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Analysis of an evolution problem for controlled drug release

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Abstract

We consider a reaction-diffusion system arising from a model of controlled drug release. We derive a single nonlinear evolution equation, which is proved to be uniquely solvable in the classical sense and equivalent to the original system of two coupled PDE's. We discuss numerical approximation techniques which have been applied to obtain numerical simulations of the solutions.

Key words : *reaction-diffusion equations, nonlinear parabolic equation, numerical simulation*

1. Introduction

In recent years, several mathematical models for controlled drug release have been proposed, compared and analyzed. We refer to [12, 13] for a general overview and to [10, 11] for fundamental seminal works on the subject. The most advanced description (at least to our knowledge) is provided by Frenning in [6, 7] and consists of a two phase model (solid and dissolved drug) for drug dissolution and diffusion accounting for a finite dissolution rate. In particular, we refer here to the simpler case [6] where dissolved drug does not interact with

the substrate. In terms of suitable dimensionless variables and parameters, the model is described by the following system (see [1] for more details)

$$\begin{cases} c_t - \alpha c_{xx} = 3(s^+)^{2/3}(1-c) & 0 < x < 1,\ 0 < t < T \\ s_t = -3(s^+)^{2/3}(1-c) & \\ c(x,0) = 0, \quad s(x,0) = \sigma(x) & \\ c_x(0,t) = 0, \quad c(1,t) = 0. & \end{cases} \tag{1}$$

Here (x,t) respectively denote the space and time variables, $c = c(x,t)$ and $s = s(x,t)$ represent the drug concentrations in the dissolved and the solid phase, (normalized with respect to the saturation concentration for the dissolved drug), $\alpha > 0$ is the diffusion coefficient, and σ is a non-negative, dimensionless function describing the possibly position-dependent initial solid loading. Finally, $f^+ = \max\{f, 0\}$ denotes the positive part of a function f.

The plan of the paper is as follows. To introduce the reader to the problem, we start in Section 2 with a discussion of the qualitative behavior of solutions, based on numerical approximations of the solutions of the model at hand. Then, we perform a detailed analysis of the model, aimed at establishing unique solvability, lower-upper bounds, and regularity of the solutions. In Section 3 we prove some a priori estimates on the solutions of the differential system (1) and derive some (formally) equivalent boundary value problems for a *single* parabolic equation. In Section 4 we prove unique (global) solvability to one of such problems. Furthermore, we show that the solution has enough regularity (up to the parabolic boundary) to rigorously prove the equivalence between the parabolic problem and the original system. Finally, in Section 5 we summarize the numerical approximation scheme applied in Section 2 to illustrate the drug release dynamics in different conditions. This makes it possible to reproduce the reported results and to further investigate the behavior of the system.

2. Qualitative illustration of the problem

Controlled drug release, *i.e.* drug release with a prescribed release rate, can be achieved by casting a drug into a solid substrate with prescribed porosity, being able to slowly release the drug provided that it is exposed to a suitable solvent to be absorbed into the substrate. Then, drug release is the final consequence of three main steps: solvent absorption into the substrate, dissolution of drug from solid to dissolved phase, release of dissolved drug. The model (1) neglects the first step, as it lays on the assumption that the substrate is fully saturated with solvent. For an extension of the present model to include solvent absorption and substrate degradation, we refer for instance to [14, 15, 5]. Drug dissolution is accounted for by introducing the reaction term $3(s^+)^{2/3}(1-c)$, while drug diffusion is modelled by the diffusion term αc_{xx}. The parameter α, controlling the balance between diffusion and reaction, is indeed one of the most significant to determine the behavior of the system. However, most of the times a slow release rate is desirable, since the released drugs can be toxic in high

concentrations. This is for instance the case of release devices such as patches, implantable tablets, drug eluting stents. For this reason, the small diffusion regime is the most interesting from the point of view of applications. The initial state of the system, namely $\sigma(x)$, is another significant parameter. If the initial drug load is larger than the saturation level of dissolved drug, taken here as reference concentration equal to the unit, we say that the substrate has been charged with a saturated loading. In the opposite case we talk about unsaturated loading.

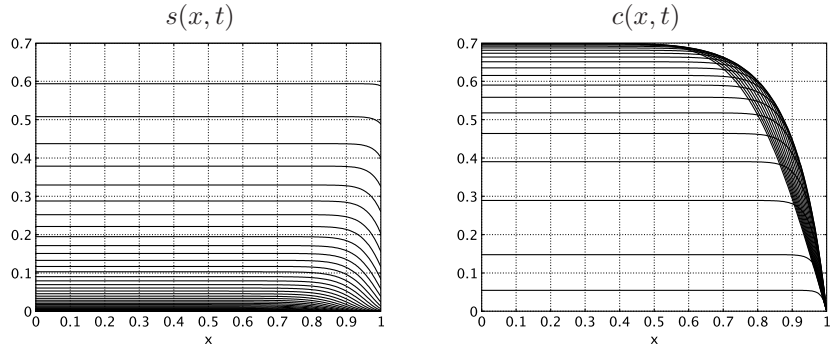
The initial and boundary conditions are chosen such as to model the following physical situation. We assume that at the initial time all the drug is loaded in the solid phase, and thus $c(x,0) = 0$ for all x. The extreme points of the substrate respectively represent an inert boundary at $x = 0$, where no drug is released, and a perfect washing condition at $x = 1$, where the external medium is assumed to be able to wash out the drug at any time.

