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FINITE DIFFERENCES-FINITE ELEMENTS ANALYSIS AND NUMERICAL SIMULATION OF A LIGHT-TRIGGERED DRUG DELIVERY MODEL

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ABSTRACT: Light-triggered drug delivery is a promising area of research that has been deeply investigated in the field of anti-cancer therapy. The main goal is maximizing drug concentration in the cancer tissue while minimizing drug toxicity. This technique is based on smart materials that carry the drug to the target site and release it in response to an external light stimulus.

In this paper, we propose a system of partial differential equations governing light-triggered drug release from a polymeric platform. To simulate the model, we study a fully discrete finite difference method (FDM) that in space can be interpreted as a piecewise linear finite element method (FEM) with quadrature. We prove that the FDM is second order superconvergent in a discrete H^1-norm in the spatial direction, and first order convergent in a discrete L^2-norm in the temporal direction. Numerical results illustrating the theoretical findings are given. We also include computational simulations based on a laboratory experiment that show the relevance of the proposed mathematical model.

KEYWORDS: Finite difference method, Piecewise linear finite element method, Convergence analysis, Superconvergence, Supraconvergence, Stimuli-responsive materials, Light-triggered drug delivery.

Chemotherapeutic drugs administration through the circulatory system is one of the most conventional approaches to fight cancer. The drugs attack the tumor cells in different phases of their cell cycle, altering their ability to grow and/or to proliferate causing their dead. However, the chemical agents are not selective, interfering also with the cell cycle of non-cancer cells. This drawback leads to severe side effects and has serious implications in the life of cancer patients. Other severe disadvantages of traditional chemotherapy are: high-dose drug requirement, development of multiple drug resistance and non-specific drug targeting ([15], [18], [20]).

To avoid some of these disadvantages it is crucial to develop techniques that allow the controlled and localized delivery of drugs at the tumor site. Localized release is crucial to minimize undesirable side effects provoked by drugs with high toxicity, while controlled release is crucial to maintain the drug

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concentration in its therapeutic window. The therapeutic window importance is two fold: first, undesirable side effects can occur when the maximum safety range is surpassed; second, the failure to reach the minimum therapeutic range leads to no therapeutic effect and increases the risk of drug's resistance by the tumor ([15], [18], [20]).

The development of controlled and localized drug delivery systems had a burst with the paradigm of nanomedicine based on nanotechnology. Some of the stimuli-responsive drug nanocarriers being studied include dendrimers, liposomes, micelles, metal particles, polymeric nanoparticles, carbon nanotubes and hydrogels ([12, 10, 23, 29]). To tune the drug release from the nanocarriers, endogeneous (pH, redox, enzymes) and exogeneous (temperature, ultrasound, light, electric fields, magnetic fields) stimuli are being explored ([11, 9, 7, 21, 29, 28]).

In this work we focus our discussion on near infrared (NIR) light-triggered drug delivery from hydrogels. Hydrogels are polymeric materials that can store large amounts of water or biological fluids, which makes them highly biocompatible. The physical and chemical properties of hydrogels are also highly tunable, and properties like temperature and degradation rate can be controlled by an external stimulus. These properties make hydrogels an ideal candidate for controlled and localized drug delivery ([12, 25, 13]). In this context, external stimulus based on NIR light have two appealing characteristics, namely: minimal adverse effects on human tissue and relatively deep tissue penetration. Light is also easy to operate and several parameters like intensity, duration and wavelength can be manipulated to fine tune the drug release rate ([25, 21, 16, 10, 13, 24, 17, 18, 20, 27]). For instance, once a NIR light-responsive hydrogel is in contact with the target tissue the drug entrapped in the polymeric matrix can be released by the stimulus of light radiation. A diffusion type release takes place, and it can be originated by different factors: temperature rise, hydrogel swelling due to increase osmotic pressure or disintegration of the polymeric matrix (i.e. photocleavage) ([30]). Moreover, such processes are reversible, meaning that diffusion is controlled and regulated over time. The desired release rates are obtained manipulating light parameters (e.g., intensity and duration) and hydrogel composition ([12, 25, 16, 24]).

An in vivo experiment involving tumor eradication by drug delivery from a NIR light-responsive hydrogel is discussed in [16]. For the laboratory experiment, tumor-bearing nude mice were divided into two groups: one was injected with a drug, and the other was injected with a drug-loaded NIR light-responsive hydrogel. The group injected with the NIR light-responsive hydrogel was further divided into two subgroups: one was exposed to suitable NIR light radiation and the other was not. Over the following 12h period the group treated with the combination of smart hydrogel plus light radiation exhibited a more significant concentration of drug around the tumor site than the other groups. That same group also presented a much smaller tumor after two weeks. Moreover, further analysis did not show significant damages in the normal tissues of such group. These results suggest that smart drug delivery systems can become a valuable tool for cancer therapy.

However, as stated by the authors of [16], the translation to human clinical application requires future investigations concerning the design of more efficient hydrogels. Mathematical modeling and simulation can make a significant contribution to this effort. A reliable mathematical simulation tool is a cheap and fast way to provide new insights into drug delivery by light-responsive hydrogels. By simulation, light intensity and exposure time, drug diffusion coefficients and reaction parameters governing the interaction between hydrogel, bounded drug and light, can be tuned to find the optimal free drug concentration profile.

Consider a polymeric platform $\Omega = (a, b)^3$ where a drug is linked by cleavable bonds. The polymeric structure is exposed to NIR light irradiation and due to the light absorption, the links between the polymeric chains and the drug particles break. The bound drug is converted in free drug that is allowed to diffuse according to Fick's law. To construct a mathematical description of the physical phenomena involved we need to establish a mathematical law for the light intensity. For that, we use the Beer-Lambert equation. Considering that the incidence light direction is orthogonal to the yoz plane, the Beer-Lambert equation for the NIR light intensity I (W/cm^2) takes the form

$$\frac{dI}{dx} = -\beta I, \quad (x, y, z) \in \Omega,$$

where β is the absorption coefficient that depends on the polymer molar concentration and on the specific absorption coefficient. Assuming that, at the surface $x = a$, incident light intensity is known, I_0, we get

$$I(x, y, z) = I_0 \exp(-\beta x), \quad (x, y, z) \in \Omega. \tag{1}$$

Let $c_b(x,y,z,t)$ (g/cm^3) and $c_f(x,y,z,t)$ (g/cm^3) be the bound and free drug concentrations at $(x,y,z) \in \overline{\Omega}$, $t \in [0,T]$, and let ϕ $(cm^2/(Ws))$ be the conversion rate of bound drug to free drug in the presence of NIR light with intensity I. Then, the behavior of c_b is described by

$$\frac{\partial c_b}{\partial t}(x,y,z,t) = -\phi I(x,y,z)c_b(x,y,z,t), \tag{2}$$

for $(x,y,z,t) \in \Omega \times (0,T]$. Let D (cm^2/s) be the diffusion coefficient of the free drug through the polymeric structure. Then

$$\frac{\partial c_f}{\partial t}(x,y,z,t) = \nabla \cdot (D\nabla c_f(x,y,z,t)) + \phi I(x,y,z)c_b(x,y,z,t), \tag{3}$$

for $(x,y,z,t) \in \Omega \times (0,T]$, which is a classical Fick's diffusion equation with an additional right-hand-side term that takes into account the unbinding reaction described by equation (2). To simplify, we assume that the initial bound drug distribution is known and that no free drug exists at initial time, that is

$$c_b(x,y,z,0) = c_{b,0}(x,y,z), \quad c_f(x,y,z,0) = 0, \quad (x,y,z) \in \Omega. \tag{4}$$

We also assume that all drug particles that reach the boundary $\partial\Omega$ are immediately removed, that is

$$c_f(x,y,z,t) = 0, \quad (x,y,z) \in \partial\Omega \times (0,T]. \tag{5}$$

The goal of this work is the finite difference analysis and numerical simulation of system (1)-(5). For the theoretical study we use a stylized version of (1)-(5), in particular, we drop the light intensity equation (1) and we rewrite the equations (2),(3) in the following one-dimensional form

$$\frac{\partial c_f}{\partial t} = \frac{\partial}{\partial x}\left(D(c_f)\frac{\partial c_f}{\partial x}\right) + F(c_f, c_b), \tag{6}$$

$$\frac{\partial c_b}{\partial t} = S(c_f, c_b), \tag{7}$$

where $F, S : \mathbb{R}^2 \to \mathbb{R}$ are suitable reaction functions and $D : \mathbb{R} \to \mathbb{R}$ is a diffusion coefficient that is allowed to depend on c_f. Here, for simplicity, we have dropped the dependency on x and t. The equations (6),(7) are completed with the initial conditions

$$c_b(x,0) = c_{b,0}(x), \quad c_f(x,0) = c_{f,0}(x), \quad x \in \Omega, \tag{8}$$

and the boundary conditions

$$c_f(a,t) = c_f(b,t) = 0, \quad t \in (0,T]. \tag{9}$$

Some numerical methods have been proposed for problems similar to (6)-(9), particularly for the semilinear case with nonlinear reaction and linear diffusion. Fully nonlinear equations/systems were analyzed, e.g., in [22, 3, 26, 14]. In [22], a coupled reaction-diffusion system was considered in the context of heat transport. A FDM was proposed and optimal error estimates in discrete L^2 and H^1 norms were obtained considering uniform grids. Optimal convergence estimates in the L^2-norm were also obtained in [3] for a general class of nonlinear reaction-diffusion equations discretized by mixed finite elements. Finite volume schemes with high order of accuracy were developed in [26] for general nonlinear advection-diffusion-reaction equations. Stability analysis for discontinuous Galerkin methods applied to the same class of equations was the subject of [14]. Let us also mention that FDMs for other type of problems have been previously investigated by some of the authors of this work ([5, 6, 8]).

Here, we give the convergence analysis of a fully discrete (in space and time) FDM for system (6)-(9). In space, the FDM can be seen as a piecewise linear FEM with quadrature. The discretization in time is based on an implicit-explicit (IMEX) scheme. Our main contributions are:

(1) Supra-superconvergence in space in a discrete H^1-norm;
(2) Optimal convergence in time in a discrete L^2-norm;
(3) The proof of the convergence results requires lower regularity assumptions than those usually considered in the literature;
(4) The numerical simulation and validation of the motivational model (1)-(5).

The rest of the paper is organized as follows. In Section 2 we introduce some notation and present the fully discrete FDM. In Section 3 we develop the convergence analysis of the space discretization and in Section 4 we study the fully discretization. Section 5 aims to illustrate the convergence results and to apply the proposed numerical tool in the context of light-triggered drug delivery. Finally, in Section 6 we present some conclusions.

