Pré-Publicações do Departamento de Matemática
Universidade de Coimbra
Preprint Number 06–36

INTEGRO-DIFFERENTIAL MODELS FOR PERCUTANEOUS DRUG ABSORPTION

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ABSTRACT: In this paper we propose a new mathematical models for percutaneous absorption of a drug based on integro-differential equations. We study the qualitative properties of the solution of the models and its numerical approximation. Simulation of proposed numerical methods is carried out.

KEYWORDS: Integro-differential model, Numerical approximation, Stability, Convergence.

1. Introduction

Mathematical models based on well known Fick's law

$$J(x,t) = -D\nabla c(x,t) - \nu c(x,t), \tag{1}$$

where $c(x,t)$ is the concentration at point x at time t, D is the diffusion coefficient, ν is the advection rate (representing cell creation), have been largely used to describe percutaneous drug absorption.

These models are established combining (1) with the conservation law

$$\frac{\partial c}{\partial t} = -\nabla J - \gamma c + \mu, \tag{2}$$

where γ is the reaction rate and μ is a parameter related to the permeability of the duct membrane. Without being exhaustive we mention the parabolic equation

$$\frac{\partial c}{\partial t} = D\Delta c + \nu\nabla c - \gamma c + \mu, \tag{3}$$

considered for instance in [9] and [16] (see also [11]). It is well known that the solution of the equation (3) has the unphysical property that if a sudden change in drug concentration occurs at a certain point it is felt instantaneously everywhere. Moreover, there is an overestimation of the traveling waves velocity.

The drawback observed in equation (3) is also present in the Fisher equation (see [6]-[8], [12]-[14], [15]) and in the classical heat equation (see [4], [5],

Received August 23, 2006.
This work was supported by Centre for Mathematics of University of Coimbra.

[10]). In order to overcome these unphysical properties, in the context of the Fisher's equation, the flux defined by the Fick's law is replaced by a flux with a memory term ([6]-[8]). This approach was also followed in the context of heat conduction problems being introduced in the expression of the flux defined by Fourier law a memory term ([5], [10]).

Following the procedure presented in the last mentioned papers, we replace in the Fick's law (1) $J_1(x,t) := -D\nabla c(x,t)$ by

$$J_1(x, t+\tau), \tag{4}$$

where τ is a small parameter related with the memory of the skin. In fact, taking the limit when $\tau \to 0$ we obtain the traditional Fick's flux.

Taking the first order approximation to $J_1(x, t+\tau)$ into account we easily deduce

$$J_1(x,t) \simeq -\frac{D}{\tau}\int_0^t e^{-\frac{t-s}{\tau}} \Delta c(x,s)\, ds,$$

which replaced in (1) allows to obtain the integro-differential equation

$$\frac{\partial c}{\partial t} = \frac{D}{\tau}\int_0^t e^{-\frac{t-s}{\tau}} \Delta c(x,s)\, ds + \nu \nabla c - \gamma c + \mu. \tag{5}$$

We consider an element of skin with length L with a initial drug distribution

$$c(x,0) = c_{init}(0),\ x \in [0, L]. \tag{6}$$

For the behavior of the concentration at the end points of the skin element we consider

$$c(0,t) = c_0(t),\ Bc(L,t) = c_L(t),\ t \in [0,T], \tag{7}$$

where the boundary operator B is defined by

$$Bc(L,t) = c(L,t)$$

if we assume that the drug concentration is known at $x = L$, or

$$Bc(L,t) = \nabla c(L,t)$$

if the space drug variation at $x = L$ is known. B can also define the natural boundary condition

$$Bc(L,t) = \frac{D}{\tau}\int_0^t e^{-\frac{t-s}{\tau}} \nabla c(L,s)\, ds - \frac{1}{2}\nu c(L,t).$$

This last quantity represents the drug flux at $x = L$ introduced in our model.

From analytical point of view our aim in this paper is to study the behavior of the total drug mass contained in the skin element at each time

$t \in [0, T]$ and the norm of the past of the concentration gradient considering the introduced model (5)-(7).

From numerical point of view our aim is to study a numerical method that allows to obtain numerical approximations to the concentration. The numerical solution should present qualitative properties that can be seen as discretizations of the behavior of the continuous solution.

The approach followed in this paper was considered in other contexts, for instance in reaction-diffusion equations with memory that were studied in [1] and [3], and in the study of the effect of memory terms in the heat equation which was analyzed in [2].

The paper is organized as follows. In Section 2 we establish energy estimates for the solution of the initial boundary value problem (5)-(7). These estimates allow to characterize the behavior of the solution and the past in time of its gradient when the initial condition is perturbed. In Section 3 a semi-discrete approach is considered in order to obtain a semi-discrete approximation to the concentration. In that section, the stability and convergence of the semi-discrete approximation is studied and a nonstandard convergence order is proved. A fully discrete numerical method obtained combining the implicit Euler method with a rectangular rule is studied in Section 4. Stability and convergence of such method is proved. Finally, in Section 5, numerical experiments illustrating the theoretical results, proved in the paper, are presented. We also compare, from a numerical point of view, the differential model (3) with the integro-differential model (5).

