

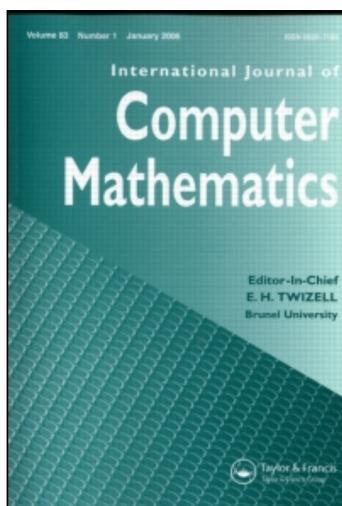
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## International Journal of Computer Mathematics

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713455451>

### Integro-differential models for percutaneous drug absorption

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Online Publication Date: 01 April 2007

**To cite this Article** Barbeiro, S. and Ferreira, J. A. (2007) 'Integro-differential models for percutaneous drug absorption', International Journal of Computer Mathematics, 84:4,451 — 467

**To link to this Article:** DOI: 10.1080/00207160701210091

**URL:** <http://dx.doi.org/10.1080/00207160701210091>

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## Integro-differential models for percutaneous drug absorption

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(Received 05 October 2006; revised version received 14 December 2006; accepted 07 January 2007)

In this paper we propose new mathematical models for percutaneous absorption of a drug. The new models are established by introducing, in the classical Fick's law, a memory term being the advection–diffusion equations of the classical models replaced by integro-differential equations. The well-posedness of the models is studied with Dirichlet, Neumann and natural boundary conditions. Methods for the computation of numerical solutions are proposed. Stability and convergence of the introduced methods are studied. Finally, numerical simulations illustrating the behaviour of the model are included.

*Keywords:* Convergence; Integro-differential model; Numerical approximation; Stability

*AMS Subject Classifications:* 35B30; 35B35; 65M06; 65M12; 65M15

### 1. Introduction

Mathematical models based on the well-known Fick's law

$$J(x, t) = -D\nabla c(x, t) - \nu c(x, t), \quad (1)$$

where  $c(x, t)$  is the concentration at point  $x$  at time  $t$ ,  $D$  is the diffusion coefficient,  $\nu$  is the advection rate (representing cell creation) and  $\nabla c(x, t)$  is the concentration gradient, have been largely used to describe percutaneous drug absorption. These models are established by combining (1) with the conservation law

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

where  $\gamma$  is the reaction rate,  $\mu$  is a parameter related to the permeability of the duct membrane and  $\nabla J$  is the flux gradient. Without being exhaustive we mention the parabolic equation

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

where  $\Delta c$  represents the Laplacian of the concentration, considered for instance in [1, 2] (see also [3]). It is well known that the solution of equation (3) has the unphysical property that

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if a sudden change in drug concentration occurs at a certain point it is felt instantaneously everywhere. Moreover, there is an overestimation of the travelling waves velocity.

The drawback observed in equation (3) is also present in the Fisher equation [4–10] and in the classical heat equation [11–13]. In order to overcome these unphysical properties, in the context of the Fisher equation, the flux defined by Fick's law is replaced by a flux with a memory term [4–6]. This approach was considered in the context of heat conduction problems, and consists of introducing a memory term in the expression of the flux defined by Fourier law [12, 13].

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

$$J_1(x, t + \tau), \quad (4)$$

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

Taking the first approximation  $J_1(x, t + \tau) \simeq J_1(x, t) + \tau(\partial J_1/\partial t)(x, t)$  into account we easily deduce

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

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

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

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

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

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

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

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

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

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

From the analytical point of view our aim in this paper is to study the behaviour of the total drug mass contained in the skin element at each time  $t \in [0, T]$  and the norm of the integral over time of the drug concentration gradient, defined by the model (5)–(6).

From the numerical point of view our aim is to study a numerical method that allows us to obtain numerical approximations to the concentration. The numerical solution should present qualitative properties that can be seen as discretizations of the behaviour 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 [14, 15], and in the study of the effect of memory terms in the heat equation which was analysed in [16].