1. Preliminaries

To discretize the differential system (6)-(9) we start by introducing in $\overline{\Omega}$ a sequence of nonuniform grids. Let Λ be a sequence of vectors $h = (h_1, \ldots, h_N)$

of nonnegative entries such that $\sum_{i=1}^{N} h_i = b - a$ and $h_{max} = \max_{i=1,\dots,N} h_i \to 0$. For $h \in \Lambda$, we introduce in $\overline{\Omega}$ the nonuniform grid

$$\overline{\Omega}_h = \{a = x_0, x_1, \cdots, x_{N-1}, x_N = b\}$$

Let W_h be the space of grid functions defined in $\overline{\Omega}_h$ and let $W_{h,0}$ denote the subspace of W_h of the grid functions null on the boundary $\partial\Omega_h$. In $W_{h,0}$ we introduce the following inner product

$$(u_h, v_h)_h = \sum_{i=1}^{N-1} h_{i+1/2} u_h(x_i) v_h(x_i),$$

with $h_{i+1/2} = \frac{h_i + h_{i+1}}{2}$ and $u_h, v_h \in W_{h,0}$. Let $\|\cdot\|_h$ be the norm induced by $(\cdot,\cdot)_h$. We observe that holds the following: for $u_h \in W_{h,0}$ we have

$$\|u_h\|_\infty \leq \sqrt{b-a}\|D_{-x}u_h\|_+, \tag{10}$$

where $\|u_h\|_\infty = \max_{i=1,\dots,N-1} |u_h(x_i)|$. In fact, as $u_h(x_i) = \sum_{j=1}^{i} h_j D_{-x}u_h(x_j)$ for $i = 1, \dots, N$, then we obtain

$$|u_h(x_i)| \leq \sqrt{b-a}\|D_{-x}u_h\|_+,$$

that leads to (10).

Let P_h be the piecewise linear interpolation operator and let Q_h be the piecewise linear constant operator defined in $W_{h,0}$ and $\widehat{W}_h$, respectively, where the last space includes the grid functions defined in Ω_h. Let $P_h c_{f,h}$ and $Q_h c_{b,h}$ be the finite element approximations for c_f and c_b, respectively, defined by (6)-(9) that satisfy

$$\begin{aligned}(\frac{\partial P_h c_{f,h}}{\partial t}(t), P_h u_h) = &-(D(P_h c_{f,h}(t))\frac{\partial P_h c_{f,h}}{\partial x}(t), P_h u_h') \\ &+ (F(P_h c_{f,h}(t), Q_h c_{b,h}(t)), P_h u_h),\end{aligned} \tag{11}$$

$$(\frac{\partial Q_h c_{s,h}}{\partial t}(t), Q_h v_h) = (S(P_h c_{f,h}(t), Q_h c_{b,h}(t)), Q_h v_h), \tag{12}$$

for $u_h \in W_{h,0}, v_h \in \widehat{W}_h$, $t \in (0,T]$. System (11),(12) is completed with the initial conditions

$$\begin{aligned}(P_h c_{f,h}(0), P_h u_h) = (P_h R_h c_{f,0}, P_h u_h),\ u_h \in W_{h,0},\\ (Q_h c_{b,h}(0), Q_h v_h) = (Q_h R_h c_{b,0}, Q_h v_h),\ v_h \in \widehat{W}_h.\end{aligned} \tag{13}$$

In (13), $R_h : C(\overline{\Omega}) \to W_H$ denotes the restriction operator.

To compute a fully discrete (in space) finite difference solution $c_{f,h}(t) \in W_{h,0}$, $c_{b,h}(t) \in \widehat{W}_h$, we introduce the average operator

$$M_x u_h(x_i) = \frac{u_h(x_i) + u_h(x_{i-1})}{2}$$

and the finite difference operators

$$D_{-x} u_h(x_i) = \frac{u_h(x_i) - u_h(x_{i-1})}{h_i}, \quad D_x^* u_h(x_i) = \frac{u_h(x_{i+1}) - u_h(x_i)}{h_{i+1/2}}.$$

We also introduce the notation

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

and $\|u_h\|_+ = \sqrt{(u_h, u_h)_+}$, for $u_h \in W_h$.

Then we define the fully discrete (in space) approximations $c_{f,h}(t) \in W_{h,0}$ and $c_{b,h}(t) \in \widehat{W}_h$ by the following discrete scheme

$$(c'_{f,h}(t), u_h)_h = -(D(M_x c_{f,h}(t)) D_{-x} c_{f,h}(t), D_{-x} u_h)_+ + (F(c_{f,h}(t), c_{b,h}(t)), u_h)_h, \tag{14}$$

$$(c'_{b,h}(t), v_h)_h = (S(c_{f,h}(t), c_{b,h}(t)), v_h)_h, \tag{15}$$

$u_h \in W_{h,0}, v_h \in \widehat{W}_h$, $t \in (0, T]$, with the initial conditions

$$(c_{f,h}(0), u_h)_h = (R_h c_{f,0}, u_h),\ (c_{b,h}(0), v_h) = (R_h c_{b,0}, v_h)_h,\ u_h \in W_{h,0}, v_h \in \widehat{W}_h. \tag{16}$$

From (14)-(16), it can be shown that $c_{f,h}(t) \in W_h$ and $c_{b,h}(t) \in \widehat{W}_h$ satisfy the following

$$c'_{f,h}(t) = D_x^*(M_x c_{f,h}(t) D_{-x} c_{f,h}(t)) + F(c_{f,h}(t), c_{b,h}(t)) \tag{17}$$

$$c'_{b,h}(t) = S(c_{f,h}(t), c_{b,h}(t)), \tag{18}$$

in $\Omega_h \times (0, T]$,

$$c_{f,h}(0) = R_h c_{f,0},\ c_{b,h}(0) = R_h c_{b,0} \tag{19}$$

and

$$c_{f,h}(a, t) = c_{f,h}(b, t) = 0,\ t \in (0, T]. \tag{20}$$

To define fully discrete schemes in time and space, we introduce in the time domain $[0, T]$ the uniform grid $\{t_m, m = 0, \dots, M\}$ with $t_0 = 0$, $t_M = T$, and

$t_{m+1} = t_m + \Delta t$, for $m = 0, \dots, M-1$. We consider the IMEX scheme

$$D_{-t}c_{f,h}^m = D_x^*\left(D(M_x c_{f,h}^{m-1})D_{-x}c_{f,h}^m\right) + F(c_{f,h}^{m-1}, c_{b,h}^{m-1}) \tag{21}$$

$$D_{-t}c_{b,h}^m = S(c_{f,h}^{m-1}, c_{b,h}^{m-1}) \tag{22}$$

in Ω_h and for $m = 1, \dots, M$, with the following conditions

$$c_{f,h}^0 = R_h c_{f,0}, \quad c_{b,h}^0 = R_h c_{b,0} \text{ in } \Omega_h, \tag{23}$$

and

$$c_{f,h}^m(x_0) = c_{f,h}^m(x_N) = 0,\ m = 1, \dots, M. \tag{24}$$

In (21), D_{-t} denotes the backward finite difference operator

$$D_{-t}u_h^m = \frac{u_h^m - u_h^{m-1}}{\Delta t}.$$

Using an explicit discretization for the diffusion coefficient D and the nonlinear terms F and S, we avoid the solution of a nonlinear system of equations at each time step. IMEX schemes are often considered for nonlinear reaction-diffusion problems ([19]).

We remark that the initial boundary value problem (IBVP) (21)-(24) can be rewritten in the following equivalently form

$$\begin{aligned}(D_{-t}c_{f,h}^m, v_h)_h = &-(D(M_x c_{f,h}^{m-1})D_{-x}c_{f,h}^m, D_{-x}v_h)_+ \\ &+ (F(c_{f,h}^{m-1}, c_{b,h}^{m-1}), v_h)_h,\ \forall v_h \in W_{h,0},\end{aligned} \tag{25}$$

$$(D_{-t}c_{b,h}^m, w_h)_h = (S(c_{f,h}^{m-1}, c_{b,h}^{m-1}), w_h)_h, \forall w_h \in \widehat{W}_h, \tag{26}$$

for $m = 1, \dots, M$, with the following conditions

$$\begin{aligned}(c_{f,h}^0, v_h)_h &= (R_h c_{f,0}, v_h)_h,\ \forall v_h \in W_{h,0}, \\ (c_{b,h}^0, w_h)_h &= (R_h c_{b,0}, w_h)_h = 0,\ \forall w_h \in \widehat{W}_h.\end{aligned} \tag{27}$$

In what follows, we study the stability and convergence properties of the solutions of the finite difference problems (17)-(20) and (21)-(24) or, equivalently, of the finite element problems (14)-(16) and (25)-(27). We assume the following smoothness conditions:

(HD$_0$) $D(x) \geq D_0 > 0, x \in \mathbb{R}$,
(HD$_\ell$) $|D(x) - D(\tilde{x})| \leq C_D|x - \tilde{x}|,\ x, \tilde{x} \in \mathbb{R}$,
(HF) $|F(x,y)| \leq C_F|y|,\ x, y \in \mathbb{R}$,
(HS) $|S(x,y)| \leq C_S|y|,\ x, y \in \mathbb{R}$,
(HF$_\ell$) $|F(x,y) - F(\tilde{x},\tilde{y})| \leq C_{F_\ell}|y - \tilde{y}|,\ x, \tilde{x}, y, \tilde{y}, \in \mathbb{R}$,

(HS_ℓ) $|S(x,y)-S(\tilde{x},\tilde{y})| \leq C_{S_\ell}|y-\tilde{y}|$, $x,\tilde{x},y,\tilde{y},\in \mathbb{R}$.

2. Analysis of the semi-discrete approximation

2.1. Stability. We start by establishing the uniform boundedness of $c_{f,h}(t), t \in [0,T], h \in \Lambda$.

Proposition 1. *Let $c_{f,h}(t) \in W_{h,0}, c_{b,h}(t) \in \widehat{W}_h, t \in [0,T], h \in \Lambda$, be defined by (17)-(20) with initial conditions $c_{f,h}(0) \in W_{h,0}, c_{b,h}(0) \in \widehat{W}_h$. If the assumption ($HD_0$), (HF) and (HS) hold, then there exists a positive constant C, h and t independent, such that*

$$\begin{aligned} &\|c_{f,h}(t)\|_h^2 + \|c_{b,h}(t)\|_h^2 + 2D_0\int_0^t e^{C(t-s)}\|D_{-x}c_{f,h}(s)\|_+^2 ds \\ &\qquad \leq e^{Ct}\Big(\|c_{f,h}(0)\|_h^2 + \|c_{b,h}(0)\|_h^2\Big), \end{aligned} \tag{28}$$

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

Proof: From (14) and (15) with $u_h = c_{f,h}(t), v_h = c_{b,h}(t)$ and considering the smoothness assumptions (HD_0), (HF) and (HS) we easily get

$$\begin{aligned} &\frac{1}{2}\frac{d}{dt}\Big(\|c_{f,h}(t)\|_h^2 + \|c_{b,h}(t)\|_h^2\Big) + D_0\|D_{-x}c_{f,h}(t)\|_+^2 \\ &\qquad \leq C_F\frac{1}{2}(\|c_{f,h}(t)\|_h^2 + \|c_{b,h}(t)\|_h^2) + C_S\|c_{b,h}(t)\|_h^2 \\ &= \frac{1}{2}C_F\|c_{f,h}(t)\|_h^2 + (\frac{1}{2}C_F + C_S)\|c_{b,h}(t)\|_h^2. \end{aligned}$$

The last inequality leads to (28) with $C = C_F + 2C_S$. ■

As corollary of the last result we conclude the following uniform boundedness result which is consequence of inequality (10).

Corollary 1. *Under the conditions of Proposition 1, there exists a positive constant C, h and t independent, such that*

$$\int_0^t \|c_{f,h}(s)\|_\infty^2 ds \leq C, t \in [0,T], h \in \Lambda, \tag{29}$$

provided that $\|c_{f,h}(0)\|_h^2 + \|c_{b,h}(0)\|_h^2, h \in \Lambda$, is bounded.