2. Integro-differential models

In this section we study the stability properties of initial boundary value problems (IBVP) (5)-(7). Our aim is to study the difference between two solutions of the IBVP (5)-(7) and so we consider (5) with $\mu = 0$. The estimates are established using the energy method. The $L^2([0, L])$-norm is denoted by $\|.\|_{L^2([0,L])}$. We also use the following notation: by $v(t)$ we denote the x-function if v is defined in $[0, L] \times [0, T]$ and t is fixed.

Theorem 1. *Let c be a solution of the IBVP (5)-(7) with $\mu = 0$ and homogeneous Dirichlet boundary conditions. Then holds*

$$\|c(t)\|^2_{L^2([0,L])} + \frac{D}{\tau}\|\int_0^t e^{-\frac{t-s}{\tau}}\nabla c(s)\,ds\|^2_{L^2([0,L])} \le e^{Mt}\|c_{init}\|^2_{L^2([0,L])}, \qquad (8)$$

where $M = \max\{-2\gamma, -\dfrac{2}{\tau}\}$.

Proof: Multiplying (5) by c with respect to the L^2 inner product, $(.,.)$, and integrating by parts we obtain

$$(\frac{\partial c}{\partial t}(t), c(t)) = -\frac{D}{\tau}(\int_0^t e^{-\frac{t-s}{\tau}}\nabla c(s)\,ds, \nabla c(t)) - \gamma\|c(t)\|^2_{L^2([0,L])}. \tag{9}$$

Considering

$$\begin{aligned}(\int_0^t e^{-\frac{t-s}{\tau}}\nabla c(s)\,ds, \nabla c(t)) &= \frac{1}{2}\frac{d}{dt}\|\int_0^t e^{-\frac{t-s}{\tau}}\nabla c(s)\,ds\|^2_{L^2([0,L])}\\ &+\frac{1}{\tau}\|\int_0^t e^{-\frac{t-s}{\tau}}\nabla c(s)\,ds\|^2_{L^2([0,L])},\end{aligned}$$

in (9), we obtain

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|c(t)\|^2_{L^2([0,L])} &= -\frac{1}{2}\frac{D}{\tau}\frac{d}{dt}\|\int_0^t e^{-\frac{t-s}{\tau}}\nabla c(s)\,ds\|^2_{L^2([0,L])}\\ &-\frac{D}{\tau^2}\|\int_0^t e^{-\frac{t-s}{\tau}}\nabla c(s)\,ds\|^2_{L^2([0,L])} - \gamma\|c(t)\|^2_{L^2([0,L])},\end{aligned}$$

which allows to get

$$\begin{aligned}&\frac{d}{dt}\Big(\|c(t)\|^2_{L^2([0,L])} + \frac{D}{\tau}\|\int_0^t e^{-\frac{t-s}{\tau}}\nabla c(s)\,ds\|^2_{L^2([0,L])}\Big)\\ &\leq M\Big(\|c(t)\|^2_{L^2([0,L])} + \frac{D}{\tau}\|\int_0^t e^{-\frac{t-s}{\tau}}\nabla c(s)\,ds\|^2_{L^2([0,L])}\Big).\end{aligned}$$

Taking $y(t) = \|c(t)\|^2_{L^2([0,L])} + \dfrac{D}{\tau}\|\displaystyle\int_0^t e^{-\frac{t-s}{\tau}}\nabla c(s)\,ds\|^2_{L^2([0,L])}$ we obtain the inequality

$$\frac{d}{dt}y(t) \leq My(t).$$

Then holds

$$y(t) \leq e^{Mt}y(0)$$

and we conclude (8).

□

Theorem 1 is crucial to establish the uniqueness of the solution of the IBVP (5)-(7) with Dirichlet boundary conditions as well to study the sensitivity of the solution of the mentioned problem with respect to perturbations of the initial condition.

Corollary 1. *Let c and $\tilde{c}$ be solutions of (5)-(7) with Dirichlet boundary conditions and initial conditions c_{init} and $\tilde{c}_{init}$, respectively. Then holds*

$$\|(c-\tilde{c})(t)\|^2_{L^2([0,L])}+\frac{D}{\tau}\|\int_0^t e^{-\frac{t-s}{\tau}}\nabla(c-\tilde{c})(s)\,ds\|^2_{L^2([0,L])} \le e^{Mt}\|c_{init}-\tilde{c}_{init}\|^2_{L^2([0,L])},$$

where $M=\max\{-2\gamma,-\frac{2}{\tau}\}$.