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 us to characterize the behaviour of the solution and the integral over 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 non-standard convergence order is proved. A fully discrete numerical method obtained by combining the implicit Euler method with a rectangular rule is studied in section 4. The stability and convergence of this 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  $\| \cdot \|_{L^2([0, L])}$ . 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*

$$\|c(t)\|_{L^2([0, L])}^2 + \frac{D}{\tau} \left\| \int_0^t e^{-((t-s)/\tau)} \nabla c(s) ds \right\|_{L^2([0, L])}^2 \leq e^{Mt} \|c_{\text{init}}\|_{L^2([0, L])}^2, \tag{8}$$

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

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

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

Considering

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

in (9), we obtain

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

which allows us to get

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

Taking

$$y(t) = \|c(t)\|_{L^2([0,L])}^2 + \frac{D}{\tau} \left\| \int_0^t e^{-((t-s)/\tau)} \nabla c(s) ds \right\|_{L^2([0,L])}^2$$

we obtain the inequality

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

Then

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

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 as to study the sensitivity of the solution of the 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  $c_{\text{init}}$  and  $\tilde{c}_{\text{init}}$ , respectively. Then*

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

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

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

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

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

we have

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

and

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

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

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

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

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

Finally we consider the Neumann boundary condition at  $x = L$ . Noting 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 by considering only the spatial discretization.

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

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

and

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

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  $x$ ,

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

Let us 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

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

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

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

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

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

and

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

Using the energy method a discrete version of Theorem 1 can be shown. 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  $E_h(t) = c_h(t) - (R_h c)(t)$ , we have*

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

where

$$\begin{aligned} T_h(t) = & \frac{D}{\tau} \int_0^t e^{-((t-s)/\tau)} D_{2,x}(R_h c)(s) - R_h \left( \frac{\partial^2 c}{\partial x^2} \right) (s) ds \\ & + \nu D_{c,x}(R_h c)(t) - \nu R_h \left( \frac{\partial c}{\partial x} \right) (t) \end{aligned}$$

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

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

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

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

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

Considering that we have

$$\begin{aligned} \left(\frac{dE_h}{dt}(t), E_h(t)\right)_h &= \frac{1}{2} \frac{d}{dt} \|E_h(t)\|_{L^2(I_h)}^2, \\ (T_h(t), E_h(t))_h &\leq \eta^2 \|E_h(t)\|_{L^2(I_h)}^2 + \frac{1}{4\eta^2} \|T_h(t)\|_{L^2(I_h)}^2 \end{aligned}$$

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

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

we obtain

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

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

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

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

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

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  $x = x_0$ ,  $L^2(\bar{I}_h)$ , we consider the inner product

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

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

As we have

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

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

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

Since for any constant  $\delta$

$$\begin{aligned} \frac{D}{\tau} \int_0^t e^{-((t-s)/\tau)} D_{c,x} E_N(s) ds E_N(t) &= \frac{D}{\tau} \int_0^t e^{-((t-s)/\tau)} \frac{\sqrt{h^3}}{6} \frac{\partial^3 c}{\partial x^3}(\xi, s) ds \sqrt{h} E_N(t) \\ &\leq \frac{h^3}{4\delta^2} \left( \frac{D}{\tau} \int_0^t e^{-((t-s)/\tau)} \frac{1}{6} \frac{\partial^3 c}{\partial x^3}(\xi, s) ds \right)^2 \\ &\quad + h\delta^2 E_N^2(t), \end{aligned}$$

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

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

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

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

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:

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

with  $\chi$  arbitrary small. The error of the semi-discretization of (24) satisfies

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

Using the equality

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

we obtain

$$\begin{aligned} \left( \chi D_{c,x} E_N(t) + \frac{D}{\tau} \int_0^t e^{-((t-s)/\tau)} D_{c,x} E_N(s) ds \right) E_N(t) &\leq \xi^2 \|D_{-x} E_h(t)\|_{L^2(+I_h)}^2 \\ &\quad + \frac{L}{4\xi^2} \left( \chi \frac{h^2}{6} \frac{\partial^3 c}{\partial x^3}(\xi_1, t) + \frac{D}{\tau} \int_0^t e^{-((t-s)/\tau)} \frac{h^2}{6} \frac{\partial^3 c}{\partial x^3}(\xi_2, s) ds \right)^2, \end{aligned}$$