Proposition 2. *Let $c_{f,h}(t), \tilde{c}_{f,h}(t) \in W_{h,0}, c_{b,h}(t), \tilde{c}_{b,h}(t) \in \widehat{W}_h, t \in [0,T], h \in \Lambda$, be defined by (17)-(20) with initial conditions $c_{f,h}(0), \tilde{c}_{f,h}(0) \in W_{h,0}$,*

$c_{b,h}(0), \tilde{c}_{b,h}(0) \in \widehat{W}_h$. *If the assumptions (HD$_0$), (HD$_\ell$) (HF$_\ell$) and (HS$_\ell$) hold, then, for* $\omega_{f,h}(t) = c_{f,h}(t) - \tilde{c}_{f,h}(t)$ *and* $\omega_{b,h}(t) = c_{b,h}(t) - \tilde{c}_{b,h}(t)$ *we have*

$$\begin{aligned} \|\omega_{f,h}(t)\|_h^2 + \|\omega_{b,h}(t)\|_h^2 \ & +2(D_0 - \epsilon^2) \int_0^t e^{\int_s^t \gamma(\mu) d\mu} \|D_{-x}\omega_{f,h}(s)\|_+^2 ds \\ & \leq e^{\int_0^t \gamma(s)\, ds} \Big(\|\omega_{f,h}(0)\|_h^2 + \|\omega_{b,h}(0)\|_h^2 \Big), \end{aligned} \tag{30}$$

for $t \in [0, T], h \in \Lambda$, *where*

$$\gamma(s) = \max\{\frac{1}{2\epsilon^2} C_D^2 \|D_{-x}c_{f,h}(s)\|_\infty^2 + C_{F_\ell}, C_{F_\ell} + 2C_{S_\ell}\} \tag{31}$$

and $\epsilon \neq 0$ *is an arbitrary constant.*

Proof: It can be shown that for $\omega_{f,h}(t)$ and $\omega_{b,h}(t)$ we have

$$\begin{aligned} \tfrac{1}{2}\tfrac{d}{dt}\Big(\|\omega_{f,h}(t)\|_h^2 + \|\omega_{b,h}(t)\|_h^2 \Big) & + (D(M_x\tilde{c}_{f,h}(t)) D_{-x}\omega_{f,h}(t), D_{-x}\omega_{f,h}(t))_+ \\ & \leq ((D(M_x\tilde{c}_{f,h}(t)) - D(M_x c_{f,h}(t))) D_{-x}c_{f,h}(t), D_{-x}\omega_{f,h}(t))_+ \\ & +(F(c_{f,h}(t), c_{b,h}(t)) - F(\tilde{c}_{f,h}(t), \tilde{c}_{b,h}(t)), \omega_{f,h}(t))_h \\ & +(S(c_{f,h}(t), c_{b,h}(t)) - S(\tilde{c}_{f,h}(t), \tilde{c}_{b,h}(t)), \omega_{b,h}(t))_h. \end{aligned} \tag{32}$$

Taking in (32) into account the assumptions (HD$_0$), (HD$_\ell$), (HF$_\ell$) and (HS$_\ell$) we get

$$\begin{aligned} \tfrac{1}{2}\tfrac{d}{dt}\Big(\|\omega_{f,h}(t)\|_h^2 + \|\omega_{b,h}(t)\|_h^2 \Big) \ & +D_0 \|D_{-x}\omega_{f,h}(t)\|_+^2 \\ & \leq C_D \|D_{-x}c_{f,h}(t)\|_\infty \|\omega_{f,h}(t)\|_h \|D_{-x}\omega_{f,h}(t)\|_+ \\ & +C_{F_\ell} \|\omega_{f,h}(t)\|_h \|\omega_{b,h}(t)\|_h \\ & +C_{S_\ell} \|\omega_{b,h}(t)\|_h^2. \end{aligned} \tag{33}$$

From inequality (33) we obtain

$$\begin{aligned} \tfrac{d}{dt}\Big(\|\omega_{f,h}(t)\|_h^2 + \|\omega_{b,h}(t)\|_h^2 \Big) \ & +2(D_0 - \epsilon^2) \|D_{-x}\omega_{f,h}(t)\|_+^2 \\ & \leq \gamma(t) \Big(\|\omega_{f,h}(t)\|_h^2 + \|\omega_{b,h}(t)\|_h^2 \Big). \end{aligned} \tag{34}$$

with $\gamma(t)$ defined by (31) and $\epsilon \neq 0$ an arbitrary constant. Inequality (30) follows from (34).

■

To conclude stability from (30) we need to impose the boundedness of $\displaystyle\int_0^t \gamma(s) ds$, $t \in [0, T], h \in \Lambda$, that depends on $\|D_{-x}c_{f,h}(t)\|_\infty$. This result does not follows from Proposition 1 neither from existence results for ordinary differential problems ([4]). These facts limit the stability analysis of the IBVP (17)-(20). We observe that the spatial truncation error $T_h(t)$ associated with the spatial discretization introduced before is of first order with respect to the norm $\|.\|_\infty$. Then, the energy method followed in the proof of Proposition 2 with $c_{f,h}(t) = R_h c_f(t), c_{b,h}(t) = R_h c_b(t)$, where R_h denotes the restriction operator, allows us to obtain the following estimates for $E_{f,h}(t) = R_h c_f(t) - \tilde{c}_{f,h}(t)$ and $E_{b,h}(t) = R_h c_b(t) - \tilde{c}_{b,h}(t)$:

$$\begin{aligned} &\|E_{f,h}(t)\|_h^2 + \|E_{b,h}(t)\|_h^2 + \int_0^t e^{\int_s^t \gamma(\mu)d\mu} \|D_{-x}E_{f,h}(s)\|_+^2 ds \\ &\qquad \leq \int_0^t e^{\int_s^t \gamma(\mu)d\mu} \|T_{f,h}(s)\|_h^2 ds + e^{\int_0^t \gamma(\mu)d\mu} \Big(\|E_{f,h}(0)\|_h^2 + \|E_{b,h}(0)\|_h^2 \Big), \end{aligned} \tag{35}$$

for $t \in [0, T], h \in \Lambda$, and with

$$\gamma(s) = \max\{\frac{1}{2\epsilon^2} C_D^2 \|D_{-x}R_h c_f(s)\|_\infty^2 + C_{F_\ell}, C_{F_\ell} + 2C_{S_\ell}\} \tag{36}$$

being $\epsilon \neq 0$ an arbitrary constant.

As

$$|D_{-x}\tilde{c}_{f,h}(x_i,t)|^2 \leq 2\Big(|D_{-x}E_{f,h}(x_i,t)|^2 + |D_{-x}R_h c_f(x_i,t)|^2\Big),$$

and

$$|D_{-x}E_{f,h}(x_i,t)|^2 \leq \frac{1}{h_{min}} \|D_{-x}E_{f,h}(t)\|_+^2,$$

then, the uniform boundedness of $\displaystyle\int_0^t \|D_{-x}\tilde{c}_{f,h}(s)\|_\infty^2 ds$, for $t \in [0, T]$ and $h \in \Lambda$, follows if

$$\|E_{f,h}(0)\|_h^2 + \|E_{b,h}(0)\|_h^2 \leq C h_{max}^2, \tag{37}$$

and if we impose the following condition to the sequence Λ

$$\exists C_G > 0 : \frac{h_{max}^2}{h_{min}} \leq C_G,\ h \in \Lambda, \text{ with } h_{max} \text{ small enough.} \tag{38}$$

From Proposition 2, we conclude the stability of the IBVP (17)-(20) in $\tilde{c}_{f,h}(t), \tilde{c}_{b,h}(t), t \in [0, T], h \in \Lambda$, provided (37) and (38) hold.

In what follows we establish that

$$\|E_{f,h}(t)\|_h^2 + \|E_{b,h}(t)\|_h^2 + \int_0^t \|D_{-x}E_{f,h}(s)\|_+^2 ds \\ \le Ch_{max}^4 + C\Big(\|E_{f,h}(0)\|_h^2 + \|E_{b,h}(0)\|_h^2\Big),$$

provided that $c_f(t) \in H^3(\Omega) \cap H_0^1(\Omega)$. Consequently, if

$$\|E_{f,h}(0)\|_h^2 + \|E_{b,h}(0)\|_h^2 \le Ch_{max}^4, \tag{39}$$

condition (38) can be weakened and it can be replaced by the following one

$$\exists C_G > 0 : \frac{h_{max}^4}{h_{min}} \le C_G,\ h \in \Lambda, \text{ with } h_{max} \text{ small enough.} \tag{40}$$

Then, if $c_f(t) \in H^3(\Omega) \cap H_0^1(\Omega)$, the IBVP (17)-(20) is stable in $\tilde{c}_{f,h}(t), \tilde{c}_{b,h}(t), t \in [0,T], h \in \Lambda$, provided that (39) and (40) hold.

2.2. Convergence for lower smooth solutions. In this section, we derive an error bound for the solution of the FDM (17)-(20) avoiding the use of Taylor formula that requires that $c_f(t) \in C^4(\overline{\Omega})$. Relying on the Bramble-Hilbert lemma ([2]), we are able to established our error bound under lower regularity assumptions on the solution of the continuous problem (6)-(9).

Let $E_{f,h}(t)$ and $E_{b,h}(t)$ be the error terms associated with $c_f(t)$ and $c_b(t)$, respectively. We use the following notations

$$(g)_h(x_i) = \frac{1}{h_{i+1/2}} \int_{x_{i-1/2}}^{x_{i+1/2}} g(x)dx, i = 1, \dots, N-1$$

and

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

We have successively

$$
\begin{aligned}
((\frac{\partial c_f}{\partial t}(t))_h, E_{f,h}(t))_h = \;& ((\frac{\partial}{\partial x}(D(c_f(t))\frac{\partial c_f}{\partial x}(t)) + F(c_f(t), c_b(t)))_h, E_{f,h}(t))_h \\
= \;& -(D(\widehat{R}_h c_f(t))\widehat{R}_h \frac{\partial c_f}{\partial x}(t), D_{-x}E_{f,h}(t))_+ \\
& +(D(M_x R_h c_f(t))D_{-x}R_h c_f(t), D_{-x}E_{f,h}(t))_+ \\
& -(D(M_x R_h c_f(t))D_{-x}R_h c_f(t), D_{-x}E_{f,h}(t))_+ \\
& +((F(c_f(t), c_b(t)))_h - F(R_h c_f(t), R_h c_b(t)), E_{f,h}(t))_h \\
& +(F(R_h c_f(t), R_h c_b(t)), E_{f,h}(t))_h \\
= \;& \sum_{\ell=1}^{2} T_{h,\ell}(t) - (D(M_x R_h c_f(t))D_{-x}R_h c_f(t), D_{-x}E_{f,h}(t))_+ \\
& +(F(R_h c_f(t), R_h c_b(t)), E_{f,h}(t))_h,
\end{aligned}
$$

where

$$
\begin{aligned}
T_{h,1}(t) \;& = -(D(\widehat{R}_h c_f(t))\widehat{R}_h \tfrac{\partial c_f}{\partial x}(t), D_{-x}E_{f,h}(t))_+ \\
& +(D(M_x R_h c_f(t))D_{-x}R_h c_f(t), D_{-x}E_{f,h}(t))_+,
\end{aligned}
\tag{41}
$$

and

$$
T_{h,2}(t) = ((F(c_f(t), c_b(t)))_h - F(R_h c_f(t), R_h c_b(t)), E_{f,h}(t))_h. \tag{42}
$$