Let us consider now the model usually present in the literature: the IBVP (3), (6), (7) with homogeneous Dirichlet boundary conditions. It is well known that for the solution of this problem holds the following

$$\|c(t)\|^2_{L^2([0,L])} \le e^{-2(\frac{D}{L^2}+\gamma)t}\|c_i\|^2_{L^2([0,L])}. \tag{10}$$

Estimate (10) does not give any information on the behavior of the gradient of the concentration while for the solution of (5)-(7) with homogeneous Dirichlet boundary conditions we have

$$\lim_{t\to+\infty}\|c(t)\|_{L^2([0,L])}=0 \tag{11}$$

and

$$\lim_{t\to+\infty}\|\int_0^t e^{-\frac{t-s}{\tau}}\nabla c(s)\,ds\|_{L^2([0,L])}=0. \tag{12}$$

Finally we remark that if the Dirichlet boundary condition at $x=L$ is replaced by the natural boundary condition

$$\frac{D}{\tau}\int_0^t e^{-\frac{t-s}{\tau}}\nabla c(L,s)\,ds=\frac{1}{2}\nu c(L,t) \tag{13}$$

then Theorem 1 holds. In fact we only need to observe that

$$\begin{aligned}(\int_0^t e^{-\frac{t-s}{\tau}}\Delta c\,ds,c)-\frac{1}{2}\nu(\nabla c,c) &= \int_0^t e^{-\frac{t-s}{\tau}}\nabla c(L,s)\,dsc(L,t)\\ &\quad -(\int_0^t e^{-\frac{t-s}{\tau}}\nabla c\,ds,\nabla c(t))-\frac{1}{2}\nu c^2(L,t)\\ &= -(\int_0^t e^{-\frac{t-s}{\tau}}\nabla c\,ds,\nabla c(t)).\end{aligned}$$

Finally we consider Neumann boundary condition at $x = L$. Attending that if $\nabla c(L,t) = 0$ then (13) holds provided that $\nu = 0$, we conclude, in this case, that Theorem 1 also holds.

3. Supraconvergence in semi-discretizations

The numerical method that we consider in Section 4 can be constructed considering spatial discretization combined with time integration. Attending to this fact, in this section we start by studying the properties of the semi-discrete approximation, i.e., the solution of the ordinary differential system obtained considering only the spatial discretization.

We consider a spatial uniform grid $I_h = \{0 = x_0, x_2, \ldots, x_N = L\}$, with step size h. By $c_i(t)$ we denote the semi-discrete approximation to $c(x_i,t)$ defined by

$$\frac{dc_i}{dt}(t) = \frac{D}{\tau}\int_0^t e^{-\frac{t-s}{\tau}} D_{2,x}c_i(s)\,ds + \nu D_{c,x}c_i(t) - \gamma c_i(t) + \mu,\ 1 \le i \le N-1, t > 0, \tag{14}$$

and

$$c_0(t), c_N(t),\ t \ge 0,\ c_i(0),\ 0 \le i \le N,\ \text{given}, \tag{15}$$

if Dirichlet boundary conditions are considered. In (14), $D_{c,x}$ and $D_{2,x}$ are defined by

$$D_{c,x}c_i(t) = \frac{c_{i+1}(t) - c_{i-1}(t)}{2h}, \quad D_{2,x}c_i(t) = \frac{c_{i+1}(t) - 2c_i(t) + c_{i-1}(t)}{h^2}.$$

In what follows we also need the backward finite differences with respect to x,

$$D_{-x}c_i(t) = \frac{c_i(t) - c_{i-1}(t)}{h}.$$

Lets consider in the space of grid functions which are null at x_0 and x_N, denoted by $L^2(I_h)$, the following norm

$$\|v_h\|^2_{L^2(I_h)} = h\sum_{i=1}^{N-1} v_i^2.$$

This norm is induced by the L^2 discrete inner product

$$(v_h, w_h)_h = h\sum_{i=1}^{N-1} v_i w_i,\ v_h, w_h \in L^2(I_h).$$

For an easier notation we introduce also $\|.\|_{L^2(+I_h)}$, defined by

$$\|v_h\|^2_{L^2(+I_h)} = h\sum_{i=1}^{N} v_i^2,$$

and

$$(v_h, w_h)_{h,+} = h\sum_{i=1}^{N} v_i w_i.$$

Using the discrete energy method it can be shown a discrete version of Theorem 1. In this section we only study the convergence properties of the solution of (14)-(15) but in the next section we establish a fully discrete version of that theorem. Let R_h be the restriction operator to the mesh.

Theorem 2. *Let $c_h(t) = (c_i(t))_{i=0}^N$ be the solution of (14)-(15). Then, for $E_h(t) = c_h(t) - (R_h c)(t)$, holds*

$$\|E_h(t)\|^2_{L^2(I_h)} + \frac{D}{\tau}\|\int_0^t e^{-\frac{t-s}{\tau}} D_{-x}E_h(s)\,ds\|^2_{L^2(+I_h)} \leq \int_0^t \|T_h(s)\|^2_{L^2(I_h)} e^{M(t-s)}\,ds, \tag{16}$$

where

$$T_h(t) = \frac{D}{\tau}\int_0^t e^{-\frac{t-s}{\tau}} D_{2,x}(R_h c)(s) - R_h(\frac{\partial^2 c}{\partial x^2})(s)\,ds + \nu D_{c,x}(R_h c)(t) - \nu R_h(\frac{\partial c}{\partial x})(t)$$

and $M = \max\{-2\gamma + 1, -\frac{2}{\tau}\}$.

