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APPROXIMATING COUPLED HYPERBOLIC-PARABOLIC SYSTEMS ARISING IN ENHANCED DRUG DELIVERY

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Abstract: In this paper we study a system of partial differential equations defined by a hyperbolic equation and a parabolic equation. The convective term of the parabolic equation depends on the solution and eventually on the gradient of the solution of the hyperbolic equation. This system arises in the mathematical modeling of several physical processes as for instance ultrasound enhanced drug delivery. In this case the propagation of the acoustic wave, which is described by a hyperbolic equation, induces an active drug transport that depends on the acoustic pressure. Consequently the drug diffusion process is governed by a hyperbolic and a convection-diffusion equation.

Here, we propose a numerical method that allows us to compute second-order accurate approximations to the solution of the hyperbolic and the parabolic equation. The method can be seen as a fully discrete piecewise linear finite element method or as a finite difference method. The convergence rates for both approximations are unexpected. In fact we prove that the error for the approximation of the pressure and concentration is of second-order with respect to discrete versions of the H^1-norm and L^2-norm, respectively.

Keywords: Wave equation, convection-diffusion equation,finite difference method, piecewise linear FEM, ultrasound, dug delivery.

1. Introduction

In this paper we consider the coupled system defined by the wave equation

$$a\frac{\partial^2 p}{\partial t^2} + b\frac{\partial p}{\partial t} = \nabla \cdot (E\nabla p) + f_1, \text{ in } \Omega \times (0,T], \tag{1}$$

and the parabolic equation

$$\frac{\partial c}{\partial t} + \nabla \cdot (v(p,\nabla p)c) - \nabla \cdot (D(p)\nabla c) = f_2, \text{ in } \Omega \times (0,T]. \tag{2}$$

This system is complemented with the initial conditions

$$\begin{cases} \dfrac{\partial p}{\partial t}(0) = p_{v,0} \\ \\ p(0) = p_0 \text{ in } \Omega, \end{cases} \tag{3}$$

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$$c(0) = c_0 \text{ in } \Omega, \tag{4}$$

and homogeneous Dirichlet boundary conditions

$$p(t) = 0 \text{ on } \partial\Omega \times (0, T], \tag{5}$$

$$c(t) = 0 \text{ on } \partial\Omega \times (0, T]. \tag{6}$$

To simplify we assume that $\Omega = (0,1)^2$ and $\partial\Omega$ represents its boundary. In (1), a and b denote positive functions with non negative lower bounds in $\overline{\Omega}$, a_0 and b_0, respectively, E is a diagonal matrix with entries e_1 and e_2 both with positive lower bound e_0 in $\overline{\Omega}$. In (2), $v(p)$ denotes the convective velocity that can be p or ∇p dependent, $v(p, \nabla p) = (v_1(p, \frac{\partial p}{\partial x}), v_2(p, \frac{\partial p}{\partial y}))$, $D(p)$ is a diagonal matrix with entries d_1 and d_2 that can be dependent on p, $d_1 = d_1(p)$, $d_2 = d_2(p)$, and both with positive lower bound d_0 in $\overline{\Omega}$. If $w : \overline{\Omega} \times [0, T] \to \mathbb{R}$, then for $t \in (0, T]$, $w(t) : \overline{\Omega} \times [0, T] \to \mathbb{R}$ is given by $w(t)(x, y) = w(x, y, t)$, $(x, y) \in \overline{\Omega}$.

System (1)-(6) can be used to model drug delivery to a target tissue when certain physical enhancers are used. The drug molecules absorption by the target tissue is in general very low due to the physio-chemical properties of the drug molecules or due to the low permeability of the target region. To increase the drug absorption, penetration enhancers have been used; they can be divided into two main classes: physical and chemical enhancers. In both classes the main objective is to break the natural physical barriers to drug transport and consequent drug absorption. In transdermal drug delivery such enhancers have been used with great success. While the first group, the chemical enhancers, act by changing the properties of the stratum corneum increasing drug transport by diffusion, the second one, the physical enhancers, act by creating a convective flow that facilitates drug transport. In this group we include ultrasound, iontophoresis, and electroporation ([1]). In the following we focus on ultrasound enhanced drug delivery.

Application of ultrasound to enhance drug transport through biological tissues is a well-established and efficient technology. It has a huge number of medical applications and it is particularly useful for drug delivery across impermeable biological barriers (e.g., cell membrane) and on the delivery of large or low diffusivity molecules (see [2], [3], [4], [5],[6], [7], [8], [9], [10], [11]). For instance in cancer treatment, ultrasound is combined with a drug polymeric carrier like polymeric micelles or liposomes or microbubbles that transport the drug to the vicinity of the cancer tissue. Under the action of ultrasound it was observed an increase in the amount of drug released and absorbed ([12], [3]).

Ultrasound consists of pressure waves propagating through a medium. As the ultrasound wave propagates, it induce a vibration in the molecules of the medium. This vibration is originated by successive events of compression and expansion, induced by the wave, and which cause the pressure in the medium to increase and decrease, respectively. The application of ultrasound to the human body has different biological effects. For example, it may lead to an increase in temperature particularly when localized and high intensity pulses are used. It has been shown that temperature rise can increase drug accumulation in tumors [13]. The exposition to ultrasound can also originate what is sometimes designated by acoustic radiation forces [14]. These forces can produce the so-called acoustic-streaming which is a convective flow in the fluid phase of the medium. This convective field can also be explored to increase the delivery rate of drug molecules to specific sites [15].

Ultrasound can also lead to the formation of vapor zones within a fluid. This phenomenon is usually called cavitation and arise because the local pressure decreases until it reaches the pressure of the liquid itself leading to the formation of microbubbles containing vapor. These microbubbles oscillate and induce a fluid flow with velocity proportional to the amplitude of the oscillations. If drug particles are imbedded in this fluid, they will be easily spread by diffusion and convection. It should be remarked that ultrasound induced cavitation can be of two types: stable or inertial. Unlike stable cavitation, in inertial cavitation the microbubble oscillation results in an explosion. We note that cavitation, inertial or stable, can originate micro ruptures in cell membranes, increasing its permeability and facilitating the intracellular delivery of drug molecules [14].

Ultrasound propagation in soft biological tissue is governed by the equation [2]

$$\frac{1}{c^2}\frac{\partial^2 p}{\partial t^2} + \frac{2a}{c}\frac{\partial p}{\partial t} = \rho\nabla\cdot\left(\frac{1}{\rho}\nabla p\right),$$

where c is the speed of sound of the material, ρ is the material density, p is the acoustic pressure, and a is the attenuation parameter. For soft biological tissue this parameter a is typically described by a power law given by $a = \overline{a}f^b$, with $\overline{a}$ a parameter that depends on the type of tissue, f the wave frequency, and b a constant that is usually assumed to be close to one [4]. Assuming for simplicity that $\nabla\rho = 0$ and ignoring attenuation effects, we obtained the linear acoustic wave equation

$$\frac{\partial^2 p}{\partial t^2} = c^2 \Delta p, \tag{7}$$

which is a particularization of (1).

Let us consider that soft tissue can be seen as a porous medium filled with a fluid containing a solute (e.g., drug molecules). When ultrasound is applied to enhance the solute transport the fluid velocity and the solute diffusion are mainly due to cavitation phenomena, thermal effects, and convection [7, 6]. Although each one of these mechanisms have distinct implications on drug transport they all contribute to an enhanced drug diffusion. Therefore, the evolution of drug concentration in the soft tissue can be described by classical convection-diffusion equation (2) where $v(p)$ depends on p. For instance in [16], for the one-dimensional case, the diffusion equation (2) was used with $v(p) = v + v^*$ and $D(p) = \alpha v(p) + D_d$, where v is the steady state fluid velocity, v^* is the enhanced velocity due to the acoustic pressure, D_d is the molecular diffusion coefficient, and α is the dispersivity. Similar relations were used in [17]. In that work the acoustic pressure was defined by (7) and the concentration evolution was described by (2) with $v(p) = \phi\sqrt{\dfrac{p}{\rho}} + v^*$ and $D(p) = \alpha v(p) + D_d$. According to the authors, v^* is mainly due to cavitation phenomena.

The main problem on the computation of numerical approximations for the solution of the hyperbolic-parabolic IBVP (1)-(6) is the dependence of the convective term v in (2) on the solution of the hyperbolic equation and its gradient. To compute a second-order approximation for the concentration we need to compute a second-order approximation for the gradient of the hyperbolic solution. In this work we propose a fully discrete piecewise linear finite element method for the introduced IBVP that allows us to compute second-order approximations for the solutions of the hyperbolic equation (1) and diffusion equation (2), with respect to a discrete H^1-norm and L^2-norm respectively. The paper is organized as follows: in Section 2 we present some remarks on the existence and uniqueness of solution of the IBVP (1)-(6) in a convenient weak sense. Section 3 is devoted to the design of the fully discrete in space piecewise linear finite element method. The convergence analysis of the proposed method is given in Section 4. Numerical experiments illustrating the main results are introduced in Section 5. In this section we also use the proposed method to illustrate drug transport enhanced by ultrasound.

We remark that the results that we present here are not expected. Our numerical scheme is based on piecewise linear finite elements which, as it is well known, leads to first-order approximations for the hyperbolic equation with respect to the H^1-norm. Therefore, only first-order approximations for the solution of the parabolic equation (2) are expected. Fully discrete piecewise linear methods with similar convergence properties were discussed in [18, 19, 20, 21, 22].

2. Remarks on the existence and uniqueness of solution

In what follows we establish a set of conditions on the data of the IBVP (1)-(6) that allow us to conclude the existence and uniqueness of its solution (p, c) in a certain sense. In this case the existence and uniqueness of such solution can be studied establishing the existence and uniqueness of the wave equation IBVP (1), (3), (5) and the existence and uniqueness of the diffusion IBVP (2), (4), (6).

We start by introducing a convenient functional context. Let $L^2(\Omega)$ and $[L^2(\Omega)]^2$ be the usual Sobolv spaces where we consider the usual inner products $(.,.)$, $((.,.))$ and corresponding norms that we denote by $\|.\|$. In the Sobolev space $H^1_0(\Omega)$ we consider the usual norm $\|.\|_1$ and by $H^{-1}(\Omega)$ we denote the dual of $H^1_0(\Omega)$ being $< .,. >$ the notation for the dual product defined in $H^{-1}(\Omega) \times H^1_0(\Omega)$. By $L^2(0, T, X)$, where X represents a vector space of functions defined in Ω with the norm $\|.\|_X$, we denote the space of functions $w(t) : \Omega \to \mathbb{R}$ such that

$$\|w\|_{L^2(0,T,X)} = \Big(\int_0^T \|w(t)\|^2_X dt \Big)^{1/2} < \infty.$$

The space of continuous functions $w : [0, T] \to X$ is denoted by $C([0, T], X)$.