Then, taking into account (14), we deduce

$$
\begin{aligned}
(E'_{f,h}(t), E_{f,h}(t))_h = \;& -(D(M_x R_h c_f(t))D_{-x}R_h c_f(t), D_{-x}E_{f,h}(t))_+ \\
& +(F(R_h c_f(t), R_h c_b(t)), E_{f,h}(t))_h \\
& +\sum_{\ell=1}^{3} T_{h,\ell}(t) - (c'_{f,h}(t), E_{f,h}(t))_h
\end{aligned}
$$

where

$$
T_{h,3}(t) = (R_h \frac{\partial c_f}{\partial t}(t), E_{f,h}(t))_h - ((\frac{\partial c_f}{\partial t}(t))_h, E_{f,h}(t))_h. \tag{43}
$$

Furthermore, we also have

$$
\begin{aligned}
(E'_{f,h}(t), E_{f,h}(t))_h = \;& -(D(M_x R_h c_f(t))D_{-x}R_h c_f(t), D_{-x}E_{f,h}(t))_+ \\
& +(D(M_x c_{f,h}(t))D_{-x}c_{f,h}(t), D_{-x}E_{f,h}(t))_+ \\
& +(F(R_h c_f(t), R_h c_b(t)) - F(c_{f,h}(t), c_{b,h}(t)), E_{f,h}(t))_h \\
& +\sum_{\ell=1}^{3} T_{h,\ell}(t),
\end{aligned}
$$

that leads to

$$\begin{array}{rl}\frac{1}{2}\frac{d}{dt}\|E_{f,h}(t)\|_h^2 \leq & -D_0\|D_{-x}E_{f,h}(t)\|_+^2\\ & +C_{D_\ell}\|D_{-x}R_hc_f(t)\|_\infty\|E_{f,h}(t)\|_h\|D_{-x}E_{f,h}(t)\|_+\\ & +C_{F_\ell}\|E_{f,h}(t)\|_h\|E_{b,h}(t)\|_h\\ & +\displaystyle\sum_{\ell=1}^{3}T_{h,\ell}(t),\end{array} \tag{44}$$

provided that (HD$_0$), (HD$_\ell$) and (HF$_\ell$) hold.

For the error $E_{b,h}(t)$ we have

$$(E'_{b,h}(t),E_{b,h}(t))_h=(S(R_hc_f(t),R_hc_b(t))-S(c_{f,h}(t),c_{b,h}(t)),E_{b,h}(t))_h,$$

and taking into account the assumption (HS$_\ell$)

$$\frac{1}{2}\frac{d}{dt}\|E_{b,h}(t)\|_h^2\leq C_{S_\ell}\|E_{b,h}(t)\|_h^2. \tag{45}$$

In what follows we establish upper bounds for the terms $T_{h,\ell}(t), \ell=1,2,3$. The results presented in [1] for elliptic equations have a central role here.

Proposition 3. *Let $T_{h,1}(t)$ be defined by (41). If $c_f(t)\in H^3(\Omega)\cap H_0^1(\Omega)$ and (HD$_\ell$) holds, then there exists a positive constant C_{T_1}, h and t independent, such that*

$$|T_{h,1}(t)|\leq C_{T_1}\frac{1}{\epsilon^2}\Big(C_D^2\|\frac{\partial c_f}{\partial x}(t)\|_\infty^2+\|D\|_\infty^2\Big)\|c_f(t)\|^2_{H^3(\Omega)}h_{max}^4+2\epsilon^2\|D_{-x}E_{f,h}(t)\|_+^2, \tag{46}$$

for $t\in(0,T]$ and $h\in\Lambda$. In (46),$\epsilon\neq 0$ is an arbitrary constant.

Proof: As

$$\begin{array}{rl}T_{h,1}(t)= & -((D(\widehat{R}_hc_f(t))-D(M_xR_hc_f(t)))\widehat{R}_h\frac{\partial c_f}{\partial x}(t),D_{-x}E_{f,h}(t))_+\\ & +(D(M_xR_hc_f(t))(\widehat{R}_h\frac{\partial c_f}{\partial x}(t)-D_{-x}R_hc_f(t),D_{-x}E_{f,h}(t))_+,\end{array}$$

we have

$$\begin{array}{rl}|T_{h,1}(t)|\leq & \|\frac{\partial c_f}{\partial x}(t)\|_\infty C_D\|\widehat{R}_hc_f(t)-M_xR_hc_f(t)\|_+\|D_{-x}E_{f,h}(t)\|_+\\ & +\|D\|_\infty\|\widehat{R}_h\frac{\partial c_f}{\partial x}(t)-D_{-x}R_hc_f(t)\|_+\|D_{-x}E_{f,h}(t)\|_+\\ & := T_{h,1}^{(1)}(t)+T_{h,1}^{(2)}(t),\end{array}$$

with

$$T_{h,1}^{(1)}(t)=\|\frac{\partial c_f}{\partial x}(t)\|_\infty C_D\|\widehat{R}_hc_f(t)-M_xR_hc_f(t)\|_+\|D_{-x}E_{f,h}(t)\|_+$$

and

$$T_{h,1}^{(2)}(t) = \|D\|_\infty \|\widehat{R}_H \frac{\partial c_f}{\partial x}(t) - D_{-x}R_H c_f(t)\|_+ \|D_{-x}E_{f,h}(t)\|_+.$$

Considering Theorem 1 of [1], it can be shown that there exist two positive constants C_1 and C_2, h and t independent, such that

$$|T_{h,1}^{(1)}(t)| \leq \|\frac{\partial c_f}{\partial x}(t)\|_\infty C_D C_1 \Big(\sum_{i=1}^N h_i^4 \|c_f(t)\|^2_{H^2(x_{i-1},x_i)}\Big)^{1/2} \|D_{-x}E_{f,h}(t)\|_+ \quad (47)$$

and

$$|T_{h,1}^{(2)}(t)| \leq \|D\|_\infty C_2 \Big(\sum_{i=1}^N h_i^4 \|c_f(t)\|^2_{H^3(x_{i-1},x_i)}\Big)^{1/2} \|D_{-x}E_{f,h}(t)\|_+. \quad (48)$$

Inequalities (47) and (48) easily lead to (46).

■

The next two propositions establish estimates for $T_{h,2}(t)$ and $T_{h,3}(t)$. Their proofs can also be seen in Theorem 1 of [1].

Proposition 4. *Let $T_{h,2}(t)$ be defined by (42). If $F(c_f(t), c_b(t)) \in H^2(\Omega)$, then there exists a positive constant C_{T_2}, h and t independent, such that*

$$|T_{h,2}(t)| \leq C_{T_2} \frac{1}{\epsilon^2} \|F(c_f(t), c_b(t))\|^2_{H^2(\Omega)} h^4_{max} + \epsilon^2 \|D_{-x}E_{f,h}(t)\|^2_+, \quad (49)$$

for $t \in (0, T], h \in \Lambda$. In (49), $\epsilon \neq 0$ is an arbitrary constant.

Proposition 5. *Let $T_{h,3}(t)$ be defined by (43). If $c_f'(t) \in H^2(\Omega)$, then there exists a positive constant C_{T_3}, h and t independent, such that*

$$|T_{h,3}(t)| \leq C_{T_3} \frac{1}{\epsilon^2} \|c_f'(t)\|^2_{H^2(\Omega)} h^4_{max} + \epsilon^2 \|D_{-x}E_{f,h}(t)\|^2_+, \quad (50)$$

for $t \in (0, T], h \in \Lambda$. In (50), $\epsilon \neq 0$ is an arbitrary constant.

Using the constructed tools we establish now an upper bound for $\|E_{f,h}(t)\|^2_h + \|E_{b,h}(t)\|^2_h$. We start by noting that from (44),(45) and considering the upper bound established in Propositions 3-5 we obtain

$$\begin{aligned}
&\frac{d}{dt}\Big(\|E_{f,h}(t)\|_h^2+\|E_{b,h}(t)\|_h^2\Big)+2(D_0-5\epsilon^2)\|D_{-x}E_{f,h}(t)\|_+^2\\
&\quad\le\Big(\frac{1}{2\epsilon^2}C_D^2\|D_{-x}R_hc_f(t)\|_\infty^2+C_{F_\ell}\Big)\|E_{f,h}(t)\|_h^2\\
&\quad+\Big(C_{F_\ell}+2C_{S_\ell}\Big)\|E_{b,h}(t)\|_h^2+\widehat{T}_h(t),
\end{aligned}\tag{51}$$

where

$$\begin{aligned}
\widehat{T}_h(t)=C_{\widehat{T}}\frac{1}{\epsilon^2}\Big(\Big(C_D^2\|\frac{\partial c_f}{\partial x}(t)\|_\infty^2+\|D\|_\infty^2\Big)\|c_f(t)\|_{H^3(\Omega)}^2\\
+\|F(c_f(t),c_b(t))\|_{H^2(\Omega)}^2+\|c_f'(t)\|_{H^2(\Omega)}^2\Big)h_{max}^4,
\end{aligned}\tag{52}$$

being $C_{\widehat{T}}=2\max_{i=1,2,3}\{C_{T_i}\}$.

From (51), we are now in position to establish the main result of this section.

Theorem 1. *Let $c_f\in L^2(0,T,H^3(\Omega)\cap H_0^1(\Omega))\cap C^1([0,T],C(\overline{\Omega}))\cap H^1(0,T,H^2(\Omega))$ and $c_b\in C^1([0,T],C(\Omega))$ be solution of the IBVP (6)-(9), where D,F and S satisfy the assumptions (HD_0), (HD_ℓ), (HF_ℓ) and (HS_ℓ). For $h\in\Lambda$, let $c_{f,h}\in C^1([0,T],W_{h,0}),c_{b,h}\in C^1([0,T],\widehat{W_h})$ be solution of the FDM (17)-(20) or, equivalently, of the FEM (14)-(16). Then, for the errors $E_{f,h}(t)=R_hc_f(t)-c_{f,h}(t),E_{b,h}(t)=R_hc_b(t)-c_{b,h}(t),\ t\in[0,T],h\in\Lambda$, holds the following*

$$\begin{aligned}
\|E_{f,h}(t)\|_h^2+\|E_{b,h}(t)\|_h^2\ &+\ 2(D_0-5\epsilon^2)\int_0^t e^{\int_s^t\gamma(\mu)d\mu}\|D_{-x}E_{f,h}(s)\|_+^2\,ds\\
&\le\int_0^t e^{\int_s^t\gamma(\mu)d\mu}\widehat{T}_h(s)\,ds,
\end{aligned}\tag{53}$$

for $t\in[0,T],h\in\Lambda$. In (53), $\epsilon\neq0$ is an arbitrary constant, γ is defined by

$$\gamma(t)=\max\{\frac{1}{2\epsilon^2}C_D^2\|D_{-x}R_hc_f(t)\|_\infty^2+C_{F_\ell},C_{F_\ell}+2C_{S_\ell}\}\tag{54}$$

and $\widehat{T}_h(t)$ is given by (52).

Choosing in (53) ϵ conveniently we obtain the following corollary.