Proof: The semi-discrete approximation error, $E_h(t)$, satisfies

$$\frac{dE_h}{dt}(t) = \frac{D}{\tau}\int_0^t e^{-\frac{t-s}{\tau}} D_{2,x}E_h(s)\,ds + \nu D_{c,x}E_h(t) - \gamma E_h(t) + T_h(t). \tag{17}$$

Multiplying (17) by $E_h(t)$ with respect to the inner product $(.,.)_h$ and using summation by parts we get

$$\begin{aligned}(\frac{dE_h}{dt}(t), E_h(t))_h &= -\frac{D}{\tau}(\int_0^t e^{-\frac{t-s}{\tau}} D_{-x}E_h(s)\,ds, D_{-x}E_h(t))_{h,+} \\ &\quad -\gamma\|E_h(t)\|^2_{L^2(I_h)} + (T_h(t), E_h(t))_h. \end{aligned} \tag{18}$$

Considering that we have

$$(\frac{dE_h}{dt}(t), E_h(t))_h = \frac{1}{2}\frac{d}{dt}\|E_h(t)\|^2_{L^2(I_h)},$$

$$(T_h(t), E_h(t))_h \leq \eta^2 \|E_h(t)\|^2_{L^2(I_h)} + \frac{1}{4\eta^2}\|T_h(t)\|^2_{L^2(I_h)}$$

for any constant $\eta \neq 0$, and

$$\begin{aligned}(\int_0^t e^{-\frac{t-s}{\tau}} D_{-x}E_h(s)\,ds, D_{-x}E_h(t))_{h,+} &= \frac{1}{2}\frac{d}{dt}\|\int_0^t e^{-\frac{t-s}{\tau}} D_{-x}E_h(s)\,ds\|^2_{L^2(+I_h)}\\ &+\frac{1}{\tau}\|\int_0^t e^{-\frac{t-s}{\tau}} D_{-x}E_h(s)\,ds\|^2_{L^2(+I_h)},\end{aligned}$$

we obtain

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|E_h(t)\|^2_{L^2(I_h)} &= -\frac{1}{2}\frac{D}{\tau}\frac{d}{dt}\|\int_0^t e^{-\frac{t-s}{\tau}} D_{-x}E_h(s)\,ds\|^2_{L^2(+I_h)}\\ &-\frac{D}{\tau^2}\|\int_0^t e^{-\frac{t-s}{\tau}} D_{-x}E_h(s)\,ds\|^2_{L^2(+I_h)} - \gamma\|E_h(t)\|^2_{L^2(I_h)}\\ &+\eta^2\|E_h(t)\|^2_{L^2(I_h)} + \frac{1}{4\eta^2}\|T_h(t)\|^2_{L^2(I_h)}.\end{aligned} \tag{19}$$

The inequality (16) follows by taking in (19) $\eta = \dfrac{1}{\sqrt{2}}$ and using the Gronwall Lemma.

□

Since $T_h(t)$ is a second order term, from (16), $\int_0^t e^{-\frac{t-s}{\tau}} D_{-x}E_h(s)\,ds$ is also a second order term. While this convergence order was expected for E_h, it is not standard for $\int_0^t e^{-\frac{t-s}{\tau}} D_{-x}E_h(s)\,ds$.

If mixed boundary conditions are considered: the Dirichlet boundary condition at $x = L$ is replaced by a Neumann boundary condition for the particular case $\nu = 0$, we consider the semi-discrete approximation $c_h(t)$ defined by

$$\frac{dc_i}{dt}(t) = \frac{D}{\tau}\int_0^t e^{-\frac{t-s}{\tau}} D_{2,x}c_i(s)\,ds - \gamma c_i(t) + \mu,\ 1 \leq i \leq N, t > 0, \tag{20}$$

and

$$c_0(t), D_{c,x}c_N(t),\ t \geq 0,\ c_i(0),\ 0 \leq i \leq N,\ \text{given.} \tag{21}$$

For the definition of $D_{c,x}c_N(t)$ we need the point $x_{N+1} = L + h$. In this case, in the space of grid functions defined in I_h null at $x = x_0$, $L^2(\overline{I}_h)$, we consider the inner product

$$(v_h, w_h)_{h,x_N} = h\sum_{i=1}^{N-1} v_i w_i + \frac{h}{2} v_N w_N,\ v_h, w_h \in L^2(\overline{I}_h).$$

The norm induced by this inner product is denoted by $\|.\|_{L^2(\overline{I}_h)}$.

As we have

$$(D_{2,x}v_h, w_h)_{h,x_N} = -(D_{-x}v_h, D_{-x}w_h)_{h,+} + D_{c,x}v_N w_N,\ v_h, w_h \in L^2(\overline{I}_h), \quad (22)$$

an estimate for the semi-discrete error $E_h(t)$ associated with the discretization (20)-(21) is obtained following the proof of Theorem 2 and being aware of the new term

$$\frac{D}{\tau}\int_0^t e^{-\frac{t-s}{\tau}} D_{c,x}E_N(s)\,ds E_N(t).$$

Since for any constant δ

$$\frac{D}{\tau}\int_0^t e^{-\frac{t-s}{\tau}} D_{c,x}E_N(s)\,ds E_N(t) = \frac{D}{\tau}\int_0^t e^{-\frac{t-s}{\tau}} \frac{\sqrt{h^3}}{6}\frac{\partial^3 c}{\partial x^3}(\xi, s) ds \sqrt{h} E_N(t)$$
$$\leq \frac{h^3}{4\delta^2}\Big(\frac{D}{\tau}\int_0^t e^{-\frac{t-s}{\tau}} \frac{1}{6}\frac{\partial^3 c}{\partial x^3}(\xi, s) ds\Big)^2 + h\delta^2 E_N^2(t),$$