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

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

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

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

#### 4. Fully numerical discretizations

We now present a complete numerical discretization for the IBVP (5)–(7). We consider a uniform temporal grid  $\{t_j, j = 0, \dots, M\}$  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  $\frac{\partial c}{\partial t}(x_i, t_n)$  with backward finite differences, i.e.

$$D_{-t}c_i^n = \frac{D}{\tau} k \sum_{j=1}^n (e^{-((t_n-t_j)/\tau)} D_{2,x}c_i^j) + v D_{c,x}c_i^n - \gamma c_i^n + \mu, \quad 1 \leq i \leq N - 1, n \geq 1, \quad (25)$$

and

$$c_0^j, c_N^j, j = 1, \dots, M, c_i^0, \quad i = 1, \dots, N - 1, \text{ given}, \quad (26)$$

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

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

In Theorem 3 we study the behaviour of the total drug mass at each discrete time  $t_n$  and the norm of the integral over time 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 us to establish the stability properties of  $c_h^j, j = 1, \dots, M$ , 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*

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

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

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

Noting that

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

then from (28), we deduce

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

The following inequality is obtained from (30)

$$\begin{aligned} \left[ 1 + 2k \left( \gamma + \frac{Dk}{2\tau L^2} \right) \right] \|c_h^{n+1}\|_{L^2(I_h)}^2 &+ \frac{D}{\tau} k^2 \left\| \sum_{j=1}^{n+1} e^{-((n+1-t_j)/\tau)} D_{-x} c_h^j \right\|_{L^2(+I_h)}^2 \\ &\leq \|c_h^n\|_{L^2(I_h)}^2 + \frac{D}{\tau} k^2 e^{-(2k/\tau)} \left\| \sum_{j=1}^n e^{-((n-t_j)/\tau)} D_{-x} c_h^j \right\|_{L^2(+I_h)}^2, \end{aligned} \quad (31)$$

using the discrete Poincaré–Friedrichs inequality

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

Finally, from (31) we obtain

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

From (32) we conclude inequality (27) noting that

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

holds. ■

As an 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*

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

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

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

is of first order with respect to  $k$  and of second order with respect to  $h$ . The next convergence result can be shown by following the proof of Theorem 3.

**THEOREM 4** *The error at  $t_{n+1}$ ,  $E_h^{n+1}$ , satisfies*

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

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

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

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

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

we conclude (33). ■

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

$$D_{-t} c_i^n = \frac{D}{\tau} k \sum_{j=1}^n e^{-((n-t_j)/\tau)} D_{2,x} c_i^j - \gamma c_i^n + \mu, \quad 1 \leq i \leq N, n \geq 1, \quad (35)$$

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

If we assume homogeneous boundary conditions and  $\mu = 0$ , then for  $c_h^n$  defined by (35)–(36) a characterization analogous to that established in Theorem 3 is true. The convergence of  $c_h^n$  to the solution of the correspondent differential problem can be shown by 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:

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

where

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

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

As for the semi-discrete approximation, it is possible to prove second-order convergence in relation to the spatial discretization of 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 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).

Let us 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 behaviour of the solutions of both models: (3), (38) (K&I model) and the integro-differential model (5), (38) (I-D model), we consider for the first model the method studied in [1] defined using the second-order finite difference operator on the discretization of the second-order spatial derivative and the Padé approximation 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.

Figures 2 and 3 illustrate the behaviour 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.

The influence of the increment of the parameter  $r$  in the behaviour of the two models can be seen by comparing figures 2 and 3.