Corollary 2. *Under the assumptions of Theorem 1, there exists a positive constant C_e, h and t independent, such that*

$$\|E_{f,h}(t)\|_h^2 + \|E_{b,h}(t)\|_h^2 + \int_0^t \|D_{-x}E_{f,h}(s)\|_+^2\, ds \leq C_e h_{max}^4, t \in [0,T], h \in \Lambda. \tag{55}$$

3. Fully discrete scheme

3.1. Stability. In this section we intend to establish conditions that guarantee the stability of the nonlinear IBVP (21)-(24). From (25),(26) with $v_h = c_{f,h}^m, w_h = c_{b,h}^m$ and considering the assumptions (HD$_0$), (HF) and (HS), we obtain

$$\begin{aligned} \|c_{f,h}^m\|_h^2 &\leq \|c_{f,h}^{m-1}\|_h^2 - 2\Delta t D_0 \|D_{-x}c_{f,h}^m\|_+^2 + 2\Delta t C_F \|c_{f,h}^m\|_h \|c_{b,h}^{m-1}\|_h, \\ \|c_{b,h}^m\|_h^2 &\leq \|c_{b,h}^{m-1}\|_h^2 + 2\Delta t C_S \|c_{b,h}^m\|_h \|c_{b,h}^{m-1}\|_h, \end{aligned} \tag{56}$$

for $m = 1, \dots, M$. Inequalities (56) allow us to establish

$$\begin{aligned} (1-\Delta t C_F)\|c_{f,h}^m\|_h^2 &+ (1-\Delta t C_S)\|c_{b,h}^m\|_h^2 + 2\Delta t D_0 \|D_{-x}c_{f,h}^m\|_+^2 \\ &\leq (1+\Delta t(C_F + C_s))\Big(\|c_{f,h}^{m-1}\|_h^2 + \|c_{b,h}^{m-1}\|_h^2\Big) \end{aligned}$$

that leads to

$$\begin{aligned} \|c_{f,h}^m\|_h^2 + \|c_{b,h}^m\|_h^2 + 2\Delta t D_0 \textstyle\sum_{\ell=1}^m \|D_{-x}c_{f,h}^\ell\|_+^2 \\ \leq \Big(\frac{1+\Delta t(C_F+C_s)}{1-\Delta t \max\{C_F, C_S\}}\Big)^m \Big(\|c_{f,h}^0\|_h^2 + \|c_{b,h}^0\|_h^2\Big), \end{aligned}$$

provided that

$$1 - \Delta t \max\{C_F, C_S\} > 0.$$

Then we conclude the following result.

Proposition 6. *Let $c_{f,h}^m \in W_{h,0}$, $c_{b,h}^m \in \widehat{W}_h$, m=0,…,M, $h \in \Lambda$ be defined by (21)-(24) with the initial conditions $c_{f,h}^0 \in W_{h,0}$, $c_{f,h}^0 \in \widehat{W}_h$. If (HD$_0$), (HF) and (HS) hold, then*

$$\|c_{f,h}^m\|_h^2 + \|c_{b,h}^m\|_h^2 + 2\Delta t D_0 \sum_{\ell=1}^m \|D_{-x}c_{f,h}^\ell\|_+^2 \leq e^{m\Delta t \theta}\Big(\|c_{f,h}^0\|_h^2 + \|c_{b,h}^0\|_h^2\Big), \tag{57}$$

$m = 1, \dots, M, h \in \Lambda, \Delta t \in (0, \Delta t_0)$, *where*

$$\theta = \frac{\max\{C_F, C_S\} + C_F + C_S}{1 - \Delta t_0 \max\{C_F, C_S\}}, \tag{58}$$

and Δt_0 is such that

$$1-\Delta t_0 \max\{C_F, C_S\} > 0. \tag{59}$$

In what follows we consider $c^0_{f,h} \in W_{h,0}$ and let $c^m_{f,h} \in W_{h,0}$, $c^m_{b,h} \in \widehat{W}_h$, $m = 0,\dots,M$, $h \in \Lambda$, be defined by (21)-(24). Let $\tilde{c}^m_{b,h} \in \widehat{W}_h$, $m = 0,\dots,M$, $h \in \Lambda$ be other solution defined by (21)-(24) with initial conditions $\tilde{c}^0_{f,h} \in W_{h,0}$. We would like to establish conditions to guarantee that, for $\rho_\epsilon > 0$, there exists a positive ρ_0, such that, if $\|\omega^0_{i,h}\|_h \le \rho_0$, $i = f, b$, then $\|\omega^m_{i,h}\|_h \le \rho_\epsilon$, $i = b, f$, $m = 1,\dots,M$, $h \in \Lambda$. Here we use the notation $\omega^m_{i,h} = c^m_{i,h} - \tilde{c}^m_{i,h}$, $i = b, f, m = 0,\dots,M, h \in \Lambda$.

Proposition 7. *Let $c^m_{f,h}, \tilde{c}^m_{f,h} \in W_{h,0}$, $c^m_{b,h}, \tilde{c}^m_{b,h} \in \widehat{W}_h$, m=1,…,M, $h \in \Lambda$, be defined by (21)-(24) with initial conditions $c^0_{f,h} \in W_{h,0}$, $c^0_{b,h} \in \widehat{W}_h$. Let $\omega^m_{i,h} = c^m_{i,h} - \tilde{c}^m_{i,h}, i = b, f, m = 0,\dots,M, h \in \Lambda$. If conditions (HD$_0$), (HD$_\ell$), (HF$_\ell$) and (HS$_\ell$) hold, then*

$$\begin{aligned}\|\omega^m_{f,h}\|^2_h + \|\omega^m_{b,h}\|^2_h + \Delta t D_0 \sum_{j=1}^m \|D_{-x}\omega^j_{f,h}\|^2_+ \\ \le e^{m\Delta t \max\limits_{j=1,\dots,M}\sigma(j)}\Big(\|\omega^0_{f,h}\|^2_h + \|\omega^0_{b,h}\|^2_h\Big),\end{aligned} \tag{60}$$

for $m = 1,\dots,M$, $h \in \Lambda$ and $\Delta t \in (0, \Delta t_0]$, with

$$1-\Delta t_0 \min\{C_{F_\ell}, C_{S_\ell}\} > 0. \tag{61}$$

$$\sigma(j) = \frac{\max\{\frac{1}{D_0}C_D^2\|D_{-x}c^j_{f,h}\|^2_\infty, C_{F_\ell}+C_{S_\ell}\} + \max\{C_{F_\ell}, C_{S_\ell}\}}{1-\Delta t_0\max\{C_{F_\ell}, C_{S_\ell}\}}. \tag{62}$$

Proof: Taking into account the assumptions (HF$_\ell$), (HS$_\ell$), it can be shown that holds the following

$$\begin{aligned}\|\omega^m_{f,h}\|^2_h &\le \|\omega^{m-1}_{f,h}\|^2_h - 2\Delta t(D(M_x c^{m-1}_{f,h})D_{-x}c^m_{f,h} \\ &\quad -D(M_x\tilde{c}^{m-1}_{f,h})D_{-x}\tilde{c}^m_{f,h}, D_{-x}\omega^m_{f,h})_+ + 2\Delta t C_{F_\ell}\|\omega^m_{f,h}\|_h\|\omega^{m-1}_{b,h}\|_h, \\ \|\omega^m_{b,h}\|^2_h &\le \|\omega^{m-1}_{b,h}\|^2_h + 2\Delta t C_{S_\ell}\|\omega^{m-1}_{b,h}\|_h\|\omega^m_{b,h}\|_h.\end{aligned} \tag{63}$$

Considering now the assumptions (HD$_0$) and (HD$_\ell$), we have successively

$$\begin{aligned}&-(D(M_x c^{m-1}_{f,h})D_{-x}c^m_{f,h} - D(M_x\tilde{c}^{m-1}_{f,h})D_{-x}\tilde{c}^m_{f,h}, D_{-x}\omega^m_{f,h})_+ \\ &\quad = -(D(M_x\tilde{c}^{m-1}_{f,h})D_{-x}\omega^m_{f,h}, D_{-x}\omega^m_{f,h})_+ \\ &\quad -((D(M_x c^{m-1}_{f,h}) - D(M_x\tilde{c}^{m-1}_{f,h}))D_{-x}c^m_{f,h}, D_{-x}\omega^m_{f,h})_+ \\ &\quad \le -D_0\|D_{-x}\omega^m_{f,h}\|^2_+ + C_D\|D_{-x}c^m_{f,h}\|_\infty\|\omega^{m-1}_{f,h}\|_h\|D_{-x}\omega^m_{f,h}\|_+.\end{aligned}$$

Inserting the last upper bound in (63) we obtain

$$\begin{array}{l}(1-\Delta t C_{F_\ell})\|\omega_{f,h}^m\|_h^2+(1-\Delta t C_{S_\ell})\|\omega_{b,h}^m\|_h^2+2\Delta t(D_0-\epsilon^2)\|D_{-x}\omega_{f,h}^m\|_+^2\\ \quad\le (1+\Delta t\frac{1}{2\epsilon^2}C_D^2\|D_{-x}c_{f,h}^m\|_\infty^2)\|\omega_{f,h}^{m-1}\|_h^2\\ \quad +(1+\Delta t(C_{F_\ell}+C_{S_\ell}))\|\omega_{b,h}^{m-1}\|_h^2,\end{array}$$

that leads to

$$\begin{array}{l}\|\omega_{f,h}^m\|_h^2+\|\omega_{b,h}^m\|_h^2+2\Delta t(D_0-\epsilon^2)\|D_{-x}\omega_{f,h}^m\|_+^2\\ \quad\le (1+\Delta t\sigma(m))\Big(\|\omega_{f,h}^{m-1}\|_h^2+\|\omega_{b,h}^{m-1}\|_h^2\Big),\end{array}\tag{64}$$

provided that

$$1-\Delta t\max\{C_{F_\ell},C_{S_\ell}\}>0.$$

In (64), $\sigma(m)$ is given by

$$\sigma(m)\ =\frac{\max\{\frac{1}{2\epsilon^2}C_D^2\|D_{-x}c_{f,h}^m\|_\infty^2,C_{F_\ell}+C_{S_\ell}\}+\max\{C_{F_\ell},C_{S_\ell}\}}{1-\Delta t\max\{C_{F_\ell},C_{S_\ell}\}}\tag{65}$$

If we fix $\epsilon^2=\frac{D_0}{2}$, then from (64) we establish

$$\|\omega_{f,h}^m\|_h^2+\|\omega_{b,h}^m\|_h^2+\Delta t D_0\sum_{j=1}^m\|D_{-x}\omega_{f,h}^j\|_+^2\le\prod_{j=0}^{m-1}(1+\Delta t\sigma(j))\Big(\|\omega_{f,h}^0\|_h^2+\|\omega_{b,h}^0\|_h^2\Big),$$

where now $\sigma(j)$ is defined by (62). The last inequality leads to

$$\begin{array}{l}\|\omega_{f,h}^m\|_h^2+\|\omega_{b,h}^m\|_h^2+\Delta t D_0\sum_{j=1}^m\|D_{-x}\omega_{f,h}^j\|_+^2\\ \quad\le (1+\Delta t\max_{j=1,\dots,m}\sigma(j))^m\Big(\|\omega_{f,h}^0\|_h^2+\|\omega_{b,h}^0\|_h^2\Big),\end{array}\tag{66}$$

and, from inequality (66), we easily get (60). ■

Now we can establish the stability conditions we are looking for. From Proposition 7, it is sufficient to consider

$$\rho_0\le\frac{\sqrt{2}}{2}\sqrt{\rho_\epsilon}e^{-\frac{1}{2}T\max_{j=1,\dots,M}\sigma(j)}.$$

It is clear that the last upper bound gives the correct answer if $c_{f,h}^m\in W_{h,0}$, $c_{b,h}^m,\in\widehat{W}_h$, $m=1,\dots,M$, $h\in\Lambda$, are defined by (21)-(24) with initial conditions $c_{f,h}^0\in W_{h,0}$, $c_{b,h}^0,\in\widehat{W}_h$, such that

$$\|D_{-x}c_{f,h}^m\|_\infty^2\le C, m=1,\dots,M,\tag{67}$$

for some positive constant C and $h\in\Lambda$, with h_{max} and Δt small enough.