For the first problem it is well known that if the coefficients $a, b \in L^\infty(\Omega)$, $E \in [L^\infty(\Omega)]^2, e_1, e_2 \ge e_0 > 0$ in $\overline{\Omega}$, $f_1 \in L^2(0, T, L^2(\Omega)), p_{v,0} \in L^2(\Omega)$ and $p_0 \in H^1_0(\Omega)$, then there exists a unique solution $p \in C([0, T], H^1_0(\Omega))$, with

$p' \in C([0,T], L^2(\Omega))$ and $p'' \in L^2(0,T,H^{-1}(\Omega))$, such that

$$\begin{cases} < ap''(t), w > +(bp'(t), w) = ((E\nabla p(t), \nabla w)) + (f_1(t), w) \text{ a.e in } [0,T], \\ \hfill \forall w \in H_0^1(\Omega) \\ p'(0) = p_{v,0} \\ p(0) = p_0. \end{cases} \tag{8}$$

Moreover such solution satisfies

$$\begin{aligned} &\|p\|_{L^\infty(0,T,H_0^1(\Omega))} + \|p'\|_{L^\infty(0,T,L^2(\Omega))} + \|p''\|_{L^2(0,T,H^{-1}(\Omega))} \\ &\qquad \le C\Big(\|f_1\|_{L^2(0,T,L^2(\Omega))} + \|p_0\|_1 + \|p_{v,0}\|\Big). \end{aligned} \tag{9}$$

In (9), $\|.\|_{L^\infty(0,T,X)}$ denotes the following norm

$$\|w\|_{L^\infty(0,T,X)} = \operatorname*{ess\,sup}_{[0,T]} \|w(t)\|_X.$$

As we will see, to study the weak solution of the concentration equation we need to impose that $p \in L^\infty(0,T,L^\infty(\Omega))$ and $\nabla p \in L^\infty(0,T,[L^\infty(\Omega)]^2)$. To obtain a solution of (8) with such smoothness we need to increase the smoothness of the data. For instance, if $f_1 \in L^2(0,T,H^2(\Omega))$, $p_0 \in H_0^1(\Omega) \cap H^3(\Omega)$, $p_{v,0} \in H_0^1(\Omega) \cap H^2(\Omega)$, then $p \in C([0,T], H_0^1(\Omega) \cap H^3(\Omega))$ and

$$\|p\|_{L^\infty(0,T,W^{1,\infty}(\Omega))} \le C\Big(\|f_1\|_{L^2(0,T,H^2(\Omega))} + \|p_{v,0}\|_{H^2(\Omega)} + \|p_0\|_{H^3(\Omega)}\Big). \tag{10}$$

In (10), $W^{1,\infty}(\Omega)$ denotes the Sobolev space of functions defined in Ω such that

$$\|w\|_{W^{1,\infty}(\Omega)} = \max_{|\alpha|\le 1} \operatorname*{ess\,sup}_{\Omega} |D^\alpha w|,$$

with $\alpha = (\alpha_1, \alpha_2) \in \mathbb{N}_0 \times \mathbb{N}_0$ and $D^\alpha w = \dfrac{\partial^{|\alpha|} w}{\partial x^{\alpha_1} \partial y^{\alpha_2}}$.

For the concentration IBVP (2), (4), (6) we are asking for a weak solution in the following sense: $c \in L^2(0,T,H_0^1(\Omega))$, $c' \in L^2(0,T,H^{-1}(\Omega))$ such that

$$\begin{cases} < c'(t), w > +a_p(c(t), w) = (f_2(t), w) \text{ a.e in } [0,T],\ \forall w \in H_0^1(\Omega) \\ c(0) = p_0, \end{cases} \tag{11}$$

where

$$a_p(w,u) = ((D(p)\nabla w, \nabla u)) - ((wv(p(t), \nabla p(t)), \nabla u)),\ w, u \in H_0^1(\Omega).$$

We suppose that the diagonal matrix D has diagonal entries with lower positive bounds. We also impose that $p \in L^\infty(0,T,L^\infty(\Omega))$, $\nabla p \in L^\infty(0,T,[L^\infty(\Omega)]^2)$ and $v : \mathbb{R} \times \mathbb{R}^2 \to \mathbb{R}^2$, $v = (v_1, v_2)$, satisfies

$$|v_i(z_1, z_2)| \leq C\Big(|z_1| + |z_2|\Big),\ \forall z_1 \in \mathbb{R}, \forall z_2 \in \mathbb{R}, i = 1, 2. \tag{12}$$

These assumptions allow us to prove that the bilinear form $a_p(.,.) : H_0^1(\Omega) \times H_0^1(\Omega) \to \mathbb{R}$ is coersive.

Then, for $f_2 \in L^2(0,T,L^2(\Omega))$, $c_0 \in H_0^1(\Omega)$, $f_1 \in L^2(0,T,H^2(\Omega))$, $p_0 \in H_0^1(\Omega) \cap H^3(\Omega)$, and $p_{v,0} \in H_0^1(\Omega) \cap H^2(\Omega)$, it can be shown that there exists a unique function $c \in C([0,T], L^2(\Omega)) \cap L^2(0,T,H_0^1(\Omega))$ such that $c' \in L^2(0,T,H^{-1}(\Omega))$, (11) holds and

$$\begin{aligned} &\|c\|_{L^\infty(0,T,L^2(\Omega))} + \|c\|_{L^2(0,T,H_0^1(\Omega))} + \|c'\|_{L^2(0,T,H^{-1}(\Omega))} \\ &\qquad \leq C\Big(\|f_2\|_{L^2(0,T,L^2(\Omega))} + \|c_0\|_1\Big). \end{aligned} \tag{13}$$

We remark that the constant in (13) depends on the upper bound for $\|p\|_{L^\infty(0,T,W^{1,\infty}(\Omega))}$ defined in (10). We also note that we can increase the smoothness of c by increasing the smoothness of f_1, p_0, and $p_{v,0}$, in the acoustic pressure equation, and of f_2 and c_0 in the concentration equation.

3. Fully discrete piecewise linear FEM - superconvergence results

3.1. Spatial discretization. The main goal of this section is to define a second-order accurate semi-discrete approximation to the solution (p,c) of the IBVP (1)-(6). Such approximation will be derived using a piecewise linear method for the differential problems: wave IBVP (1), (3), (5) and concentration IBVP (2), (4), (6). Note however that c depends on p through the advective term. Thus, the proposed method needs to be carefully designed.

In $\overline{\Omega}$ we introduce a non-uniform rectangular grid defined by $H = (h,k)$ with $h = (h_1, \ldots, h_N)$, $h_i > 0$, $i = 1, \ldots, N$, $\sum_{i=1}^{N} h_i = 1$, and $k = (k_1, \ldots, k_M)$,

$k_j > 0$, $j = 1, \ldots, M$, $\sum_{j=1}^{M} k_j = 1$. Let $\{x_i\}$ and $\{y_j\}$ be the non-uniform grids induced by h and k in $[0, 1]$ with $x_i - x_{i-1} = h_i$, $y_j - y_{j-1} = k_j$. By $\overline{\Omega}_H$ we represent the rectangular grid introduced in $\overline{\Omega}$ that depends on H and let Ω_H and $\partial\Omega_H$ be defined by $\Omega_H = \Omega \cap \overline{\Omega}_H, \partial\Omega_H = \partial\Omega \cap \overline{\Omega}_H$.

Let $H_{max} = \max\{h_i, k_j;\ i = 1, \cdots N;\ j = 1, \cdots, M\}$. By Λ we denote a sequence of vectors $H = (h, k)$ such that $H_{max} \to 0$. Let W_H be the space of grid functions defined in $\overline{\Omega}_H$ and by $W_{H,0}$ we denote the subspace of W_H of grid functions null on $\partial\Omega_H$. Let $\mathcal{T}_H$ be a triangulation of $\overline{\Omega}$ using the set $\overline{\Omega}_H$ as vertices. We denote by diamΔ the diameter of the triangle $\Delta \in \mathcal{T}_H$. By $P_H v_H$ we denote the continuous piecewise linear interpolant of v_H with respect to $\mathcal{T}_H$.

To define a fully discrete approximation in space we introduce now fully discrete inner products and corresponding norms. In $W_{H,0}$ we define the inner product

$$(u_H, w_H)_H = \sum_{(x_i,y_j)\in\overline{\Omega}_H} |\square_{i,j}| u_H(x_i, y_j) w_H(x_i, y_j),\ u_H, w_H \in W_{H,0},$$

where $\square_{i,j} = (x_{i-1/2}, x_{i+1/2}) \times (y_{j-1/2}, y_{j+1/2}) \cap \Omega$, $|\square_{i,j}|$ denotes the area of $\square_{i,j}$, and $x_{i+1/2} = x_i + \dfrac{h_{i+1}}{2}$, $x_{i-1/2} = x_i - \dfrac{h_i}{2}$, $h_{i+1/2} = x_{i+1/2} - x_{i-1/2}$ being $y_{j\pm1/2}$ and $k_{j+1/2}$ defined analogously. Let $\|.\|_H$ be the corresponding norm.

For $u_H = (u_{1,H}, u_{2,H})$, $w_H = (w_{1,H}, w_{2,H})$, and $u_{\ell,H}, w_{\ell,H} \in W_H$, for $\ell = 1, 2$, we use the notation

$$((u_H, w_H))_H = (u_{1,H}, w_{1,H})_{H,x} + (u_{2,H}, w_{2,H})_{H,y},$$

where

$$(u_{1,H}, w_{1,H})_{H,x} = \sum_{i=1}^{N} \sum_{j=1}^{M-1} h_i k_{j+1/2} u_{1,H}(x_i, y_j) w_{1,H}(x_i, y_j),$$

being $(u_{2,H}, w_{2,H})_{H,y}$ defined analogously.