with $\xi \in (L-h, L+h)$. In the same way as before, taking $\delta^2 = \eta^2 = \frac{\gamma}{4}$, it can be shown that

$$\|E_h(t)\|^2_{L^2(\bar{I}_h)} + \frac{D}{\tau}\|\int_0^t e^{-\frac{t-s}{\tau}} D_{-x}E_h(s)\,ds\|^2_{L^2(+I_h)} \leq \int_0^t \tilde{T}_h(s) e^{M(t-s)}\,ds, \quad (23)$$

where $M = \max\{-\gamma, -\frac{2}{\tau}\}$ and

$$\tilde{T}_h(\rho) = h^3\frac{2}{\gamma}\Big(\frac{D}{\tau}\int_0^\rho e^{-\frac{\rho-s}{\tau}} \frac{\partial^3 c}{\partial x^3}(\xi, s) ds\Big)^2 + \frac{2}{\gamma}\|T_h(\rho)\|^2_{L^2(\bar{I}_h)}.$$

We observe that in the last estimate there is an error term of order 3/2 which corresponds to the discretization of the boundary. We can improve this result and obtain a second order estimate by adding a new diffusive term to the equation:

$$\frac{\partial c}{\partial t} = \chi\Delta c(x,t) + \frac{D}{\tau}\int_0^t e^{-\frac{t-s}{\tau}} \Delta c(x,s)\,ds - \gamma c, \quad (24)$$

with χ arbitrary small. The error of the semi-discretization of (24) satisfies

$$\frac{dE_h}{dt}(t) = \chi D_{2,x}E_h(t) + \frac{D}{\tau}\int_0^t e^{-\frac{t-s}{\tau}} D_{2,x}E_h(s)\,ds - \gamma E_h(t) + T_h(t).$$

Using the equality

$$E_N(t) = \sum_{j=1}^{N} hD_{-x}E_j(t),$$

we obtain

$$\Big(\chi D_{c,x}E_N(t) + \frac{D}{\tau}\int_0^t e^{-\frac{t-s}{\tau}} D_{c,x}E_N(s)\,ds\Big)E_N(t) \le \xi^2\|D_{-x}E_h(t)\|^2_{L^2(^+I_h)}$$
$$+\frac{L}{4\xi^2}\Big(\chi\frac{h^2}{6}\frac{\partial^3 c}{\partial x^3}(\xi_1,t) + \frac{D}{\tau}\int_0^t e^{-\frac{t-s}{\tau}}\frac{h^2}{6}\frac{\partial^3 c}{\partial x^3}(\xi_2,s)\,ds\Big)^2,$$

where $\xi_1, \xi_2 \in (L-h, L+h)$. Lets consider $\xi^2 = \frac{\chi}{2}$. Using (22) and following the proof of Theorem 2 (considering $\eta^2 = \frac{\gamma}{2}$) we conclude that

$$\|E_h(t)\|^2_{L^2(\bar{I}_h)} + \frac{D}{\tau}\|\int_0^t e^{-\frac{t-s}{\tau}} D_{-x}E_h(s)\,ds\|^2_{L^2(^+I_h)} \le \int_0^t \hat{T}_h(s)e^{M(t-s)}\,ds,$$

where $M = \max\{-\gamma, -\frac{2}{\tau}\}$ and

$$\hat{T}_h(\rho) = \frac{L}{2\chi}\Big(\chi\frac{h^2}{6}\frac{\partial^3 c}{\partial x^3}(\xi_1,\rho) + \frac{D}{\tau}\int_0^\rho e^{-\frac{\rho-s}{\tau}}\frac{h^2}{6}\frac{\partial^3 c}{\partial x^3}(\xi_2,s)\,ds\Big)^2 + \gamma\|T_h(\rho)\|^2_{L^2(\bar{I}_h)}.$$

4. Fully numerical discretizations

We now present a complete numerical discretization for the IBVP (5)-(7). We consider an uniform temporal grid $\{t_j, j = 0,\ldots,M\}$ with $t_0 = 0, t_M = T$ and with step size k. By c_i^n we denote a numerical approximation to $c(x_i,t_n)$. The method is obtained by discretizing the integral with a rectangular rule and $\dfrac{\partial c}{\partial t}(x_i,t_n)$ with backward finite differences, i.e.,

$$D_{-t}c_i^n = \frac{D}{\tau}k\sum_{j=1}^{n}\big(e^{-\frac{t_n-t_j}{\tau}}D_{2,x}c_i^j\big) + \nu D_{c,x}c_i^n - \gamma c_i^n + \mu,\ 1\le i\le N-1, n\ge 1, \tag{25}$$

and

$$c_0^j,\ c_N^j,\ j=1,\ldots,M, c_i^0, i=1,\ldots,N-1, \text{ given}, \tag{26}$$

if Dirichlet boundary conditions are considered. In (25) we use the notations

$$D_{-t}c_i^n = \frac{c_i^n - c_i^{n-1}}{k}, \quad D_{c,x}c_i^n = \frac{c_{i+1}^n - c_{i-1}^n}{2h}, \quad D_{2,x}c_i^n = \frac{c_{i+1}^n - 2c_i^n + c_{i-1}^n}{h^2}.$$

In Theorem 3 we study the behavior of the total drug mass at each discrete time t_n and the norm of the past of the concentration gradient of the numerical solution which is effectively computed by our method. This result is a discrete version of Theorem 1 and allows to establish the stability properties of $c_h^j, j = 1, \ldots, M$, with Dirichlet boundary conditions.