In the next section we establish that the errors $E_{f,h}^m = R_h c_f(t_m) - c_{f,h}^m$, $E_{b,h}^m = R_h c_b(t_m) - c_{b,h}^m$ for $c_{f,h}^m$ and $c_{b,h}^m$, respectively, satisfy the following

$$\begin{aligned}\|E_{f,h}^m\|_h^2 + \|E_{b,h}^m\|_h^2 + \Delta t \sum_{j=1}^m \|D_{-x}E_{f,h}^j\|_+^2 \\ \leq C_1(\Delta t^2 + h_{max}^4) + C_2\Big(\|E_{f,h}^0\|_h^2 + \|E_{b,h}^0\|_h^2\Big),\end{aligned} \tag{68}$$

for $m = 1, \ldots, M, h \in \Lambda$, provided that convenient smoothness assumptions hold for c_f and c_b. In the next section we specify such smoothness conditions.

The upper bound (68) can be used to conclude that (67) holds. In fact, as

$$\|D_{-x}c_{f,h}^m\|_\infty^2 \leq 2\Big(\|D_{-x}E_{f,h}^m\|_\infty^2 + \|D_{-x}R_h c_f(t_m)\|_\infty^2\Big)$$

and

$$\|D_{-x}E_{f,h}^m\|_\infty^2 \leq \frac{1}{h_{min}}\|D_{-x}E_{f,h}^m\|_+^2.$$

To conclude (67) we observe that, taking into account (68), we have successively

$$\begin{aligned}\|D_{-x}E_{f,h}^m\|_\infty^2 &\leq \frac{1}{h_{min}\Delta t}\Delta t \sum_{j=1}^m \|D_{-x}E_{f,h}^j\|_+^2 \\ &\leq \frac{1}{h_{min}\Delta t}\Big(C_1\Big(\Delta t^2 + h_{max}^4\Big) + C_2\Big(\|E_{f,h}^0\|_h^2 + \|E_{b,h}^0\|_h^2\Big)\Big) \\ &\leq C_1\Big(\frac{\Delta t}{h_{min}} + \frac{h_{max}^4}{h_{min}\Delta t}\Big) + \frac{1}{h_{min}\Delta t}C_2\Big(\|E_{f,h}^0\|_h^2 + \|E_{b,h}^0\|_h^2\Big).\end{aligned}$$

Then, if

$$\|E_{f,h}^0\|_h \leq Ch_{max}^p, \|E_{b,h}^0\|_h \leq Ch_{max}^p, \tag{69}$$

for $p = 1, 2$, we conclude (67) provided that the spatial stepsizes sequence Λ and the time stepsize Δt satisfy

$$\frac{\Delta t}{h_{min}} \leq C_G,\ \frac{h_{max}^{2p}}{h_{min}\Delta t} \leq C_G, \tag{70}$$

for Δt and h_{max} small enough. In (70), C_G is a positive constant h and Δt independent.

Finally, we can state that under the conditions (70), to have stability in $c_{f,h}^m \in W_{h,0}$, $c_{b,h}^m, \in \widehat{W}_h$, $m = 1, \ldots, M$, $h \in \Lambda$, it is enough to fix the initial data $c_{f,h}^0 \in W_{h,0}$, $c_{b,h}^0, \in \widehat{W}_h$, $h \in \Lambda$, satisfying (69). We observe that for $p = 2$ we relax the smoothness conditions on the time-space grid but we impose a more severe condition on the initial condition. If $p = 1$, we impose a more restrictive condition on the time-space grid and we relax the condition for the initial data.

3.2. Convergence for non smooth solutions. This section is focused in the convergence analysis of the IMEX scheme (21)-(24). In the main result of this paper, Theorem 2, we establish an upper bound for the error of the numerical solution computed with such method.

Theorem 2. *Let*

$$c_f \in C([0,T], H^3(\Omega) \cap H_0^1(\Omega)) \cap C^2([0,T], C(\overline{\Omega})) \cap C^1(0,T,H^2(\Omega))$$

and $c_b \in C^2([0,T], C(\Omega))$ *be solution of the IBVP (6)-(9), where* D, F *and* S *satisfy the assumptions* (HD_0), (HD_ℓ), (HF_ℓ) *and* (HS_ℓ). *For* $h \in \Lambda$, $\Delta t \in (0, \Delta t_0]$, *let* $c_{f,h}^m \in W_{h,0}, c_{b,h}^m \in \widehat{W}_h$, *for* $m = 0, \dots, M$, *be defined by the IMEX scheme (21)-(24) with initial conditions* $c_{f,h}^0 \in W_{h,0}$, $c_{b,h}^0 \in \widehat{W}_h$. *Then, for the errors* $E_{f,h}^m = R_h c_f(t_m) - c_{f,h}^m$, $E_{b,h}^m = R_h c_b(t_m) - c_{b,h}^m$, *holds the following*

$$\begin{aligned}\|E_{f,h}^m\|_h^2 \ &+ \|E_{b,h}^m\|_h^2 + 2\Delta t(D_0 - 5\epsilon^2)\Big(\sum_{j=1}^{m-1}\prod_{i=j+1}^{m}(1+\sigma(i))\|D_{-x}E_{f,h}^j\|_+^2 \\ &\qquad\qquad\qquad\qquad + \|D_{-x}E_{f,h}^m\|_+^2\Big) \\ &\le \prod_{j=1}^{m}(1+\Delta t\sigma(j))\Big(\|E_{f,h}^0\|_h^2 + \|E_{b,h}^0\|_h^2\Big) \\ &+ \frac{\Delta t}{1-\Delta t_0\max\{C_{F_\ell}, 2C_{S_\ell}\}}\Big(\sum_{j=1}^{m-1}\big(\prod_{i=j+1}^{m}(1+\Delta t\sigma(i))\big)T_h^j + T_h^m\Big),\end{aligned} \tag{71}$$

for $m = 1, \dots, M$, $h \in \Lambda$ *and* $\Delta t \in (0, \Delta t_0]$. *In (71),* $\sigma(j)$ *is defined by*

$$\sigma(j) \ = \frac{\max\{\frac{1}{\epsilon^2}C_{D_\ell}^2\|D_{-x}R_h c_f(t_j)\|_\infty^2, C_{F_\ell} + C_{S_\ell}\} + \max\{C_{F_\ell}, 2C_{S_\ell}\}}{1-\Delta t_0\max\{C_{F_\ell}, 2C_{S_\ell}\}}, \tag{72}$$

$\epsilon \neq 0$ *is an arbitrary constant,* Δt_0 *is fixed by*

$$1 - \Delta t_0 \max\{C_{F_\ell}, 2C_{S_\ell}\} > 0, \tag{73}$$

the error term T_h^j is defined by

$$\begin{array}{ll} T_h^j & = C\dfrac{1}{2\epsilon^2}\displaystyle\sum_{i=1}^N h_i^4\big(\|\dfrac{\partial c_f}{\partial t}(t_j)\|^2_{H^2(x_{i-1},x_i)} + \|F(c_f(t_j),c_b(t_j))\|^2_{H^2(x_{i-1},x_i)} \\ & \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad + \|c_f(t_j)\|^2_{H^3(x_{i-1},x_i)}\big) \\ & +\Delta t C\displaystyle\int_{t_{j-1}}^{t_j}\big(\dfrac{1}{2\epsilon^2}\|R_h\dfrac{\partial^2 c_f}{\partial t^2}(s)\|_h^2 + \dfrac{1}{C_{S_\ell}}\|R_h\dfrac{\partial^2 c_b}{\partial t^2}(s)\|_h^2\big)ds, \end{array} \tag{74}$$

for $j = 1,\cdots,m$. In (74), C is a positive constant h and Δt independent.

Proof: We start the proof remarking that we have

$$(D_{-t}E^m_{f,h},E^m_{f,h})_h = ((\frac{\partial c_f}{\partial t}(t_m))_h, E^m_{f,h})_h - (D_{-t}c^m_{f,h},E^m_{f,h})_h + T^{(1)}_{FD}, \tag{75}$$

where

$$T^{(1)}_{FD} = (D_{-t}R_hc_f(t_m) - (\frac{\partial c_f}{\partial t}(t_m))_h, E^m_{f,h})_h.$$

We also have

$$\begin{array}{ll} (\dfrac{\partial c_f}{\partial t}(t_m))_h, E^m_{f,h})_h & = -((D(\widehat{R}_hc_f(t_m))\widehat{R}_h\dfrac{\partial c_f}{\partial x}(t_m), D_{-x}E^m_{f,h})_+ \\ & +((F(R_hc_f(t_m),R_hc_b(t_m)))_h, E^m_{f,h})_h \\ & = -((D(M_xc_f(t_{m-1}))D_{-x}R_hc_f(t_m), D_{-x}E^m_{f,h})_+ \\ & +(F(R_hc_f(t_{m-1}),R_hc_b(t_{m-1})), E^m_{f,h})_h \\ & +T^{(2)}_{FD} + T^{(3)}_{FD}, \end{array} \tag{76}$$

where

$$\begin{array}{ll} T^{(2)}_{FD} & = -(D(\widehat{R}_hc_f(t_m))\widehat{R}_h\dfrac{\partial c_f}{\partial x}(t_m), D_{-x}E^m_{f,h})_+ \\ & +((D(M_xc_f(t_{m-1}))D_{-x}R_hc_f(t_m), D_{-x}E^m_{f,h})_+ \end{array}$$

and

$$T^{(3)}_{FD} = ((F(R_hc_f(t_m),R_hc_b(t_m)))_h - F(R_hc_f(t_{m-1}),R_hc_b(t_{m-1})), E^m_{f,h})_h.$$

Inserting (76) in (75) we obtain

$$
\begin{aligned}
(D_{-t}E^m_{f,h}, E^m_{f,h})_h \; &= -((D(M_x c_f(t_{m-1}))D_{-x}R_h c_f(t_m), D_{-x}E^m_{f,h})_+ \\
&+((D(M_x c^{m-1}_{f,h})D_{-x}c^m_{f,h}, D_{-x}E^m_{f,h})_+ \\
&+(F(R_h c_f(t_{m-1}), R_h c_b(t_{m-1})), E^m_{f,h})_h - (F(c^{m-1}_{f,h}, c^{m-1}_{b,h}), E^m_{f,h})_h \\
&+\sum_{\ell=1}^{3} T^{(\ell)}_{FD}.
\end{aligned}
\tag{77}
$$

From (77), considering the assumption (HD_0), (HD_ℓ), (HF_ℓ), it can be shown that

$$
\begin{aligned}
(1-\Delta t C_{F_\ell})\|E^m_{f,h}\|^2_h \; &+2\Delta t(D_0-\epsilon^2)\|D_{-x}E^m_{f,h}\|^2_+ \\
&\leq (1+\Delta t\frac{1}{2\epsilon^2}C^2_{D_\ell}\|D_{-x}R_h c_f(t_m)\|^2_\infty)\|E^{m-1}_{f,h}\|^2_h \\
&+\Delta t C_{F_\ell}\|E^{m-1}_{b,h}\|^2_h + 2\Delta t\sum_{j=1}^{3} T^{(j)}_{FD}.
\end{aligned}
\tag{78}
$$

Furthermore, we also have

$$
(1-\Delta t C_{S_\ell})\|E^m_{b,h}\|^2_h \leq (1+\Delta t C_{S_\ell})\|E^{m-1}_{b,h}\|^2_h + 2\Delta t T^{(4)}_{FD}, \tag{79}
$$

with

$$
T^{(4)}_{FD} = (D_{-t}R_h c_b(t_m) - R_h\frac{\partial c_b}{\partial t}(t_{m-1}), E^m_{b,h})_h.
$$

From (78) and (79) we conclude

$$
\begin{aligned}
(1-\Delta t C_{F_\ell})&\|E^m_{f,h}\|^2_h + (1-\Delta t C_{S_\ell})\|E^m_{b,h}\|^2_h + 2\Delta t(D_0-\epsilon^2)\|D_{-x}E^m_{f,h}\|^2_+ \\
&\leq \Big(1+\Delta t\max\{\frac{1}{2\epsilon^2}C^2_{D_\ell}\|D_{-x}R_h c_f(t_m)\|^2_\infty, C_{F_\ell}+C_{S_\ell}\}\Big) \\
&\qquad\qquad\Big(\|E^{m-1}_{f,h}\|^2_h + |\|E^{m-1}_{b,h}\|^2_h\Big) \\
&\quad +2\Delta t\sum_{j=1}^{4} T^{(j)}_{FD}.
\end{aligned}
\tag{80}
$$

In what follows we establish estimates for $T^{(j)}_{FD}, j=1,\ldots,4$.