Let D_{-x} and D_{-y} be the first-order backward finite difference operators with respect to the variables x and y, respectively, and let ∇_H be the discrete version of the gradient operator ∇ defined by $\nabla_H u_H = (D_{-x} u_H, D_{-y} u_H)$. We use the following notation

$$\begin{aligned}\|\nabla_H u_H\|_H &= \Big((D_{-x}u_H, D_{-x}u_H)_{H,x} + (D_{-y}u_H, D_{-y}u_H)_{H,y}\Big)^{1/2}\\ &= \Big(\|D_{-x}u_H\|_H^2 + \|D_{-y}u_H\|_H^2\Big)^{1/2}, \ \ u_H \in W_H.\end{aligned}$$

We recall that holds the following Poincaré-Friedrichs inequality: there exists a positive constant C, independent of H, such that

$$\|u_H\|_H \leq C\|\nabla_H u_H\|_H, \forall u_H \in W_{H,0}. \tag{14}$$

3.2. Wave equation. We consider now the following piecewise linear finite element problem to approximate the solution of the wave IBVP: find $p_H(t) \in W_{H,0}$ such that

$$\begin{aligned}(aP_H p_H''(t), P_H w_H) + (bP_H p_H'(t), P_H w_H) = \ & -((E\nabla P_H p_H(t), \nabla P_H w_H))\\ & +(f_1(t), P_H w_H),\end{aligned} \tag{15}$$

for $t \in (0,T]$, $w_H \in W_{H,0}$, and

$$\begin{cases} P_H p_H'(0) = P_H R_H p_{v,0}\\ P_H p_H(0) = P_H R_H p_0.\end{cases} \tag{16}$$

In (16), $R_H : C(\overline{\Omega}) \to W_H$ denotes the restriction operator, where $C(\overline{\Omega})$ represents the space of continuous functions in $\overline{\Omega}$. By E_H we denote the diagonal matrix with $e_{1,H}(x_i, y_j) = e_1(x_{i-1/2}, y_j)$ and $e_{2,H}(x_i, y_j) = e_2(x_i, y_{j-1/2})$, for $(x_i, y_j) \in \Omega_H$.

The initial value problem (15), (16) is replaced by the following fully discrete in space finite element problem: find $p_H(t) \in W_{H,0}$ such that

$$(a_H p_H''(t), w_H)_H + (b_H p_H'(t), w_H)_H = -((E_H \nabla_H p_H(t), \nabla_H w_H))_H + (f_{1,H}(t), w_H)_H, \tag{17}$$

for $t \in (0,T]$, $w_H \in W_{H,0}$, and

$$\begin{cases} p_H'(0) = R_H p_{v,0}\\ p_H(0) = R_H p_0.\end{cases} \tag{18}$$

In (17), $a_H = R_H a$, $b_H = R_H b$, and

$$f_{1,H}(t)(x_i, y_j) = \frac{1}{|\square_{i,j}|}\int_{\square_{i,j}} f_1(x,y,t)\,dxdy. \tag{19}$$

We observe that the fully discrete in space finite element problem can be rewritten as a finite difference problem. In order to define such finite difference problem, we introduce the finite difference operator $\nabla_H^* = (D_x^-, D_y^-)$ where

$$D_x^- v_H(x_i, y_j) = \frac{v_H(x_{i+1}, y_j) - v_H(x_i, y_j)}{h_{i+1/2}},$$

and D_y^- is defined analogously. Then, from (17) we obtain

$$a_H p_H''(t) + b_H p_H'(t) = \nabla_H^* \cdot (E_H \nabla_H p_H(t)) + f_{1,H}(t) \text{ in } \Omega_H,\ t \in (0, T], \quad (20)$$

which is coupled with the boundary condition

$$p_H(t) = 0 \text{ on } \partial\Omega_H \times (0, T], \quad (21)$$

and the initial conditions (18).

3.3. Concentration equation. Now we introduce the piecewise linear finite element approximation for the concentration. It is given by : find $c_H(t) \in W_{H,0}$ such that

$$\begin{aligned} &(P_H c_H'(t), P_H w_H) - ((P_H c_H(t) v_H(t), \nabla P_H w_H)) \\ &= -((D(P_H p_H(t)) \nabla P_H c_H(t), \nabla P_H w_H)) + (f_2(t), P_H w_H), \end{aligned} \quad (22)$$

for $t \in (0, T]$, $w_H \in W_{H,0}$, and

$$P_H c_H(0) = P_H R_H c_0. \quad (23)$$

In (22) the convective velocity is defined by $v_H(t) = v(P_H p_H(t), \nabla P_H p_H(t))$ and $f_{2,H}$ is defined by (19) replacing f_1 by f_2.

To define a fully discrete in space piecewise linear finite element approximation for the concentration IBVP we set the following notations: let D_H^* be the finite difference operator $D_H^* w_H = (D_x^* w_H, D_y^* w_H)$ with

$$D_x^* w_H(x_i, y_j) = \frac{h_i D_{-x} w_H(x_{i+1}, y_j) + h_{i+1} D_{-x} w_H(x_i, y_j)}{h_i + h_{i+1}}, i = 1, \ldots, N-1,$$

$$D_x^* w_H(x_N, y_j) = D_{-x} w_H(x_N, y_j), D_x^* w_H(x_0, y_j) = D_{-x} w_H(x_1, y_j),$$

for $j = 1, \ldots, M-1$, being $D_y^* w_H$ defined analogously; M_H represents the average operator

$$M_H(w_1, w_2) = (M_h w_1, M_k w_2), \quad M_h(w_1(x_i, y_j)) = \frac{1}{2}(w_1(x_{i-1}, y_j) + w_1(x_i, y_j)),$$

being M_k defined analogously and $(w_1, w_2) \in [W_{H,0}]^2$.

Let $D_H(t)$ be the diagonal matrix with $d_{1,H} = d_1(M_h p_H)$ and $d_{2,H} = d_2(M_k p_H)$ in Ω_H. By $v_H(t)$ we represent the vector

$$(v_1(p_H(t), D_h^* p_H(t)), v_2(p_H(t), D_k^* p_H(t)).$$

We remark that if $w_H \in W_{H,0}$ then $w_H v_H(p_H(t), D_H^* p_H(t)) = (0,0)$ at $\partial\Omega_H$.

The initial value problem (22), (23) is now replaced by the following fully discrete in space finite element problem: find $c_H(t) \in W_{H,0}$ such that

$$(c_H'(t), w_H)_H - ((M_H(c_H(t)v_H(t)), \nabla_H w_H))_H = -((D_H(t)\nabla_H c_H(t), \nabla_H w_H))_H + (f_{2,H}(t), w_H)_H, \tag{24}$$

for $t \in (0,T]$, $w_H \in W_{H,0}$, and

$$c_H(0) = R_H c_0. \tag{25}$$

Finally, from (24) we obtain

$$c_H'(t) + \nabla_{c,H} \cdot (c_H(t) v_H(t)) = \nabla_H^* \cdot (D_H \nabla_H c_H(t)) + f_{2,H}(t) \text{ in } \Omega_H,\ t \in (0,T], \tag{26}$$

which is coupled with the boundary condition

$$c_H(t) = 0 \text{ on } \partial\Omega_H, \tag{27}$$

and the initial condition (25). The finite difference operator $\nabla_{c,H}$ is defined by

$$\nabla_{c,H} \cdot (w_1, w_2) = D_{c,x} w_1 + D_{c,y} w_2, \quad D_{c,x} w_1(x_i, y_j) = \frac{w_1(x_{i+1}, y_j) - w_1(x_{i-1}, y_j)}{h_i + h_{i+1}},$$

where $(w_1, w_2) \in [W_{H,0}]^2$, being $D_{c,y}$ defined analogously.

Let us note that (24) can be written in the matrix form

$$c_H'(t) + A(t) c_H(t) = f_{2,H}(t)$$

where the entries of the matrix $A(t)$ depend on $v_H(t)$ and $D_H(t)$. For this linear differential system, the existence of a solution is guaranteed assuming the continuity of $A(t)$ and $f_{2,H}(t)$.

4. Convergence analysis

It is well know that the piecewise linear approximations $P_Hp_h(t)$ and $P_Hc_H(t)$ satisfy

$$\|p(t) - P_Hp_H(t)\|_1 \leq CH_{max},$$
$$\|p(t) - P_Hp_H(t)\| \leq CH_{max}^2,$$
$$\|c(t) - P_Hc_H(t)\| \leq CH_{max}^2,$$

when the concentration equation is acoustic pressure independent and $p(t)$ and $c(t)$ are in $H_0^1(\Omega) \cap H^2(\Omega)$ and the family of triangulations $\mathfrak{T}_H$, not necessarily induced by a non-uniform rectangular partition, is quasi-uniform ([23]). As $v_H(t)$ in (22) depends on $\nabla P_Hp_H(t)$, considering the previous estimates, we believe that in this case

$$\|c(t) - P_Hc_H(t)\| \leq CH_{max}.$$

It is expected that the same result holds for the fully discrete approximations

$$\|R_Hp(t) - p_H(t)\|_1 \leq CH_{max},$$
$$\|R_Hp(t) - p_H(t)\| \leq CH_{max}^2,$$
$$\|R_Hc(t) - c_H(t)\| \leq CH_{max}.$$

If we look for the truncation errors associated with the spatial discretizations that lead to (20) and (26), then these estimates are expected because such truncation errors are of first-order in H_{max} when nonuniform grids are considered.

In [22] a general telegraph IBVP was considered and the discretization (17), (18) introduced before was studied. In what follows we present the main result obtained in the last paper. Later we consider such result to establish a convergence result for the approximation for the concentration defined by (24), (25).

4.1. Wave equation. We denote by $e_{H,p}(t)$ the spatial discretization error induced by the spatial discretization that leads to (17), (18), $e_{H,p}(t) = R_Hp(t) - p_H(t)$. In the Sobolev space $H^n(\Omega)$ we consider the following norm

$$\|w\|_{H^n(\Omega)} = \Big(\sum_{|\alpha|\leq n} \|D^\alpha w\|^2 \Big)^{1/2}, w \in H^n(\Omega).$$

By $C^m([0,T],H^n(\Omega))$ we represent the space of functions $v:[0,T]\to H^n(\Omega)$ such that $v^{(j)}:[0,T]\to H^n(\Omega)$, $j=0,\dots,m$, are continuous and such that

$$\|v\|_{C^m([0,T],H^n(\Omega))}=\max_{j=0,\dots,m}\|v^{(j)}(t)\|_{H^n(\Omega)}<\infty.$$

We will use the notation $\|.\|_{C^m(H^n)}$ to represent the previous norm.