Theorem 3. *Let $c_h^n = (c_i^n)_{i=0}^N$ be the solution of (25)-(26) with $\mu = 0$ at the temporal level n with homogeneous Dirichlet boundary conditions. Then holds*

$$\|c_h^{n+1}\|_{L^2(I_h)}^2 + \frac{D}{\tau}k^2 \|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau}} D_{-x}c_h^j\|_{L^2(+I_h)}^2 \leq \frac{1}{\min\{2, 1+2k\gamma\}}\|c_h^0\|_{L^2(I_h)}^2. \tag{27}$$

Proof: Let $n \geq 1$. Multiplying (25) by c_h^{n+1} with respect to the inner product $(.,.)_h$ and using summation by parts we obtain

$$\begin{aligned}\|c_h^{n+1}\|_{L^2(I_h)}^2 &= (c_h^n, c_h^{n+1})_h - \frac{D}{\tau}k^2 \sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau}} (D_{-x}c_h^j, D_{-x}c_h^{n+1})_{h,+} \\ &\quad -k\gamma\|c_h^{n+1}\|_{L^2(I_h)}^2.\end{aligned} \tag{28}$$

Attending that holds the following convenient representation of $\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau}} (D_{-x}c_h^j, D_{-x}c_h^{n+1})_{h,+}$,

$$\begin{aligned}\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau}} (D_{-x}c_h^j, D_{-x}c_h^{n+1})_{h,+} &= \frac{1}{2}\|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau}} D_{-x}c_h^j\|_{L^2(+I_h)}^2 \\ &\quad -\frac{e^{-2\frac{k}{\tau}}}{2}\|\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau}} D_{-x}c_h^j\|_{L^2(+I_h)}^2 + \frac{1}{2}\|D_{-x}c_h^{n+1}\|_{L^2(+I_h)}^2,\end{aligned} \tag{29}$$

from (28), we deduce

$$
\begin{aligned}
\|c_h^{n+1}\|^2_{L^2(I_h)} \;\leq\; & \frac{1}{2}\|c_h^n\|^2_{L^2(I_h)} + (\frac{1}{2} - k\gamma)\|c_h^{n+1}\|^2_{L^2(I_h)} \\
& -\frac{D}{2\tau}k^2\|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau}} D_{-x}c_h^j\|^2_{L^2(+I_h)} \\
& +\frac{D}{2\tau}k^2 e^{-\frac{2k}{\tau}}\|\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau}} D_{-x}c_h^j\|^2_{L^2(+I_h)} \\
& -\frac{D}{2\tau}k^2\|D_{-x}c_h^{n+1}\|^2_{L^2(+I_h)}. \qquad (30)
\end{aligned}
$$

The following inequality is obtained from (30)

$$
\begin{aligned}
(1 + 2k(\gamma + \frac{Dk}{2\tau L^2}))\|c_h^{n+1}\|^2_{L^2(I_h)} + \frac{D}{\tau}k^2\|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau}} D_{-x}c_h^j\|^2_{L^2(+I_h)} \\
\leq \|c_h^n\|^2_{L^2(I_h)} + \frac{D}{\tau}k^2 e^{-\frac{2k}{\tau}}\|\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau}} D_{-x}c_h^j\|^2_{L^2(+I_h)}, \qquad (31)
\end{aligned}
$$

using the discrete Poincaré-Friedrichs inequality

$$\|c_h^{n+1}\|^2_{L^2(I_h)} \leq L^2\|D_{-x}c_h^{n+1}\|^2_{L^2(+I_h)}.$$

Finally, from (31) we obtain

$$
\begin{aligned}
& \|c_h^{n+1}\|^2_{L^2(I_h)} + \frac{D}{\tau}k^2\|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau}} D_{-x}c_h^j\|^2_{L^2(+I_h)} \\
& \leq \|c_h^n\|^2_{L^2(I_h)} + \frac{D}{\tau}k^2\|\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau}} D_{-x}c_h^j\|^2_{L^2(+I_h)}. \qquad (32)
\end{aligned}
$$

¿From (32) we conclude inequality (27) attending that

$$\|c_h^1\|^2_{L^2(I_h)} + \frac{D}{\tau}k^2\|D_{-x}c_h^1\|_{L^2(+I_h)} \leq \frac{1}{\min\{2, 1 + 2k\gamma\}}\|c_h^0\|^2_{L^2(I_h)}$$

holds.

□

As a immediate consequence of Theorem 3 we conclude that if c_h^n and $\tilde{c}_h^n$ satisfy (25)-(26) then $c_h^n = \tilde{c}_h^n$. As a corollary of Theorem 3 we have the following stability result.