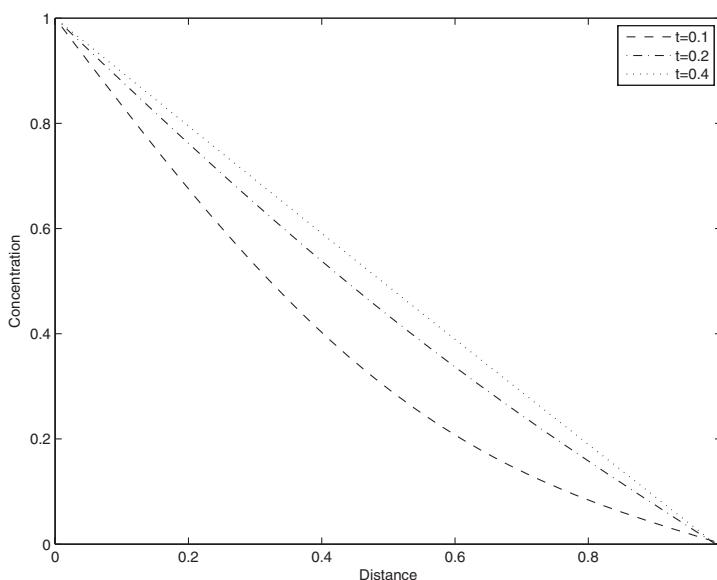


Figure 1. Concentration obtained with method (25) for  $r = 0.001$ ,  $\tau = 0.01$  using  $k = 0.01$  and  $h = 0.01$ .

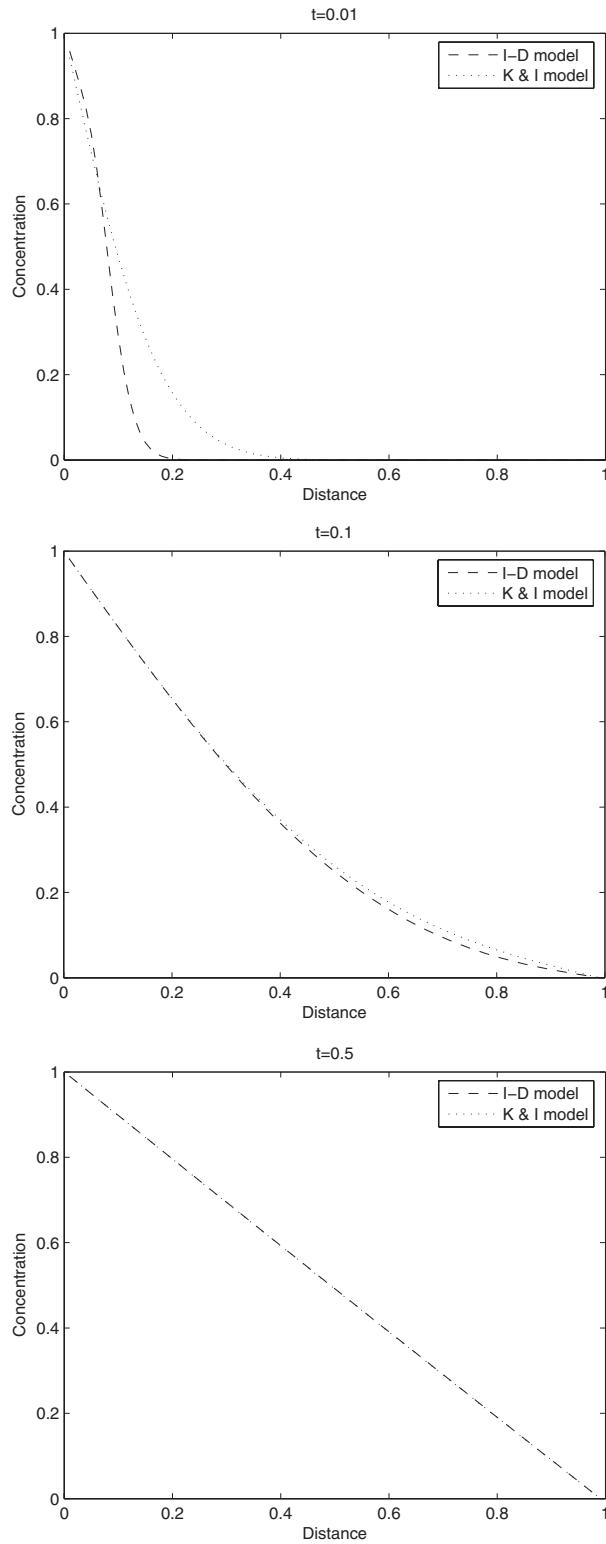


Figure 2. Concentration with  $r = 0.001$ ,  $\tau = 0.01$ , using  $k = 0.001$  and  $h = 0.01$ .