Let $H^m(0,T,H^n(\Omega))$, m, $n\in\mathbb{N}$, be the space of functions $v:(0,T)\to H^n(\Omega)$ with weak derivatives $v^{(j)}:(0,T)\to H^n(\Omega)$, $j=0,\dots,m$, such that

$$\|w\|_{H^m(0,T,H^n(\Omega))}=\Big(\sum_{j=0}^m\int_0^T\|v^{(j)}\|^2_{H^n(\Omega)}\,dt\Big)^{1/2}<\infty.$$

The previous norm will be denoted by $\|.\|_{H^m(H^n)}$.

Theorem 1. *[Theorem 2, [22]] If the solution p of the IBVP (1), (3), (5) belongs to $H^3(0,T,H^2(\Omega))\cap H^1(0,T,H^3(\Omega))$, then there exist positive constants $C_i, i=1,2$, independent of p, H, and T such that for $H\in\Lambda$ with H_{max} small enough*

$$\|e'_{H,p}(t)\|^2_H+\int_0^t\|e'_{H,p}(s)\|^2_H ds+\|\nabla_H e_{H,p}(t)\|^2_H$$
$$\leq C_1e^{C_2t}\sum_{\Delta\in\mathfrak{T}_H}(diam\Delta)^4\Big(\|p\|^2_{H^1(H^3)}+\|p\|^2_{H^3(H^2)}\Big),\ t\in[0,T].$$

To have the smoothness assumptions required in this result it is sufficient to increase the smoothness requirements for $f_1, p_{v,0}$ and p_0 : $f_1\in H^1(0,T,H^3(\Omega))$, $p_{v,0}\in H^4(\Omega)\cap H^1_0(\Omega)$, $p_0\in H^5(\Omega)\cap H^1_0(\Omega)$. We remark that we need to assume also that a, b and E are smooth.

From $\|\nabla_H e_{H,p}(t)\|_H\leq CH^2_{max}$ and (14) we conclude

$$\|e_{H,p}(t)\|_H\leq CH^2_{max}.$$

Using the last two estimates we prove in what follows that the two sequences

$$\|p_H(t)\|_\infty=\max_{(x,y)\in\overline{\Omega}_H}|p_H(x,y,t)|,$$
$$\|\nabla_H p_H(t)\|_\infty=\max_{i=1,\dots,N,j=1,\dots,M-1}|D_{-x}p_H(x_i,y_j,t)|$$
$$+\max_{i=1,\dots,N-1,j=1,\dots,M}|D_{-y}p_H(x_i,y_j,t)|,\ H\in\Lambda,\ H_{max}\text{ small enough},$$

are bounded. We will assume that the spatial grids $\Omega_H, H \in \Lambda$, satisfy

$$\frac{H_{max}^4}{H_{min}} \leq C,\ H \in \Lambda. \tag{28}$$

(1) $\|p_H(t)\|_\infty$, $H \in \Lambda$, H_{max} small enough, is bounded:

As $p_H(t) = R_H p(t) - e_{H,p}(t)$ and $p(t) \in H^3(\Omega)$ which is imbedded in $C(\overline{\Omega})$, to conclude that $\|p_H(t)\|_\infty$ is bounded we need to establish that $\|e_{H,p}(t)\|_\infty$ is bounded. We start by remarking that for $w_H \in W_{H,0}$ we have

$$\sum_{i=1}^{N-1} h_{i+1/2} w_H(x_i, y_j)^2 \leq \|\nabla_H w_H\|_H^2, j = 1, \ldots, M-1,$$

and

$$\sum_{j=1}^{M-1} k_{j+1/2} w_H(x_i, y_j)^2 \leq \|\nabla_H w_H\|_H^2, i = 1, \ldots, N-1.$$

These estimates imply the following

$$\|w_H\|_\infty^2 \leq \frac{1}{H_{min}} \|\nabla_H w_H\|_H^2. \tag{29}$$

where $H_{min} = \min\{h_1, \ldots, h_N, k_1, \ldots, k_M\}$.
As $\|\nabla_H e_{H,p}(t)\|_H^2 \leq C H_{max}^4$, using (29) we get

$$\|e_{H,p}(t)\|_\infty^2 \leq C \frac{H_{max}^4}{H_{min}}.$$

Considering now (28) we conclude that $\|e_{H,p}(t)\|_H^2$, $H \in \Lambda$, with H_{max} small enough, is bounded.

(2) $\|\nabla_H p_H(t)\|_\infty, H \in \Lambda$, is bounded

We observe that

$$\|\nabla_H p_H(t)\|_\infty \leq \|\nabla_H e_{H,p}(t)\|_\infty + \|R_H \nabla p(t)\|_\infty.$$

Considering that $p(t) \in H^3(\Omega)$ which is imbedded in $C^1(\overline{\Omega})$ we conclude that $\|R_H \nabla p(t)\|_\infty$, $H \in \Lambda$, is bounded. Moreover, as $p(., \bar{y}, t) \in H^2(0, 1)$, for $\bar{y} \in (0, 1)$, using Bramble-Hilbert Lemma ([24]) we have

$$|\frac{\partial p}{\partial x}(x_i, y_j, t) - D_{-x} p(x_i, y_j, t)| \leq C \int_{x_{i-1}}^{x_i} |\frac{\partial^2 p}{\partial x^2}(x, y_j, t)| dx, j = 1, \ldots, M-1.$$

This estimate allows us to conclude

$$|D_{-x}p_H(x_i,y_j,t) - R_H\frac{\partial p}{\partial x}(x_i,y_j,t)| \leq C\sqrt{H_{max}}\|p(y_j,t)\|_{H^2(0,1)},$$

where $p(y_j,t) : (0,1) \to \mathbb{R}$, $p(y_j,t)(x) = p(x,y_j,t)$, $x \in (0,1)$. As we also have

$$|D_{-y}p_H(x_i,y_j,t) - R_H\frac{\partial p}{\partial y}(x_i,y_j,t)| \leq C\sqrt{H_{max}}\|p(x_i,t)\|_{H^2(0,1)},$$

where $p(x_i,t) : (0,1) \to \mathbb{R}$, $p(x_i,t)(y) = p(x_i,y,t)$, $y \in (0,1)$, we finally conclude

$$\|\nabla_H p_H(t) - R_H\nabla p(t)\|_\infty \leq C\sqrt{H_{max}},$$

provided that

$$\begin{aligned} &\max_{y\in(0,1)}\int_0^1 \Big(\frac{\partial^2 p}{\partial x^2}(x,y,t)\Big)^2 dx \leq C, t\in(0,T],\\ &\max_{x\in(0,1)}\int_0^1 \Big(\frac{\partial^2 p}{\partial y^2}(x,y,t)\Big)^2 dy \leq C, t\in(0,T]. \end{aligned} \tag{30}$$

We remark that conditions (30) hold if we increase the smoothness of the acoustic pressure, for instance if we require that

$$p\in C([0,T], H^4(\Omega)\cap H_0^1(\Omega)).$$

Of course that this smoothness is achieved if we increase the smoothness of the data $f_2, p_{v,0}$ and p_0.

4.2. Concentration equation. An estimate for the error $e_{H,c}(t) = R_Hc(t) - c_H(t)$ induced by the spatial discretization introduced for the concentration is obtained in what follows. To establish the error equation for $e_{H,c}(t)$ we starting by remarking that we have

$$(e'_{H,c}(t), w_H)_H = \tau_v(w_H) + \tau_D(w_H) + \tau_c(w_H), \tag{31}$$

where

$$\tau_v(w_H) = -((M_H(v_H(t)c_H(t)), \nabla_H w_H))_H - ((\nabla\cdot(c(t)v(t)))_H, w_H)_H, \tag{32}$$

$$\tau_D(w_H) = ((D_H(t)\nabla_H c_H(t), \nabla_H w_H))_H + ((\nabla\cdot(D(t)\nabla c(t)))_H, w_H)_H, \tag{33}$$

$$\tau_c(w_H) = (c'(t), w_H)_H - ((c'(t))_H, w_H)_H, \tag{34}$$

with $(\nabla\cdot(c(t)v(t)))_H$, $(\nabla\cdot(D(t)\nabla c(t)))_H$ and $(c'(t))_H$ defined by (19) with f_1 replaced by $\nabla\cdot(c(t)v(t))$, $\nabla\cdot(D(t)\nabla c(t))$ and $c'(t)$, respectively.

To get an estimate for $\|e_{H,c}(t)\|_H$ we study the functionals $\tau_v(w_H), \tau_D(w_H)$ and $\tau_c(w_H)$ when $w_H \in W_{H,0}$.

Proposition 1. *Let us suppose that the sequence of grids $\Omega_H, H \in \Lambda$, satisfy*

$$\frac{H_{max}}{H_{min}} \leq C, \tag{35}$$

the convective term v is a Lipschtiz function with Lipschitz constant L and $p(t) \in H^3(\Omega), c(t) \in H^2(\Omega)$ such that $v(t)c(t) \in [H^2(\Omega)]^2$ and $\frac{\partial^2 p}{\partial x \partial y}(t) = \frac{\partial^2 p}{\partial y \partial x}(t)$ in Ω. Then for the functional $\tau_v(w_H)$, $w_H \in W_{H,0}$, defined by (32), holds the representation

$$\tau_v(w_H) = ((M_H(v_H(t)e_{H,c}(t)), \nabla_H w_H))_H + \tau_{v,e}(w_H), \tag{36}$$

where

$$\begin{aligned} |\tau_{v,e}(w_H)| \leq C\Big(&\Big(\sum_{\Delta \in \mathfrak{T}_H} (diam\Delta)^4 \|v(t)c(t)\|^2_{[H^2(\Delta)]^2}\Big)^{1/2} \\ &+ \|c(t)\|_\infty \Big(\sum_{\Delta \in \mathfrak{T}_H} (diam\Delta)^4 \|p(t)\|^2_{H^3(\Delta)}\Big)^{1/2} \\ &+ \|c(t)\|_\infty \Big(\|e_{H,p}(t)\|_H + \|\nabla_H e_{H,p}(t)\|_H\Big) \|\nabla_H w_H\|_H. \end{aligned}$$

Proof: We start by observing that $\tau_v(w_H)$ can be rewritten as (36) with

$$\tau_{v,e}(w_H) = \sum_{i=1}^{3} \tau_v^{(i)}(w_H)$$

where

$$\tau_v^{(1)}(w_H) = -((\nabla \cdot (c(t)v(t)))_H, w_H))_H - ((M_H(R_H(v(t)c(t)), \nabla_H w_H))_H,$$
$$\tau_v^{(2)}(w_H) = ((M_H(R_H(v(t)c(t)), \nabla_H w_H))_H - ((M_H(\tilde{v}_H(t)R_H c(t)), \nabla_H w_H))_H,$$

with $\tilde{v}_H(t) = (v_1(p(t), D_h^* p(t)), v_2(p(t), D_k^* p(t)))$,

$$\tau_v^{(3)}(w_H) = ((M_H(\tilde{v}_H(t)R_H c(t)), \nabla_H w_H))_H - ((M_H(v_H(t)R_H c(t)), \nabla_H w_H))_H.$$