Corollary 2. *If c_h^n and $\tilde{c}_h^n$ are defined by (25)-(26) with initial conditions c_h^0 and $\tilde{c}_h^0$, respectively, then $v_h^n = c_h^n - \tilde{c}_h^n$ satisfies*

$$\|v_h^{n+1}\|^2_{L^2(I_h)} + \frac{D}{\tau}k^2\|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau}} D_{-x}v_h^j\|^2_{L^2(+I_h)} \leq \frac{1}{\min\{2, 1+2k\gamma\}}\|c_h^0 - \tilde{c}_h^0\|^2_{L^2(I_h)}.$$

In what follows we establish an upper bound to the error $E_h^{n+1} = c_h^{n+1} - R_h c(.,t_{n+1})$. It is easy to show that truncation error at (x_i, t_n) given by

$$T_i^n = D_{-t}c(x_i,t_n) - \frac{D}{\tau}k\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau}} D_{2,x}c(x_i,t_j) - \nu D_{c,x}c(x_i,t_n) + \gamma c(x_i,t_n),$$

is of first order with respect to k and of second order with respect to h. Following the proof of Theorem 3 it can be shown the next convergence result.

Theorem 4. *The error at t_{n+1}, E_h^{n+1}, satisfies*

$$\|E_h^{n+1}\|^2_{L^2(I_h)} + \frac{D}{\tau}\|k\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau}} D_{-x}E_h^j\|^2_{L^2(+I_h)} \leq \frac{k}{2\gamma}\sum_{j=1}^{n+1}\|T_h^j\|^2_{L^2(I_h)}. \quad (33)$$

Proof: It can be shown that, for $n \geq 1$, E_h^{n+1} satisfies

$$\begin{aligned}(1+2k(\gamma-\eta^2)+\frac{D}{\tau L^2})\|E_h^{n+1}\|^2_{L^2(I_h)} + \frac{D}{\tau}\|k\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau}} D_{-x}E_h^j\|^2_{L(+I_h)} \\ \leq \|E_h^n\|^2_{L^2(I_h)} + \frac{D}{\tau}\|k\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau}} D_{-x}E_h^j\|^2_{L(+I_h)} + \frac{k}{2\eta^2}\|T_h^{n+1}\|^2_{L^2(I_h)},\end{aligned} \quad (34)$$

for any constant $\eta \neq 0$. Choosing $\eta = \sqrt{\gamma}$ and attending that

$$\|E_h^1\|^2_{L^2(I_h)} + \frac{Dk^2}{\tau}\|D_{-x}E_h^1\|^2_{L^2(+I_h)} \leq \frac{k}{2\gamma}\|T_h^1\|^2_{L^2(I_h)},$$

we conclude (33).

□

Finally we consider the fully discretization when mixed boundary conditions are imposed: Dirichlet boundary condition at $x = 0$ and Neumann boundary condition at $x = L$. In this case, (25)-(26) are replaced by

$$D_{-t}c_i^n = \frac{D}{\tau}k\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau}} D_{2,x}c_i^j - \gamma c_i^n + \mu, \quad 1 \le i \le N, n \ge 1, \tag{35}$$

$$c_0^j,\, D_{c,x}c_N^j,\, j = 1, \dots, M, c_i^0, i = 1, \dots, N-1, \text{ given.} \tag{36}$$

If we assume homogeneous boundary conditions and $\mu = 0$, then for c_h^n defined by (35)-(36) holds a characterization analogous to the one established in Theorem 3. The convergence of c_h^n to the solution of the correspondent differential problem can be shown following the proof of Theorem 4, and using similar reasoning as for the semi-discrete approximation. More precisely, it can be shown that the error E_h^{n+1} satisfies the following:

$$\|E_h^{n+1}\|^2_{L^2(\bar{I}_h)} + \frac{D}{\tau}\|k\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau}} D_{-x}E_h^j\|^2_{L^2(^+I_h)} \le \sum_{j=1}^{n+1} \tilde{T}_h^j, \tag{37}$$

where

$$\tilde{T}_h^j = h^3\frac{3}{2\gamma}k^2\Big(\frac{D}{\tau}\sum_{\rho=1}^{j} e^{-\frac{t_j-t_\rho}{\tau}}\frac{1}{6}\frac{\partial^3 c}{\partial x^3}(\xi_\rho, t_\rho)\Big)^2 + \frac{3k}{2\gamma}\|T_h^j\|^2_{L^2(\bar{I}_h)},$$

$\xi_\rho \in (L-h, L+h)$ and being T_h^j the truncation error.

As for the semi-discrete approximation, it is possible to prove second order convergence in relation to the spatial discretization of the equation (24) with Dirichlet boundary condition at $x = 0$ and Neumann boundary condition at $x = L$. The method is only first order convergent in relation to the time discretization.

5. Numerical results

For the simulation we consider a simple example of the model where the skin is taken to be a single barrier of unit thickness. In all numerical experiments we take $D = 1$ and $\nu = \mu = \gamma = 0$. Suppose that the concentration at the skin surface is maintained at $c = 1$ and that the concentration at the skin-capillary boundary is $c = r$. Then, the boundary conditions are

$$c(0,t) = 1,\ c(1,t) = r,\ t > 0.$$

We consider the case where initially there is no drug in the skin, i.e., for initially condition we have

$$c(x,0) = 0,\ 0 < x < 1.$$

In Figure 1 we plot the numerical approximations obtained with method (25)-(26).