1. An estimate for $T^{(1)}_{FD}$: We observe that

$$
\begin{aligned}
D_{-t}R_h c_f(t_m) - (\tfrac{\partial c_f}{\partial t}(t_m))_h \; &= D_{-t}R_h c_f(t_m) - R_h\tfrac{\partial c_f}{\partial t}(t_m) \\
&+R_h\tfrac{\partial c_f}{\partial t}(t_m) - (\tfrac{\partial c_f}{\partial t}(t_m))_h,
\end{aligned}
$$

where, as in Proposition 3, we have

$$\begin{aligned}&|(R_h\tfrac{\partial c_f}{\partial t}(t_m)-(\tfrac{\partial c_f}{\partial t}(t_m))_h,E_{f,h}^m)_h|\\&\qquad\le C\Big(\sum_{i=1}^N h_i^4\|\frac{\partial c_f}{\partial t}(t_m)\|^2_{H^2(x_{i-1},x_i)}\Big)^{1/2}\|D_{-x}E_{f,h}^m\|_+,\end{aligned}\tag{81}$$

for a positive constant C, h and t independent.

The following representation holds

$$D_{-t}R_hc_f(x_i,t_m)-\frac{\partial c_f}{\partial t}(x_i,t_m)=\frac{1}{\Delta t}\Big(\widehat{g}(1)-\widehat{g}(0)-\widehat{g}'(1)\Big),$$

with $\widehat{g}(\xi)=c_f(x_i,t_{m-1}+\xi\Delta t)$. Let $\lambda: W^{2,1}(0,1)\to \mathbb{R}$ be defined by

$$\lambda(g)=g(1)-g(0)-g'(1),\ g\in W^{2,1}(0,1).$$

As $\lambda\in (W^{2,1}(0,1))'$ and $\lambda(g)=0$ for $g=1,\xi$, from Bramble-Hilbert lemma we guarantee the existence of a positive constant C_λ such that

$$|\lambda(g)|\le C_\lambda\int_0^1|g''(\xi)|d\xi,\forall g\in W^{2,1}(0,1).$$

Consequently,

$$\begin{aligned}|D_{-t}R_hc_f(x_i,t_m)-\frac{\partial c_f}{\partial t}(x_i,t_m)|&\le C_\lambda\int_{t_{m-1}}^{t_m}|\frac{\partial^2 c_f}{\partial t^2}(x_i,\xi)|d\xi\\&\le C_\lambda\sqrt{\Delta t}\Big(\int_{t_{m-1}}^{t_m}\big(\frac{\partial^2 c_f}{\partial t^2}(x_i,\xi)\big)^2d\xi\Big)^{1/2}\end{aligned}$$

that leads to

$$\begin{aligned}&|(D_{-t}R_hc_f(t_m)-\tfrac{\partial c_f}{\partial t}(t_m),E_{f,h}^m)_h|\\&\qquad\le C\sqrt{\Delta t}\Big\|\|R_h\frac{\partial^2 c_f}{\partial t^2}\|_{L^2((t_{m-1},t_m))}\Big\|_h\|D_{-x}E_{f,h}^m\|_+,\end{aligned}\tag{82}$$

where C denotes a positive constant, h and t independent.

Finally, from (81), (82) we conclude

$$\begin{aligned}|T_{FD}^{(1)}|\ &\le C\frac{1}{4\epsilon^2}\Big(\sum_{i=1}^N h_i^4\|\frac{\partial c_f}{\partial t}(t_m)\|^2_{H^2(x_{i-1},x_i)}+\Delta t\int_{t_{m-1}}^{t_m}\|R_h\frac{\partial^2 c_f}{\partial t^2}(s)\|_h^2ds\Big)\\&\quad+2\epsilon^2\|D_{-x}E_{f,h}^m\|_+^2,\end{aligned}\tag{83}$$

where $\epsilon\neq 0$ is an arbitrary constant and C is a positive constant, h and t independent.

2. An estimate for $T_{FD}^{(2)}$: As in Proposition 3 we have

$$|T_{FD}^{(2)}| \leq C\frac{1}{4\epsilon^2}\sum_{i=1}^{N} h_i^4 \|c_f(t_m)\|^2_{H^3(x_{i-1},x_i)} + \epsilon^2\|D_{-x}E_{f,h}^m\|_+^2, \tag{84}$$

where $\epsilon \neq 0$ is an arbitrary constant and C is a positive constant, h and t independent.

3. An estimate for $T_{FD}^{(3)}$: As in Proposition 4 we have

$$|T_{FD}^{(3)}| \leq C\frac{1}{4\epsilon^2}\sum_{i=1}^{N} h_i^4 \|F(c_f(t_m), c_b(t_m))\|^2_{H^2(x_{i-1},x_i)} + \epsilon^2\|D_{-x}E_{f,h}^m\|_+^2, \tag{85}$$

where $\epsilon \neq 0$ is an arbitrary constant and C is a positive constant, h and t independent.

4. An estimate for $T_{FD}^{(4)}$: Following the proof of (82) it can be shown that

$$\begin{aligned}|(D_{-t}R_hc_b(t_m) - \tfrac{\partial c_b}{\partial t}(t_m), E_{b,h}^m)_h| &\leq C\sqrt{\Delta t}\Big\|\|R_h\frac{\partial^2 c_b}{\partial t^2}\|_{L^2((t_{m-1},t_m))}\Big\|_h \|E_{b,h}^m\|_h\\ &\leq C\Delta t\frac{1}{4\epsilon^2}\Big\|\|R_h\frac{\partial^2 c_b}{\partial t^2}\|_{L^2((t_{m-1},t_m))}\Big\|_h^2 + \epsilon^2\|E_{b,h}^m\|_h^2,\end{aligned}$$

where $\epsilon \neq 0$ is an arbitrary constant. Fixing in the last upper bound $\epsilon^2 = \dfrac{C_{S_\ell}}{2}$, we get

$$\begin{aligned}|(D_{-t}R_hc_b(t_m) - \tfrac{\partial c_b}{\partial t}(t_m), E_{b,h}^m)_h| \;&\leq C\Delta t\tfrac{1}{2C_{S_\ell}}\Big\|\|R_h\tfrac{\partial^2 c_b}{\partial t^2}\|_{L^2((t_{m-1},t_m))}\Big\|_h^2\\ &+\tfrac{C_{S_\ell}}{2}\|E_{b,h}^m\|_h^2,\end{aligned} \tag{86}$$

where C denotes a positive constant, h and t independent.

Taking into account the upper bounds (83)-(86) in (80) we deduce

$$\begin{aligned}&\|E_{f,h}^m\|_h^2 + \|E_{b,h}^m\|_h^2 + 2\Delta t(D_0 - 5\epsilon^2)\|D_{-x}E_{f,h}^m\|_+^2\\ &\quad\leq (1+\Delta t\sigma(m))\Big(\|E_{f,h}^{m-1}\|_h^2 + \||E_{b,h}^{m-1}\|_h^2\Big)\\ &\quad+\frac{\Delta t}{1-\Delta t\max\{C_{F_\ell}, 2C_{S_\ell}\}}T_h^m,\end{aligned} \tag{87}$$

with $\sigma(m)$ and T_h^m defined by (72) and (74), respectively. Finally, from (87) we easily get (71).

■

Fixing ϵ and manipulating conveniently the upper bound (71) we obtain the following corollary.

Corollary 3. *Under the assumptions of Theorem 2, there exist positive constants C_1 and C_2, h and Δt independent, such that*

$$\|E^m_{f,h}\|_h^2+\|E^m_{b,h}\|_h^2+\Delta t\sum_{j=1}^m \|D_{-x}E^j_{f,h}\|_+^2 \leq C_1(\Delta t^2+h^4_{max})+C_2\Big(\|E^0_{f,h}\|_h^2+\|E^0_{b,h}\|_h^2\Big),$$

for $m=1,\ldots,M$, $h\in\Lambda$ and $\Delta t\in(0,\Delta t_0]$, with Δt_0 fixed by (73).

4. Numerical experiments

In the first example of this section we illustrate our convergence results. For the experiments we use the the fully discrete IMEX scheme (21)-(24).

Example 1. *Let $\Omega=[0,1]$ and $t\in[0,1]$. We consider problem (6)-(9) with $S(c_f,c_b)=2c_f c_b^2$, $F(c_f,c_b)=c_f^2 c_b$, and $D(c_f)=1+c_f^2$, that is*

$$\begin{cases} \dfrac{\partial c_f}{\partial t} = \dfrac{\partial}{\partial x}\left((1+c_f^2)\dfrac{\partial c_f}{\partial x}\right)+c_f^2 c_b+g_f & (88)\\ \dfrac{\partial c_b}{\partial t} = 2c_f c_b^2+g_b, & (89)\end{cases}$$

The functions g_f and g_b are defined such that the exact solution of the problem is $c_f(x,t)=\exp(t)|x-0.5|^\alpha(x^2-x)$ and $c_b(x,t)=\exp(t)\sin(\pi x)$.

First we analyze the superconvergence error bound obtained in Corollary 3. To get the numerical rate of convergence in space we consider an initial random mesh and successively halve the spatial step size. The time step is chosen small enough (of the order of h^2_{max}) so that the spatial error dominates the time error. Following Corollary 3, the numerical error is measure by

$$\text{Error}_h^2 = \max_{m=1,\ldots,M} \|E^m_{f,h}\|_h^2+\|E^m_{b,h}\|_h^2+\Delta t\sum_{k=1}^m \|D_{-x}E^m_{f,h}\|_+^2$$

and the rate of convergence is computed by

$$\text{Rate}_h = \log_2\left(\frac{\text{Error}_h}{\text{Error}_{\frac{h}{2}}}\right).$$

When $\alpha=3.1$ we have $c_f(t)\in H^3(\Omega)\cap H^1_0(\Omega)$ and the regularity conditions of Theorem 2 are satisfied. That is not the case for $\alpha=2.1$, for which we have $c_f(t)\in H^2(\Omega)\cap H^1_0(\Omega)$. The values of Error_h and Rate_h given in Table 2 illustrate that the regularity conditions imposed on the continuous solution are sharp. We have second order convergence for $\alpha = 3.1$ and only first order convergence for $\alpha = 2.1$.