Using Lemma 5.5 of [25], we can state that there exists a positive constant C, H and p and c independent, such that

$$|\tau_v^{(1)}(w_H)| \leq C\Big(\sum_{\Delta\in\mathfrak{T}_H}(diam\Delta)^4\|v(t)c(t)\|^2_{[H^2(\Delta)]^2}\Big)^{1/2}\|\nabla_H w_H\|_H.$$

To get an estimate for $\tau_v^{(2)}(w_H)$ we introduce $g_1(x_i,y_j,t)=\frac{\partial p}{\partial x}(x_i,y_j,t)-D_h^*p(x_i,y_j,t)$. We have

$$|k_{j+1/2}g_1(x_i,y_j,t)| \leq \int_{y_{j-1/2}}^{y_{j+1/2}}\Big(k_{j+1/2}|\frac{\partial g_1}{\partial y}(x_i,y,t)|+|g_1(x_i,y,t)|\Big)dy. \quad (37)$$

Under the smoothness assumption for p, Bramble-Hilbert Lemma allow us to conclude the upper bounds

$$\int_{y_{j-1/2}}^{y_{j+1/2}}|\frac{\partial g_1}{\partial y}(x_i,y,t)|dy \leq C\int_{y_{j-1/2}}^{y_{j+1/2}}\int_{x_{i-1}}^{x_{i+1}}|\frac{\partial^3 p}{\partial x^2\partial y}|dxdy,$$

and

$$\int_{y_{j-1/2}}^{y_{j+1/2}}|g_1(x_i,y,t)|dy \leq C(h_i+h_{i+1})\int_{y_{j-1/2}}^{y_{j+1/2}}\int_{x_{i-1}}^{x_{i+1}}|\frac{\partial^3 p}{\partial x^3}(x,y,t)|dxdy$$

that leads to

$$|k_{j+1/2}g_1(x_i,y_j,t)| \leq C\Big(k_{j+1/2}\int_{y_{j-1/2}}^{y_{j+1/2}}\int_{x_{i-1}}^{x_{i+1}}|\frac{\partial^3 p}{\partial y\partial x^2}|dxdy + (h_i+h_{i+1})\int_{y_{j-1/2}}^{y_{j+1/2}}\int_{x_{i-1}}^{x_{i+1}}|\frac{\partial^3 p}{\partial x^3}(x,y,t)|dxdy\Big).$$

As for $g_2(x_i,y_j,t)=\frac{\partial p}{\partial y}(x_i,y_j,t)-D_k^*p(x_i,y_j,t)$ we have an analogous estimate we can show using the Lipschitz assumption for v that for $\tau_v^{(2)}(w_H)$ we have

$$|\tau_v^{(2)}(w_H)| \leq CL\|c(t)\|_\infty\Big(\sum_{\Delta\in\mathfrak{T}_H}(diam\Delta)^4\|p\|^2_{H^3(\Delta)}\Big)^{1/2}\|\nabla_H w_H\|_H. \quad (38)$$

Using again the Lipschitz assumption for v, the smoothness condition on the nonuniformity of the spatial grids we get for $\tau_v^{(3)}(w_H)$ the upper bound

$$|\tau_v^{(3)}(w_H)| \leq LC\|c(t)\|_\infty\Big(\|e_{H,p}(t)\|_H+\|\nabla_H e_{H,p}(t)\|_H\Big)\|\nabla_H w_H\|_H. \quad (39)$$

that concludes the proof of the representation (36).

■

Proposition 2. *Let $d_i, i = 1, 2$, be Lipschitz functions. If $c(t) \in H^3(\Omega)$, $p(t) \in H^2(\Omega)$ then for the functional $\tau_D(w_H)$, $w_H \in W_{H,0}$, defined by (33) holds the following representation*

$$\tau_D(w_H) = -((D_H(t)\nabla_H e_{H,c}(t), \nabla_H w_H))_H + \tau_{D,e}(w_H), \tag{40}$$

where

$$\begin{aligned} |\tau_{D,e}(w_H)| \le C\Big(\Big(\sum_{\Delta\in\mathfrak{T}_H}(diam\Delta)^4\|D(t)\nabla c(t)\|^2_{[H^2(\Delta)]^2}\Big)^{1/2} \\ + \|c(t)\|_{C^1}\Big(\Big(\sum_{\Delta\in\mathfrak{T}_H}(diam\Delta)^4\|p(t)\|^2_{H^2(\Delta)}\Big)^{1/2} \\ + \|e_{H,p}(t)\|_H\Big)\|\nabla_H w_H\|_H. \end{aligned}$$

Proof: We observe that $\tau_D(w_H)$ admits the representation (40) with $\tau_{D,e}(w_H)$ given by

$$\tau_{D,e}(w_H) = \sum_{i=1}^{3} \tau_D^{(i)}(w_H)$$

where

$$\tau_D^{(1)}(w_H) = ((\nabla\cdot(D(t)\nabla c(t)))_H, w_H)_H + ((\tilde{D}_H(t)\nabla_H R_H c(t), \nabla_H w_H))_H,$$

for each grid point $(x_i, jy_j) \in \Omega_H$, $\tilde{D}_H(t)$ is a diagonal matrix with entries $d_1(p(x_{i-1/2}, y_j, t))$, $d_2(p(x_i, y_{j-1/2}, t)$,

$$\tau_D^{(2)}(w_H) = (((D_H^*(t) - \tilde{D}_H(t))\nabla_H R_H c(t), \nabla_H w_H))_H$$

for each grid point $(x_i, j_j) \in \Omega_H$, $D_H^*(t)$ is a diagonal matrix with entries $d_1(M_h p(x_i, y_j, t))$, $d_2(M_k p(x_i, y_j, t))$,

$$\tau_D^{(3)}(w_H) = (((D_H(t) - D_H^*(t))\nabla_H R_H c(t), \nabla_H w_H))_H.$$

Using Lemma 5.1 of [25] it can be shown that

$$|\tau_D^{(1)}(w_H)| \le C\Big(\sum_{\Delta\in\mathfrak{T}_H}(diam\Delta)^4\|D(t)\nabla c(t)\|^2_{[H^2(\Delta)]^2}\Big)^{1/2}\|\nabla_H w_H\|_H. \tag{41}$$

To estimate $\tau_D^{(2)}(w_H)$ we introduce $g_1(x_i, y_j, t) = M_h p(x_i, y_j, t) - p(x_{i-1/2}, y_j, t)$ and for this function g_1 we also have we have (37). Bramble-Hilbert Lemma leads to

$$|k_{j+1/2} g_1(x_i, y_j, t)| \leq C\Big(k_{j+1/2} \int_{y_{j-1/2}}^{y_{j+1/2}} \int_{x_{i-1}}^{x_i} |\frac{\partial^2 p}{\partial x \partial y}| dxdy + h_i \int_{y_{j-1/2}}^{y_{j+1/2}} \int_{x_{i-1}}^{x_{i+1}} |\frac{\partial^2 p}{\partial x^2}(x, y, t)| dxdy\Big).$$

We remak that for $g_2(x_i, y_j, t) = M_k p(x_i, y_j, t) - p(x_i, y_{j-1/2}, t)$ we have an analogous relation, we conclude, considering that $d_i, i = 1, 2$, are Lipschitz functions

$$|\tau_D^{(2)}(w_H)| \leq C \|c(t)\|_{C^1} \Big(\sum_{\Delta \in \mathfrak{T}_H} (diam \Delta)^4 \|p(t)\|^2_{H^2(\Delta)} \Big)^{1/2} \|\nabla_H w_H\|_H. \quad (42)$$

As $d_i, i = 1, 2$, are Lipschitz functions, we easily conclude that

$$|\tau_D^{(3)}(w_H)| \leq C \|c(t)\|_{C^1} \|e_{H,p}(t)\|_H \|\nabla_H w_H\|_H. \quad (43)$$

Finally from (41)-(43) we conclude the proof of (40).

■

To obtain an upper bound for the functional $\tau_c(w_H)$, $w_H \in W_{H,0}$, defined by (34) we apply Lemma 5.7 of [25].

Proposition 3. *If $c(t) \in H^2(\Omega)$, for the function $\tau_c(w_H)$, $w_H \in W_{H,0}$, defined by (34) we have*

$$|\tau_c(w_H)| \leq C \Big(\sum_{\Delta \in \mathfrak{T}_H} (diam \Delta)^4 \|c'(t)\|^2_{H^2(\Delta)} \Big)^{1/2} \|\nabla_H w_H\|_H.$$

■

To simplify the presentation of one of the main results of this work, Theorem 2, we do not include in its presentation the assumptions on the coefficient functions of the wave and concentration IBVPs. We assume that they satisfy the assumptions mentioned before. We also assume that the spatial grids $\Omega_H, H \in \Lambda$, satisfy (35).

If the convective velocity $v(t)$ is a bounded function then in the next result we do not need to use the boundness of the pressure approximation sequences $\|p_H(t)\|_\infty, \|\nabla_H p_H(t)\|_\infty$, for $H \in \Lambda$, with H_{max} small enough and consequently the next result holds without the smoothness condition (30).

However, as we consider a more general function $v(t)$, we need to impose such condition.

Theorem 2. *Let us suppose that the solution* p *of the IBVP (1), (3), (5) satisfies (30) and* $\frac{\partial^2 p}{\partial x \partial y} = \frac{\partial^2 p}{\partial y \partial x}$ *in* $\Omega \times (0,T]$, *and it belongs to* $H^3(0,T,H^2(\Omega)) \cap H^1(0,T,H^3(\Omega))$. *Let us assume also that the solution* c *of the concentration IBVP (2), (4), (6) belongs to* $L^2(0,T,H^3(\Omega)\cap H^1_0(\Omega))$, $c' \in L^2(0,T,H^2(\Omega))$.