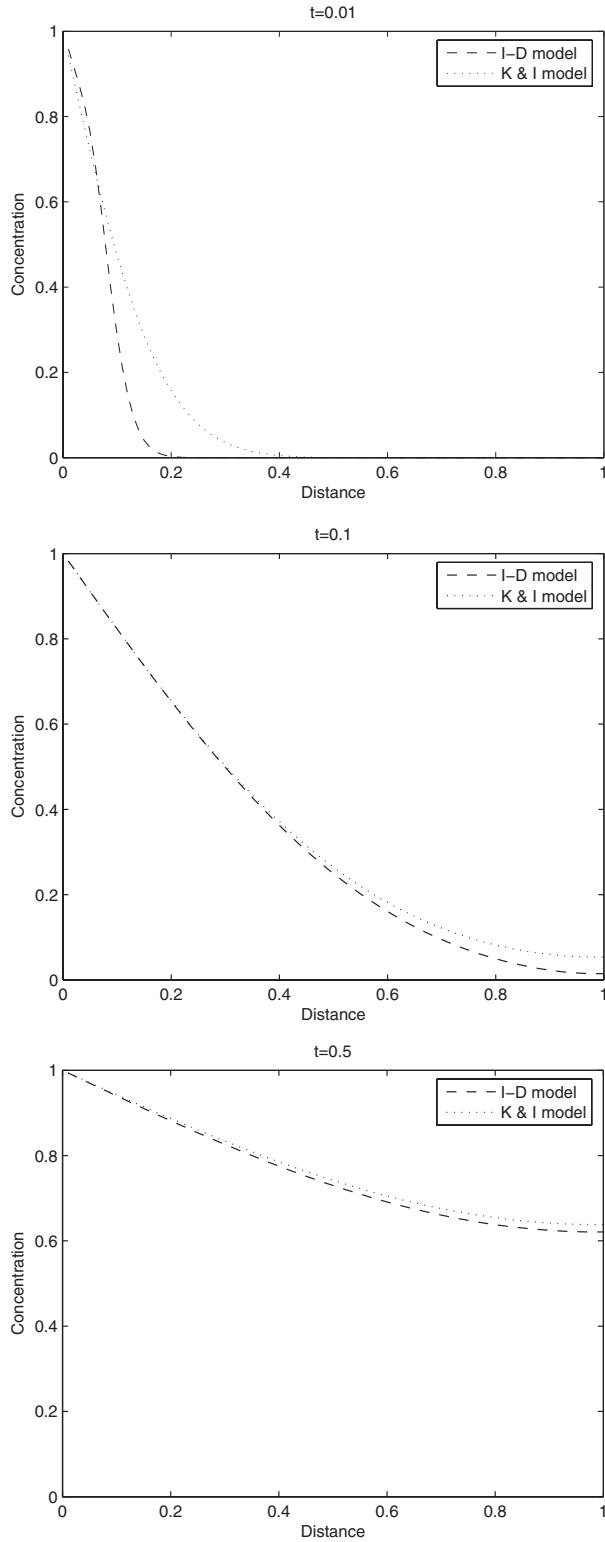


Figure 3. Concentration with  $r = 0.999$ ,  $\tau = 0.01$ , using  $k = 0.001$  and  $h = 0.01$ .

## 6. Conclusions

In this paper we consider new models for percutaneous absorption of a drug. The models are established introducing a memory term in the classical Fick's law. Then the traditional advection–diffusion equations (3), considered for instance in [1, 2] (see also [3]), are replaced by the integro-differential equations (5).

The new models allow us to characterize the drug concentration distribution in time and space for each time and for its time past. In fact, the estimate for the concentration established in Theorem 1, (8), characterizes the evolution in time of the concentration and the integral over time of the gradient of the concentration. It is known that for the solution of (3) with  $\mu = 0$  and homogeneous Dirichlet boundary conditions we have

$$\|c(t)\|_{L^2[a,b]} \leq e^{-\left(\frac{D}{(b-a)^2} + \gamma\right)t} \|C_{\text{init}}\|_{L^2[a,b]}, \quad t \geq 0. \quad (39)$$

From (39) we can characterize the distribution of the drug concentration only for each time  $t$ .