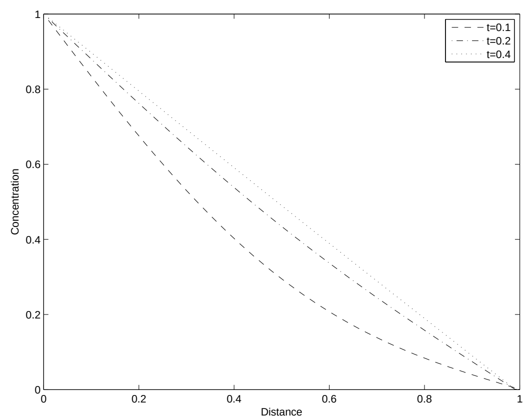

FIGURE 1. Concentration obtained with method (25) for $r = 0.001$, $\tau = 0.01$ using $k = 0.01$ and $h = 0.01$.

Lets now consider the following mixed boundary conditions

$$c(0,t) = 1,\ t > 0, \quad \nabla c(1,t) + \frac{1-r}{r} c(1,t) = 0,\ t > 0, \tag{38}$$

where we assume that the flux at the end point $x = 1$ is proportional to the concentration at this point. In order to compare the behavior of the solutions of both models: (3)-(38) (K&I model) and (5)-(38) (I-D model), we consider for the first model the method studied in [9] defined using the second order finite difference operator on the discretization of the second order spatial derivative and the Padé approximant to the exponential matrix of the resulting problem. For the model introduced in this paper, we consider the method (25)-(26). In both methods the discretization of the first order derivative which arises in the third kind boundary condition at $x = 1$ is made by using central differences.

Figure 2 and Figure 3 illustrate the behavior of the numerical approximations for the solutions of models (3)-(38) and (5)-(38). As we expected, the propagation velocity of the numerical approximations to the solution of (5)-(38) is lower.

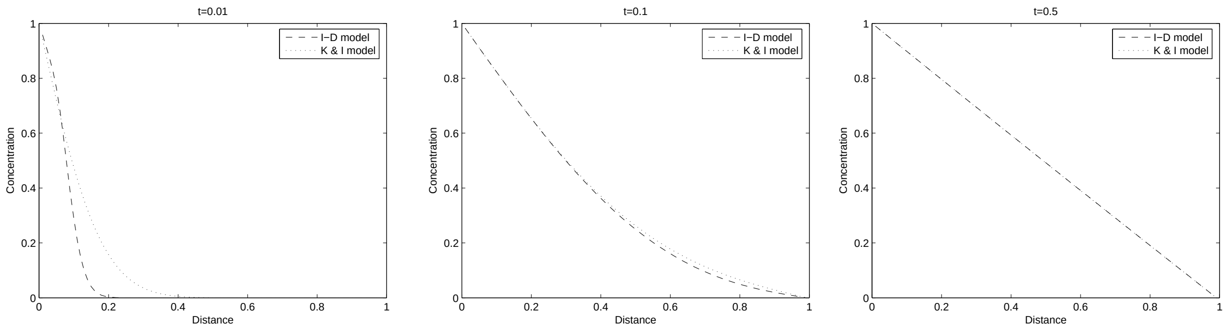

FIGURE 2. Concentration with $r = 0.001$, $\tau = 0.01$, using $k = 0.001$ and $h = 0.01$.

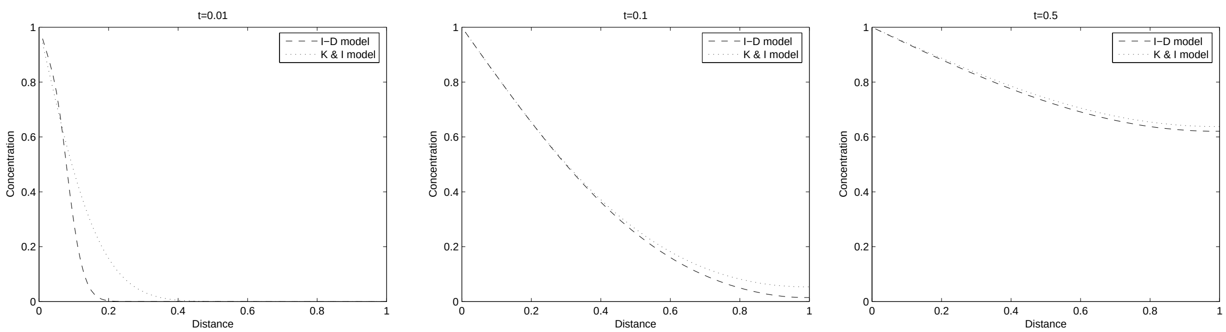

FIGURE 3. Concentration with $r = 0.999$, $\tau = 0.01$, using $k = 0.001$ and $h = 0.01$.

The influence of the increment of the parameter r in the behavior of the two models can be seen comparing Figure 2 and Figure 3.

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