If the convective velocity $v(t)$ *satisfies (12),* $v(t)c(t) \in [H^2(\Omega)]^2$, *the diffusivity tensor* $D(t)$ *is such that* $D(t)\nabla c(t) \in [H^2(\Omega)]^2$, *then, there exist positive constants* C_3, C_4, *where* C_4 *depends on the upper bound of the sequences* $\|p_H(t)\|_\infty$ *and* $\|\nabla_H p_H(t)\|_\infty$, *such that for the semi-discretization error* $e_{H,c}(t) = R_H c(t) - c_H(t)$ *of the solution of the fully discrete variational problem (24) holds the following*

$$\|e_{H,c}(t)\|_H^2 + \int_0^t \|\nabla_H e_{H,c}(s)\|_H^2 ds \le e^{C_3 t} \int_0^t \tau_c(s) ds, \tag{44}$$

where

$$\begin{aligned} |\tau_c(t)| \le C_4\Big(&\sum_{\Delta \in \mathfrak{T}_H} (diam \Delta)^4 \Big(\|v(t)c(t)\|^2_{[H^2(\Delta)]^2} + \|D(t)\nabla c(t)\|^2_{[H^2(\Delta)]^2} \\ &\qquad + \|c'(t)\|^2_{H^2(\Delta)} \Big) \\ &+ \|c(t)\|^2_{C^1} \Big(\sum_{\Delta \in \mathfrak{T}_H} (diam \Delta)^4 \|p(t)\|^2_{H^3(\Delta)} \\ &+ C_1 e^{C_2 t} \sum_{\Delta \in \mathfrak{T}_H} (diam \Delta)^4 \Big(\|p\|^2_{H^1(H^3)} + \|p\|^2_{H^3(H^2)} \Big) \Big) \end{aligned}$$

and C_1, C_2 *represent positive constants introduced in Theorem 1.*

Proof: Taking in (31), $w_H = e_{H,c}(t)$ and considering Propositions 1,2 and 3, and taking into account the error estimate established in Theorem 1, we get

$$\frac{1}{2}\frac{d}{dt}\|e_{H,c}(t)\|_H^2 + ((D_H(t)\nabla_H e_{H,c}(t), \nabla_H e_{H,c}(t)))_H \tag{45}$$

$$= ((M_H(v_H(t)e_{H,c}(t)), \nabla_H e_{H,c}(t)))_H + \epsilon_1^2 \|\nabla_H e_{H,c}(t)\|_H^2 + \tilde{\tau}_c(t), \tag{46}$$

where $\epsilon_1 \neq 0$ is an arbitrary constant

$$\begin{aligned}|\tilde{\tau}_c(t)| \leq \frac{C}{\epsilon_1^2}\Big(&\sum_{\Delta\in\mathfrak{T}_H} (diam\Delta)^4\Big(\|v(t)c(t)\|^2_{[H^2(\Delta)]^2} + \|D(t)\nabla c(t)\|^2_{[H^2(\Delta)]^2}\Big)\\ &+ \|c(t)\|^2_{C^1}\sum_{\Delta\in\mathfrak{T}_H}(diam\Delta)^4\|p(t)\|^2_{H^3(\Delta)}\\ &+ \|c(t)\|^2_{C^1}C_1e^{C_2t}\sum_{\Delta\in\mathfrak{T}_H}(diam\Delta)^4\Big(\|p\|^2_{H^1(H^3)} + \|p\|^2_{H^3(H^2)}\Big)\\ &+ \sum_{\Delta\in\mathfrak{T}_H}(diam\Delta)^4\|c'(t)\|^2_{H^2(\Delta)}\Big),\end{aligned}$$

and C denotes a generic positive constant H, c, p, t, x, y independent, C_1 and C_2 were introduced in Theorem 1.

As $d_i, i = 1, 2$, have a lower bound d_0 and v satisfies (12), from (46), we obtain

$$\begin{aligned}&\frac{1}{2}\frac{d}{dt}\|e_{H,c}(t)\|^2_H + (d_0 - \epsilon_1^2)\|\nabla_H e_{H,c}(t))\|^2_H\\ &\quad\leq C(\|p_H(t)\|_\infty + \|\nabla_H p_H(t)\|_\infty)\|e_{H,c}(t)\|_H\|\nabla_H e_{H,c}(t)\|_H + \tilde{\tau}_c(t).\end{aligned} \tag{47}$$

Considering that $\|p_H(t)\|_\infty + \|\nabla_H p_H(t)\|_\infty$ are bounded for $H \in \Lambda$, H_{max} small enough, we conclude that exists a positive constant C_P such that

$$\frac{d}{dt}\|e_{H,c}(t)\|^2_H + 2(d_0 - \epsilon_1^2 - \epsilon_2^2)\|\nabla_H e_{H,c}(t))\|^2_H \leq \frac{C_P^2}{2\epsilon_2^2}\|e_{H,c}(t)\|^2_H + 2\tilde{\tau}_c(t).$$

Choosing now ϵ_1, ϵ_2 such that $d_0 - \epsilon_1^2 - \epsilon_2^2 > 0$ we conclude from the last differential inequality the next estimate

$$\begin{aligned}&\|e_{H,c}(t)\|^2_H + \int_0^t \|\nabla_H e_{H,c}(s))\|^2_H ds\\ &\quad\leq \frac{C_P^2}{2\epsilon_2^2\min\{1, 2(d_0 - \epsilon_1^2 - \epsilon_2^2)\}}\int_0^t \|e_{H,c}(s)\|^2_H ds\\ &\quad+\frac{2}{\min\{1, 2(d_0 - \epsilon_1^2 - \epsilon_2^2)\}}\int_0^t \tilde{\tau}_c(s)ds.\end{aligned} \tag{48}$$

Applying Gronwall's Lemma to (48) we conclude the existence of positive constants C_3, C_4 such that (44) holds.

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5. Numerical examples

In this section we show some numerical experiments. Before that, we present a time discretization method for the coupled wave concentration problem (18), (20), (21), (25), (26), (27). We employ a first-order implicit-explicit method. In particular, the wave equation is solved by an implicit first-order method. The concentration equation is solved by a first-order semi-implicit method, i.e., a combination of an implicit method for the concentration and an explicit method for the pressure wave dependent terms. For the temporal domain $[0, T]$, we define the uniform time grid $\{t_m = m\Delta t,\ m = 0, \ldots, M_t\}$, with $t_{M_t} = T$, and where Δt is the time step. Let us denote by p_H^m and c_H^m the numerical approximations for $p_H(t_m)$ and $c_H(t_m)$. The fully discrete (in time and space) numerical scheme is then defined by: find p_H^m and c_H^m such that

$$a_H \frac{p_H^{m+1} - 2p_H^m + p_H^{m-1}}{\Delta t^2} + b_H \frac{p_H^{m+1} - p_H^m}{\Delta t} = \nabla_H^* \cdot (E_H \nabla_H p_H^{m+1}) + f_{1,H}^{m+1} \text{ in } \Omega_H, \tag{49}$$

for $m = 1, \ldots, M_t - 1$,

$$\frac{c_H^{m+1} - c_H^m}{\Delta t} + \nabla_{c,H} \cdot (c_H^{m+1} v_H^m) = \nabla_H^* \cdot (D_H^m \nabla_H c_H^{m+1}) + f_{2,H}^{m+1} \text{ in } \Omega_H, \tag{50}$$

for $m = 0, \ldots, M_t - 1$, and with the initial conditions

$$\frac{p_H^1 - p_H^0}{\Delta t} = R_H p_{v,0},\ p_H^0 = R_H p_0,\ c_H^0 = R_H c_0 \text{ in } \Omega_H, \tag{51}$$

and boundary conditions

$$c_H^m = 0,\ p_H^m = 0 \text{ on } \partial\Omega_H,\ m = 0, \ldots, M_t. \tag{52}$$

Note that the p_H dependent terms in (50), namely, v_H and D_H, are evaluated at time level m. This strategy allows us to solve the coupled problem in a sequential way. From time level m to time level $m+1$ we first solve equation (50) to obtain c_H^{m+1} and then we solve equation (49) (or we use (51) if $m = 0, 1$) to obtain p_H^{m+1}. Let us now define the errors

$$e_{H,p}^m = R_H p(t_m) - p_H^m \quad \text{and} \quad e_{H,c}^m = R_H c(t_m) - c_H^m.$$

We remark that the convergence analysis of the time discretization (49)-(52) can be obtained following the arguments given in [26] for a coupled elliptic-parabolic problem, and using also the results given in [22] for an hyperbolic equation.

5.1. Convergence rate test in space. The first example of this section illustrates the theoretical convergence rates of the proposed numerical method. In particular, for the wave equation (1) we set the coefficient functions $a(x, y) = y^2$, $b(x, y) = x + y$, $e_1(x, y) = xy$, and $e_2(x, y) = x$, while for the parabolic equation (2) we set $v(p, \nabla p) = (1+p+\frac{\partial p}{\partial x}, 2p+\frac{\partial p}{\partial y})$, $d_1(p) = 5+p$, and $d_2(p) = 10 + p$. In addition, the initial conditions (3), (4) and the functions f_1 and f_2 are defined such that the exact solution of the coupled system (1), (2) is given by

$$\begin{aligned} p(x, y, t) &= e^t \sin(2\pi y)(1 - \cos(2\pi x)) \\ c(x, y, t) &= e^t \sin(\pi(2x - 1)) \sin(\pi(2y - 1)). \end{aligned}$$

We also consider $\Omega = [0, 1]^2$, $T = 0.1$ and the time step $\Delta t =$1e-05. This time step is small enough so that the influence of the time discretization on the numerical error is negligible. To measure the numerical rate of convergence we define the error

$$E_p = \max_{m=1,\dots,M_t} \|D_{-t} e^m_{H,p}\|^2_H + \|\nabla_H e^m_{H,p}\|^2_H,$$

which is associated with the discretization of the wave equation (1), and the error

$$E_c = \max_{m=1,\dots,M_t} \|e^m_{H,c}\|^2_H + \|\nabla_H e^m_{H,c}\|^2_H,$$

which is associated with the discretization of the parabolic equation (2). For the simulation the domain Ω is first divided into $N_x \times N_y$ non-uniform intervals. Then, we subdivide each interval by considering the midpoint of each interval to obtain two intervals. In Table 1 we show the errors E_p and E_c for several mesh sizes, from $N_x \times N_y = 12 \times 14$ to $N_x \times N_y = 192 \times 224$.

H_{max}	E_p	E_c	N_x	N_y
9.9208e-02	2.0123e-01	1.2545e-01	12	14
4.9604e-02	5.0609e-02	3.1817e-02	24	28
2.4802e-02	1.2660e-02	7.9833e-03	48	56
1.2401e-02	3.1664e-03	1.9977e-03	96	112
6.2005e-03	7.9269e-04	4.9956e-04	192	224

TABLE 1. The errors E_p and E_c on successively refined meshes.