N	h_{max}	Error_h	Rate_h
20	5.5249E-2	4.3243E-3	-
40	2.7625E-2	1.1690E-3	1.8872
80	1.3812E-2	2.9772E-4	1.9732
160	6.9061E-3	7.5112E-5	1.9868
320	3.4531E-3	1.8920E-5	1.9891

N	h_{max}	Error_h	Rate_h
20	5.8156×10^{-2}	1.4089×10^{-2}	-
40	2.9078×10^{-2}	7.9888×10^{-3}	0.8185
80	1.4539×10^{-2}	3.8829×10^{-3}	1.0409
160	7.2695×10^{-3}	1.8877×10^{-3}	1.0405
320	3.6347×10^{-3}	9.0150×10^{-4}	1.0663

TABLE 1. Numerical convergence rates in space for Example 1, on the left $\alpha = 3.1$ and on the right $\alpha = 2.1$.

Now we analyze the time error bound obtained in Corollary 3. To get the numerical rate of convergence in time we fix the spatial mesh ($N = 320$ and $h_{max} = 3.5648 \times 10^{-3}$ and successively halve the time step. We measure the numerical error as

$$\text{Error}^2_{\Delta t} = \max_{m=1,\dots,M} \|E^m_{f,h}\|^2_h + \|E^m_{b,h}\|^2_h$$

and the rate of convergence is computed similarly as before. The results are given in Table 2, and the first order convergence rate is in accordance with Corollary 3.

Δt	$\text{Error}_{\Delta t}$	$\text{Rate}_{\Delta t}$
5.0000×10^{-1}	2.7196×10^{-1}	-
2.5000×10^{-1}	1.3394×10^{-1}	1.0218
1.2500×10^{-1}	6.6789×10^{-2}	1.0039
6.2500×10^{-2}	3.3355×10^{-2}	1.0017
3.1250×10^{-2}	1.6607×10^{-2}	1.0061

TABLE 2. Numerical convergence rate in time for Example 1 with $\alpha = 4$.

In the second example we illustrate the application of the motivational model (1)-(5) to light-triggered drug delivery.

Example 2. *This example is based on an experimental setup describe in* [16]*. It consists of a PBS (Phosphate-buffered saline) solution containing drug loaded light-sensitive hydrogels. To simulate this experiment we consider the one-dimensional domain illustrated in Figure 1. Let us rewrite the model equations for light intensity I, bounded drug c_b and free drug c_f*

$$\begin{cases} I(x) = I_0 \exp(-\beta x) \\ \dfrac{\partial c_f}{\partial t} = \dfrac{\partial}{\partial x}\left(D\dfrac{\partial c_f}{\partial x}\right) + \phi I c_b \\ \dfrac{\partial c_b}{\partial t} = -\phi I c_b, \end{cases}$$

in $(0,1)\times(0,T]$. For this problem we use no-flux boundary conditions for c_f,

$$\frac{\partial c_f}{\partial x}(0,t) = \frac{\partial c_f}{\partial x}(1,t) = 0,$$

and the following initial conditions $c_f(x,0) = 0$ and $c_b(x,0) = 1$, for $x \leq 0.25$, $c_b(x,0) = 0$, for $x > 0.25$. We denote by I_0 the constant incident light intensity, by β the attenuation coefficient, by ϕ the reaction rate parameter and by D the free drug diffusion coefficient. For the simulations, the parameters values were chosen empirically and for simplicity units are omitted. We are only interested in the qualitative behavior, namely, normalized release rates. In the following, the values $\phi = 4\times 10^{-3}$ and $\beta = 4$ are fixed.

Controlled drug release is a key advantage of responsive drug delivery system, and mathematical models can be useful to tune parameters in order to obtain the desire release rate. Drug release rate can be controlled by several factors, such as light intensity and hydrogel parameters. Here, we conduct two experiments: in the first one, we fix $D = 4\times 10^{-4}$ and change the light intensity I_0 from 5 to 10 to 15; in the second one, we fix $I_0 = 10$ and change the drug diffusion coefficient D from 2×10^{-4} to 4×10^{-4} to 8×10^{-4}. The results are given in Figures 2 and 3, respectively. As expected, free drug c_f release rates increase with increasing light intensities I_0 (Figure 2) and with increasing drug diffusivity D (Figure 3).

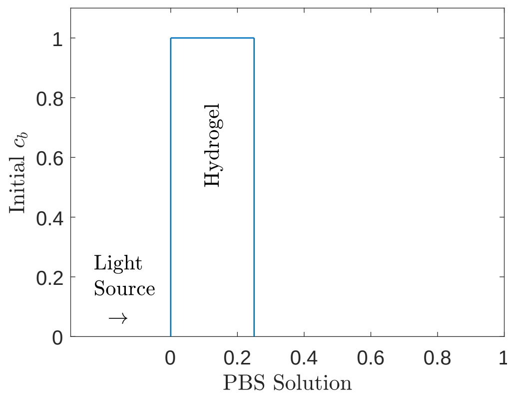

FIGURE 1. Computational 1D domain with bounded drug c_b initial distribution, light source position and hydrogel in the PBS solution.

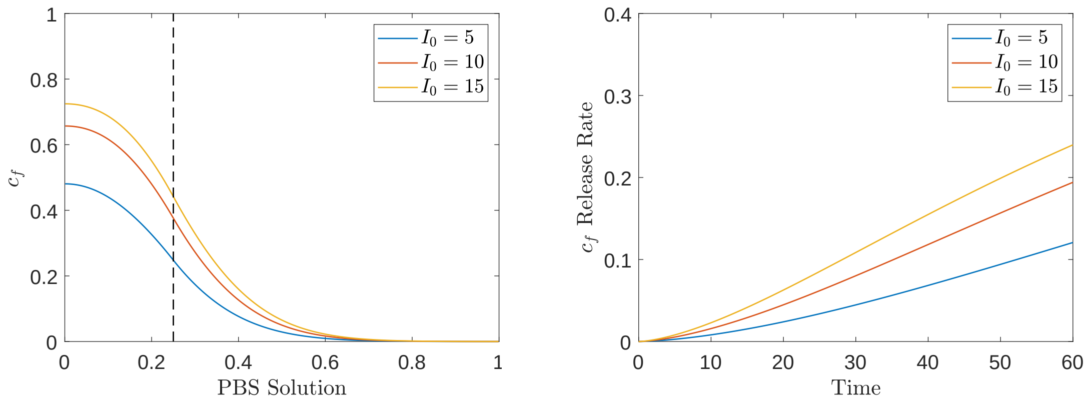

FIGURE 2. Free drug c_f concentration (on the left) and normalized release rate of free drug c_f (on the right) for three different values of incident light intensity I_0. The other parameters are fixed and equal to: $D = 4 \times 10^{-4}$, $\beta = 4$ and $\phi = 4 \times 10^{-3}$.

Identical experiments were conducted in [16]: in one, the light intensity was increased in the same proportion as in our simulation, and in the other, the percentage of agarose in the hydrogel was changed. Higher agarose percentage means that the hydrogel pores are smaller and thus the drug release rate is slower. In our simulation we change the drug diffusion coefficient D in the same proportion to simulate the change in agarose content. A comparison between experimental and simulated results is shown in Table 3. In particular, we compare the relative change in drug release rates at time $t = 60$. We observe that the total average error is 11%, a relatively low value considering the model simplicity. We conclude that the model is able to describe

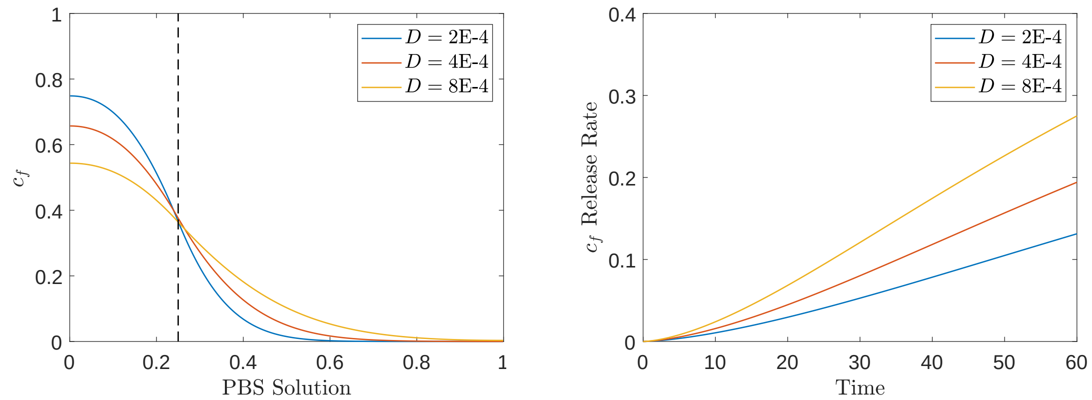

FIGURE 3. Free drug c_f concentration (on the left) and normalized release rate of free drug c_f (on the right) for three different values of the drug diffusion rate D. The other parameters are fixed and equal to: $I_0 = 10$, $\beta = 4$ and $\phi = 4 \times 10^{-3}$.

c_f Release Rate	Parameter I_0			Parameter D		
Relative Change	5	10	15	2×10^{-4}	4×10^{-4}	8×10^{-4}
Experimental	-	+41%	+103%	-	+57%	+120%
Numerical	-	+61%	+99%	-	+48%	+109%

TABLE 3. Comparison between numerical and simulation results; the values refer to relative change in drug release rates at time $t = 60$. When I_0 varies the other parameters are fixed and equal to: $D = 4 \times 10^{-4}$, $\beta = 4$, and $\phi = 4 \times 10^{-3}$. When D varies the other parameters are fixed and equal to: $I_0 = 10$, $\beta = 4$ and $\phi = 4 \times 10^{-3}$.

important features of the problem and reveals a relatively good qualitative agreement with experimental results.

5. Conclusion

In this work we consider a system of partial differential equations motivated by a mathematical model for light-triggered drug delivery. We propose a fully discrete FDM and we establish convergence estimates.

The first part of the paper is focused on the stability and convergence analysis of the space approximation. In the main convergence result - Theorem 1 - we establish a supra-superconvergence error bound in a discrete H^1-norm. We call this result a supra-superconvergence result because it can be seen in the context of finite differences or finite elements. This result allows us to conclude the uniform boundedness required to have nonlinear stability of the numerical solution. The second part of the paper is centered on the stability and convergence analysis of a time and space fully discrete IMEX scheme. Like in the semi-discrete case, nonlinear stability of the numerical solution is conclude from the convergence error estimates established in the main result of this paper - Theorem 2.

The included numerical experiments corroborate the error estimates and show the sharpness of the regularity assumptions for the theoretical solutions. Numerical comparisons with a laboratory experiment concerned with light-triggered drug delivery are also presented. We compare numerical drug release rates with experimental data for different light and drug parameters. The results suggest that the model reproduces the qualitative behavior of the experimental data. Mathematical models that give insight into the relation between parameters and drug release rates are a valuable tool to optimize therapeutic strategies.

The proposed light-triggered drug delivery model can be made more complex. For instance, we could take into account the effect of hydrogel erosion on light intensity attenuation and drug release. Other improvements are the inclusion of the binding of free drug to the target tissue and the replacement of the Beer-Lambert equation by the more accurate radiative transfer equation. The analysis of such models is left for future work.

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