and H. Terada. Novel iontophoretic administration method for local therapy of breast cancer. *Journal of Controlled Release*, 168(3):298–306, 2013.

[16] J. Naghipoor, N. Jafary, and T. Rabczuk. Mathematical and computational modeling of drug release from an ocular iontophoretic drug delivery device. *International Journal of Heat and Mass Transfer*, 123:1035–1049, 2018.

[17] N. Pavšelj and D. Miklavčič. Resistive heating and electropermeabilization of skin tissue during in vivo electroporation: A coupled nonlinear finite element model. *International Journal of Heat and Mass Transfer*, 54(11-12):2294–2302, 2011.

[18] H. Pennes. Analysis of tissue and arterial blood temperatures in the resting human forearm. *Journal of Applied Physiology*, 1(2):93–122, 1948.

[19] G. Pontrelli, M. Lauricella, J. A. Ferreira, and G. Pena. Iontophoretic transdermal drug delivery: a multi-layered approach. *Mathematical Medicine and Biology*, 34(4):559–576, 2017.

[20] M. Prausnitz and R. Langer. Transdermal drug delivery. *Nature Biotechnology*, 11(26):1261–1268, 2008.

[21] C. Rossmann and D. Haemmerich. Review of temperature dependence of thermal properties, dielectric properties, and perfusion of biological tissues at hyperthermic and ablation temperatures. *Critical Reviews in Biomedical Engineering*, 42(6):467–492, 2014.

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