Using the data from Table 1, we plot in Figure 1 the $\log(E_p)$ and $\log(E_c)$ versus $\log(H_{max})$. Assuming that the errors E_p and E_c are proportional to

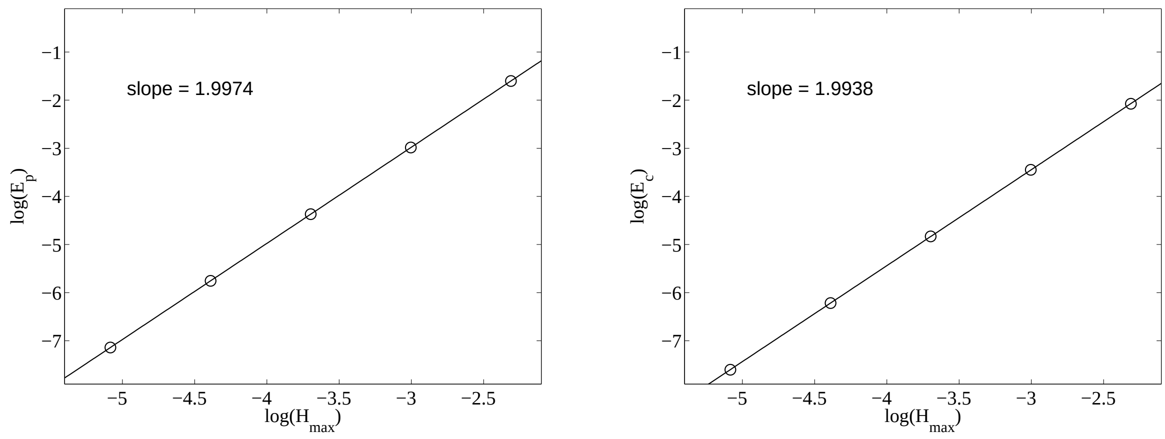

FIGURE 1. From left to right: Log-log plots of E_p and E_c versus H_{max}. The best fitting least square line is shown as a solid line.

H_{max}^{α}, for some $\alpha \in \mathbb{R}$, the convergence rate can be estimated by the slope of the best fitting least square line. The estimated values are 1.9974 for E_p and 1.9938 for E_c. These values confirm the theoretical $O(H_{max}^2)$ convergence rates. Images illustrating the numerical solutions and the numerical errors are given in Figure 2.

5.2. Application to ultrasound enhanced drug delivery. With the next example we validate the applicability of the proposed numerical method to real problems. For that, we carry out simulations with a practical application of the studied system (1)-(6), namely, ultrasound enhanced drug delivery. To model the ultrasound propagation we use the simplified wave equation

$$\frac{\partial^2 p}{\partial t^2} = c^2 \Delta p. \tag{53}$$

For the evolution of drug concentration in the tissue we use the classical convection-diffusion equation

$$\frac{\partial c}{\partial t} + \nabla \cdot (vc) = \nabla \cdot (D_m \nabla c). \tag{54}$$

Here, c is the drug concentration, D_m is the diffusion coefficient, and v is the convective velocity field generated by the ultrasound wave. We consider that this velocity field is radial around the wave source origin (x_0, y_0) and has magnitude proportional to the wave intensity, i.e,

$$v = C_1 p^2 \left(\frac{(x - x_0)}{\sqrt{(x - x_0)^2 + (y - y_0)^2}}, \frac{(y - y_0)}{\sqrt{(x - x_0)^2 + (y - y_0)^2}} \right), \quad \text{with } C_1 \geq 0.$$

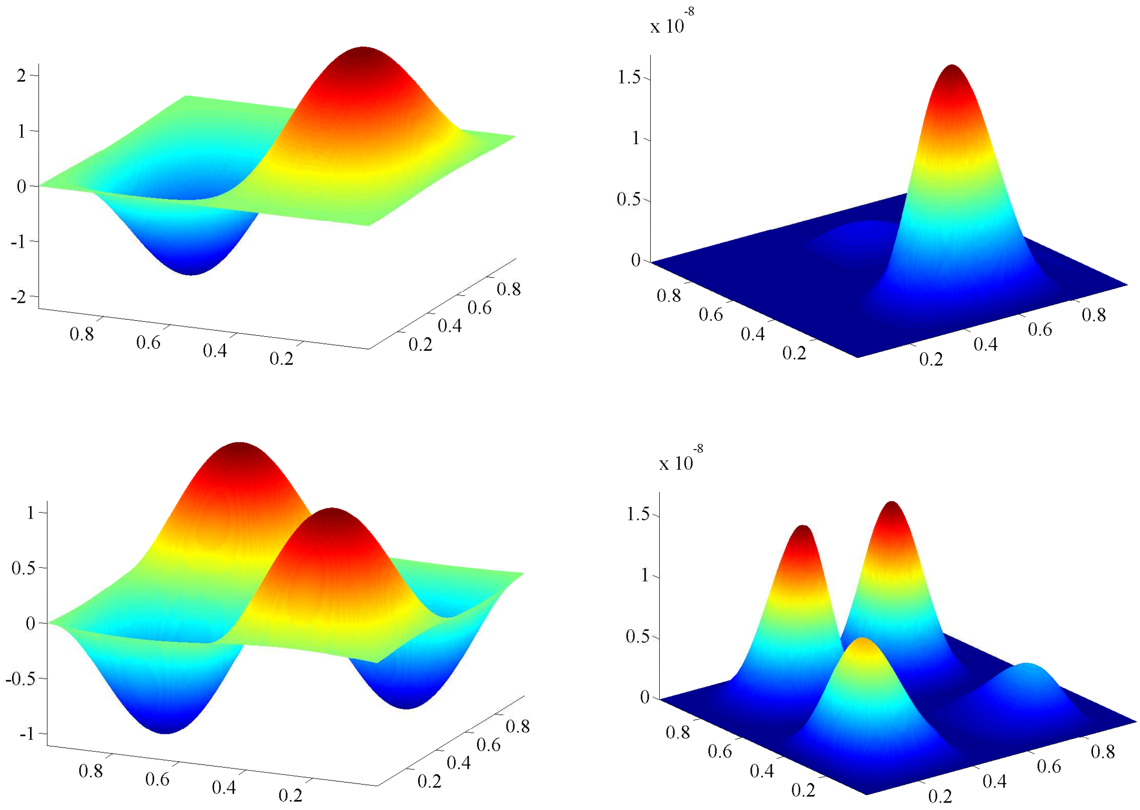

FIGURE 2. From left to right: Numerical approximation and square error of p_H^n (first row) and c_H^n (second row) at the final simulation time $T = 0.1$ and at the finer mesh.

Moreover, to model the effects of ultrasound waves on cell membrane permeabilization, we consider that the drug molecular diffusion in the tumor tissue, denoted by $D_{m,T}$, is a scalar that depends on the pressure wave intensity trough the following relation

$$D_{m,T} = \begin{cases} D_{m,c} & \text{if } \max(p^2) \leq C_2 \\ D_{m,p} & \text{if } \max(p^2) > C_2 \end{cases}$$

with C_2 a positive constant. The diffusion and acoustic parameters used in the simulation were: $c = 2$, $D_m =$ 1e-03, $D_{m,p} =$ 1e-04, $D_{m,c} =$ 1e-06, $C_1 =$ 2e-04, and $C_2 = 20$. We remark that for simplicity units are omitted. We also note that system (53), (54) can be seen as a particular case of system (1), (2).

Let us consider the configuration shown in Figure 3 (on the left), where the tumor tissue, the initial drug distribution, and the localization of the ultrasound source are depicted. Also in Figure 3 (on the right) we present the time profile of the ultrasound wave. In Figure 4, we present the results

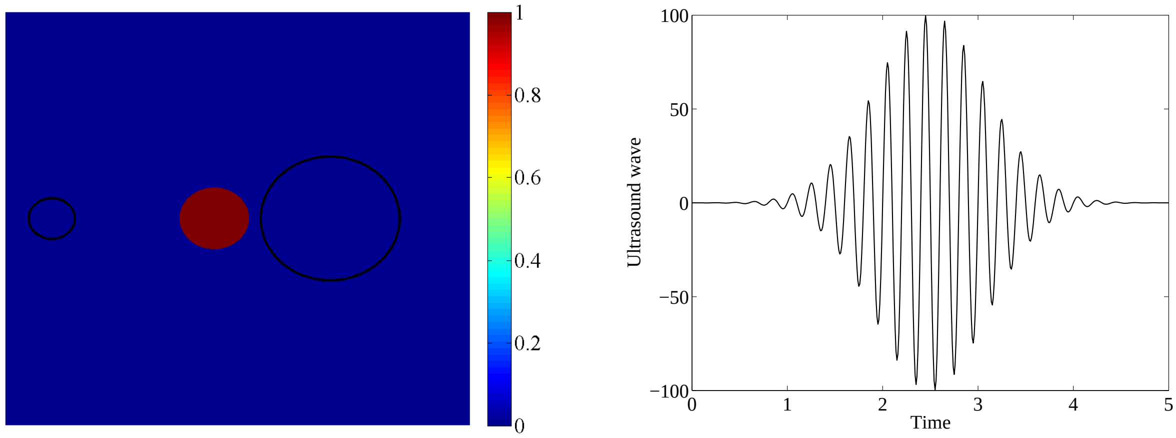

FIGURE 3. On the left: Initial drug concentration and simulation scenario. The tumor tissue is represented by the black circle on the right and the ultrasound source is represented by the black circle on the left. On the right: time profile of the ultrasound wave.

of our computational experiments. On the left we consider two simulation conditions: transport of drug under the influence of the ultrasound wave, and transport of drug only by passive diffusion, i.e., without the application of the ultrasound wave. As can be observed when ultrasound is applied the average concentration of drug inside the tumor tissue at the final time is considerably higher than that obtained only with passive diffusion. Note also that the higher flux of drug to the tumor tissue, between time equal 2 and time equal 3.5, approximately, can be easily related with the ultrasound profile. The sensitivity analysis of the model to the ultrasound wave is shown in the right plot of Figure 4. In particular, we consider the same parameters as before but where the maximum wave amplitude is reduced from 100 to 50. As expected the final average concentration of drug in the tumor tissue is lower. The lower ultrasound amplitude also explains why the high flux of drug occurs during a shorter period of time.