It is well known that the solution of 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 travelling waves velocities. Since (5) can be written in the following form

$$\frac{\partial^2 c}{\partial t^2} = \frac{D}{\tau} \Delta c - \frac{v}{\tau} \nabla \frac{\partial c}{\partial t} - \left(\frac{1}{\tau} + \gamma\right) \frac{\partial c}{\partial t} + \frac{v}{\tau} \nabla c - \frac{\gamma}{\tau} c + \frac{\mu}{\tau}, \quad (40)$$

which is a hyperbolic equation, we overcome the limitations of the parabolic equation (3).

In what concerns the numerical methods for the integro-differential problem we consider the semi-discretization (14)–(15) and the fully discrete scheme (25)–(26). The stability properties and the convergence of both discretizations were shown. We also observed that these schemes have the same qualitative properties of continuous integro-differential models. Numerically we compared the discretization (25)–(26) with the discretization of (3), (38) studied in [1]. As expected, we observe that the numerical approximations for the solution of the integro-differential model present lower propagation velocities than the propagation velocities of numerical approximations for the solutions of the differential model (3), (38).

## Acknowledgement

This work was supported by the Centre for Mathematics at the University of Coimbra.

## References

- [1] George, K., Kubota, K. and Twizell, E. H., 2004, A two-dimensional mathematical model of percutaneous drug absorption. *BioMedical Engineering Online*, **3**, 3–18.
- [2] Twizell, E.H., 2001, Aspects of Computational Bio-Mathematics. Textos de Matemática, Série B, n° 29, Departamento de Matemática da Universidade de Coimbra.
- [3] Kubota, K. and Ishizaki, T., 1986, A calculation of a percutaneous drug adsorption – I. Theoretical. *Computers in Biology and Medicine*, **16**, 17–19.
- [4] Fedotov, S., 1998, Traveling waves in a reaction–diffusion system: diffusion with finite velocity and Kolmogorov–Petrovskii–Piskunov kinetics. *Physical Review E*, **58**, 5143–5145.
- [5] Fedotov, S., 1999, Nonuniform reaction rate distribution for the generalized Fisher equation: ignition ahead of the reaction front. *Physical Review E*, **60**, 4958–4961.
- [6] Fedotov, S., 2001, Front propagation into an unstable state of reaction–transport systems, *Physical Review Letters*, **86**, 926–929.
- [7] Mendez, V. and Camacho, J., 1997, Dynamic and thermodynamics of delayed population growth. *Physical Review E*, **55**, 6476–6482.

- [8] Mendez, V. and Llebot, J., 1997, Hyperbolic reaction-diffusion equations for a forest fire model. *Physical Review E*, **56**, 6, 6557–6563.
- [9] Mendez, V., Pujol, T. and Fort, J., 2002, Dispersal probability distributions and the wave front speed problem. *Physical Review E*, **65**, 041109, 1–6.
- [10] Murray, J.D., 2003, *Mathematical Biology I, II: Spatial Models and Biomedical Applications*, 3rd edn (Berlin: Springer Verlag).
- [11] Carillo, S., 2005, Some remarks on materials with memory: Heat conduction and viscoelasticity. *Journal of Nonlinear Mathematical Physics*, **12**, 163–178.
- [12] Cattaneo, C., 1948, Sulla condizione de calore. *Atti del Seminario Matematico e Fisico dell'Universitat do Modena*, **3**, 3–21.
- [13] Joseph, D.D. and Preziosi, L., 1989, Heat waves. *Reviews of Modern Physics*, **61**, 41–73.
- [14] Araújo, A., Ferreira, J.A. and Oliveira, P. de, 2005, Qualitative behaviour of numerical traveling waves solutions for reaction diffusion equations with memory. *Applicable Analysis*, **84**, 1231–1246.
- [15] Branco, J.R., Ferreira, J.A. and Oliveira, P. de, 2007, Numerical methods for generalized Fisher–Kolmogorov–Petrovskii–Piskunov equation. *Applied Numerical Mathematics*, **57**, 89–102.
- [16] Araújo, A., Ferreira, J.A.f and Oliveira, P. de, 2006, The effect of memory terms in diffusion phenomena. *Journal of Computational Mathematics*, **24**, 91–102.