In Figure 5, we show snapshots of drug concentration and ultrasound intensity at different values of time. Both cases, passive diffusion and passive

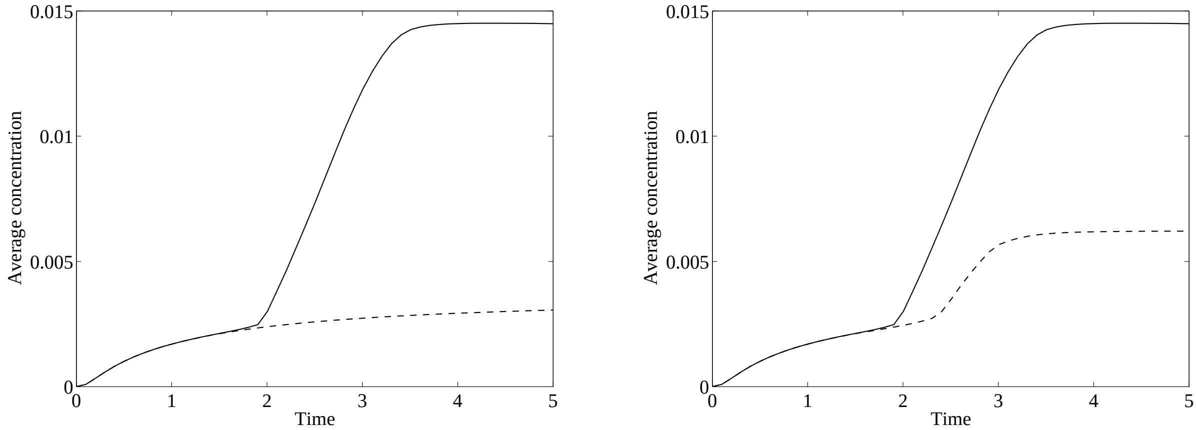

FIGURE 4. Time evolution of the average concentration of drug in the tumor tissue. On the left: Passive diffusion (dash line) and ultrasound enhanced (solid line). On the right: Ultrasound enhanced with maximum wave amplitude equal 200 (solid line) and equal 100 (dash line).

diffusion plus ultrasound, are presented. The effect of the convective transport on the concentration plume is clearly visible on the images in the left column. For better visualization the concentration in the tumor tissue represents average concentration. In Figure 6, the pressure wave and the velocity filed are shown. We refer that a time step equal 1e-02 and a uniform mesh with $H_{max} = 3.125\text{e-}03$ were used. To minimize boundary effects the domain was enlarged. It is also important to remark that in this paper we are mostly interested in the analysis of the proposed numerical method. A more detailed simulation of ultrasound enhanced drug delivery requires an independent study. This is left for future work.

6. Conclusion

In this paper we proposed a numerical method for a hyperbolic-parabolic IBVP that can be used, e.g., to describe drug delivery enhanced by ultrasound. The devised numerical scheme is based on piecewise linear finite element spaces, and it can be seen as a finite difference method defined on non-uniform rectangular partitions of the spatial domain.

The main result of this work is Theorem 2 where we proved that the numerical approximation for the solution of the parabolic problem is second-order accurate with respect to a discrete L^2-norm. The proof of this theorem

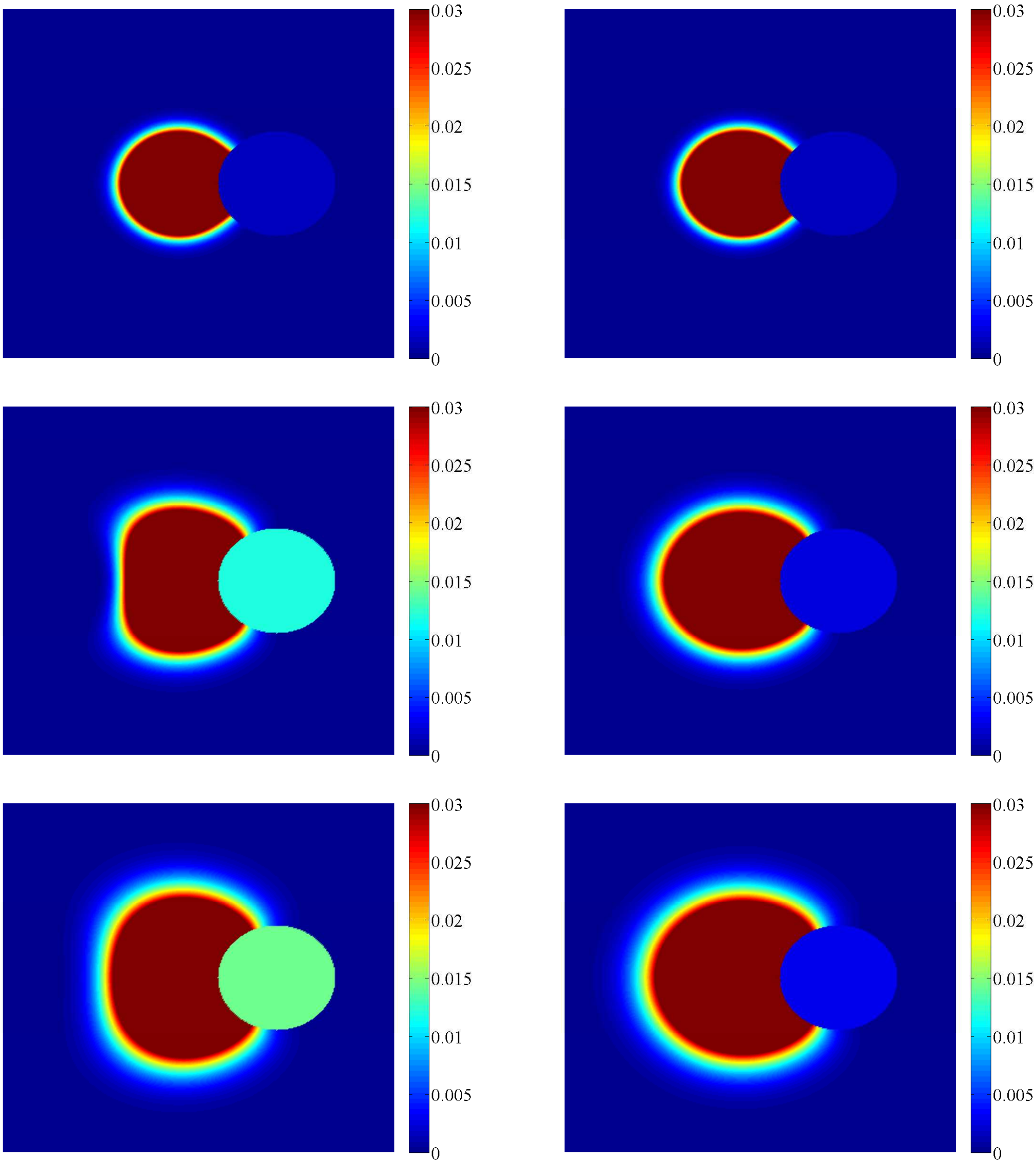

FIGURE 5. From top to bottom: Drug concentration at time equal 1, 3, and final time 5. From left to right: Transport by diffusion and ultrasound, and transport by diffusion only.

relies heavily on Theorem 1 where we established that the numerical approximation for the solution of the hyperbolic problem is second-order accurate with respect to a discrete H^1-norm. It should be mentioned that our results were obtained imposing smoothness conditions on the solution of the coupled

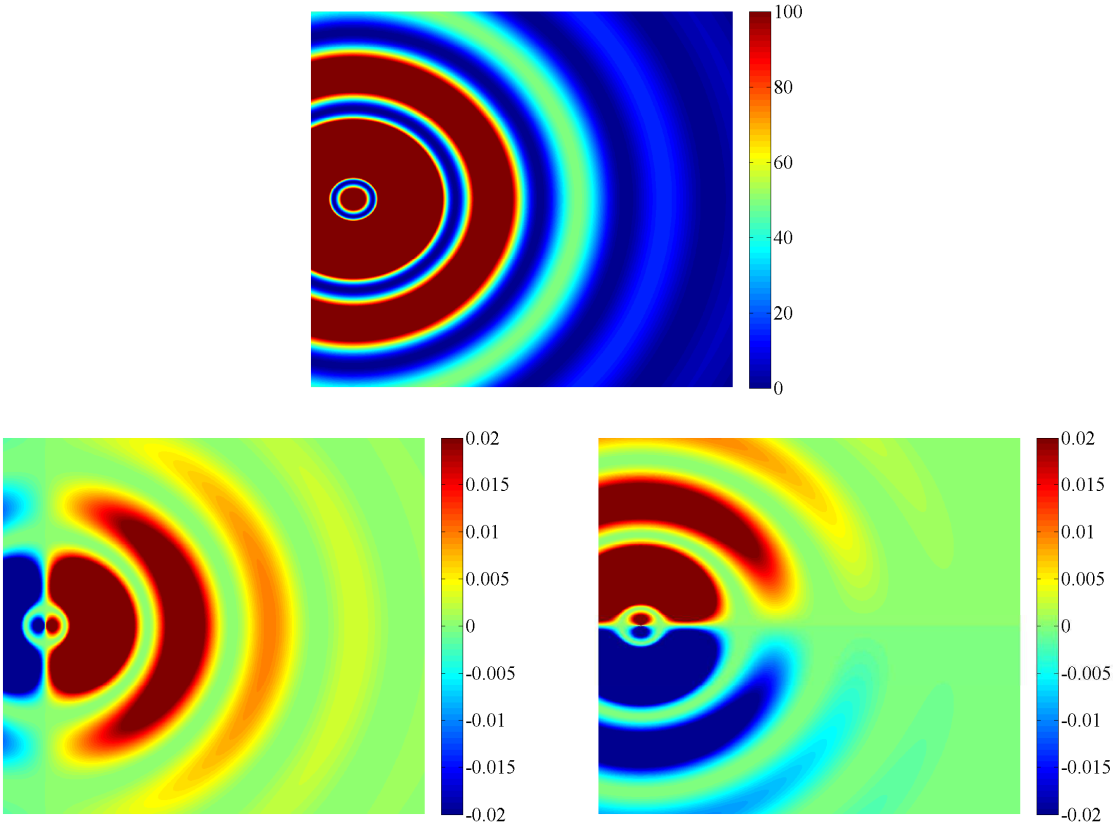

FIGURE 6. Ultrasound intensity p^2 (first row) and velocity components x and y (second row) at time level equal 3.

IBVP problem that are weaker than those usually used in the convergence analysis of finite difference schemes.

Numerical experiments illustrating the theoretical results were also given. The proposed method was also used to simulate ultrasound enhanced drug transport.

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