For a quick overview on the behavior of model (1), we then restrict to the small diffusion regime. To refer a specific example, we select $\alpha = 10^{-2}$, and we compare the evolution of concentration profiles along the interval $(0,1)$ for saturated and unsaturated loadings.

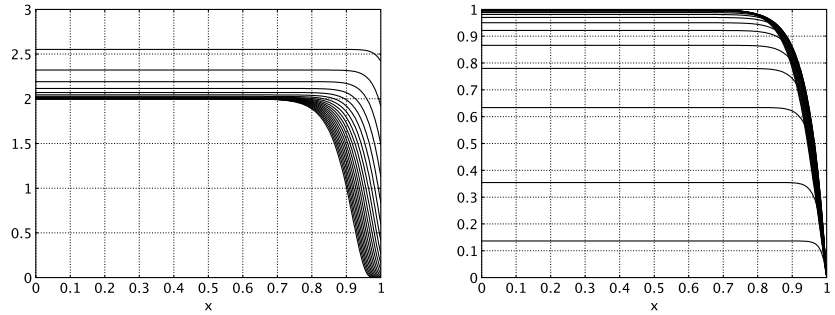
Looking at the case of unsaturated loadings, we observe that the solutions of (1) feature a simple monotone behavior in time, uniformly with respect to the space coordinate. The evolution of $c(x,t), s(x,t)$ is reported in Figure 1 (top). The reaction term $3(s^+)^{2/3}(1-c)$ promotes the consumption of s and the production of c. Since the dissolved concentration never reaches saturation, because $(1-c) \geq 0.3$, such trend is sustained until all the solid drug dissolves, and $s = 0$. Simultaneously, dissolved drug is released by diffusion from the external boundary $x = 1$.

In the saturated loading case, $\sigma = 3$, the dynamics of the system can be split in two phases. The evolution starts with a sudden decrease of solid drug concentration, that jumps from the initial state $s = \sigma$ to a *quasi*-stable state $s \approx \sigma - 1$ and $c \approx 1$, see Figure 1 (middle). Without the influence of the external boundary, the state variables s, c would converge to the equilibrium state, with $c(x,t) \lesssim 1$ and $s(x,t) \gtrsim \sigma - 1$, for any $t > 0$, $x \in (0,1)$. However, because of the interplay between the diffusion operator and the Dirichlet boundary condition $c(1,t) = 0$, the previous equilibrium state is perturbed, and the system shifts to a stable equilibrium $s = 0, c = 0$ where all drug has been released. This is the second evolution process for the saturated loading problem. As shown in Figure 1 (bottom), such transition represents an heteroclinic orbit of the system, which is associated to a propagating wave for the solid drug concentration s. We notice that the evolution of the system in the second phase is much slower than in the first one. Indeed, the first unstable equilibrium is reached for $t \simeq 2$ (non-dimensional time units), while the second transition requires $t \simeq 200$ to approach the final state.

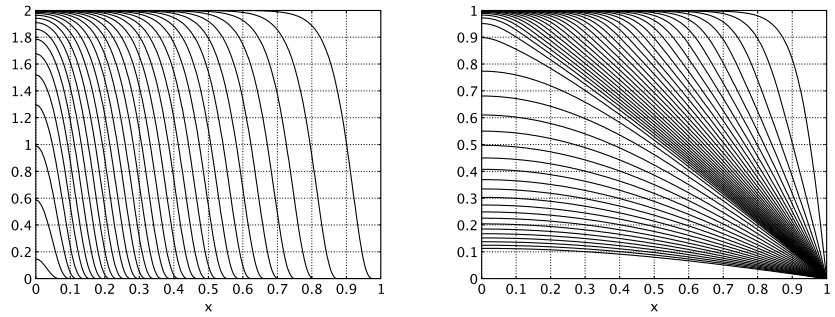
In what follows, we will dwell with the fundamental properties of solutions, such as existence, uniqueness and bounds from above and below, while for a detailed analysis of the asymptotic solutions of the system in the small diffusion regime, we refer the interested reader to [1].



Profiles for the solid and liquid concentration when $\sigma = 0.7$ and $t \in [0, 2]$.
Time evolves from top to bottom for s, and conversely for c.



Profiles for the solid and liquid concentration when $\sigma = 3$ and $t \in [0, 2]$.
Time evolves from top to bottom for s, and conversely for c.



Profiles for the solid and liquid concentration when $\sigma = 3$ and $t \in [2, 200]$.
Time evolves from right to left for both s and c.

Figure 1: Numerical solutions of the differential problem (1) for different combinations of the initial loading and different time scales.

3. General properties of the solutions

It is the aim of this section to provide an equivalent formulation of the differential system (1) as a problem for a single unknown, for which we will establish existence and uniqueness of classical solutions.

3.1. A priori estimates

To start with, we use the maximum principle to derive some estimates on any (possible) solution.

Proposition 1 *Let (c, s) be a solution of (1), with σ a piecewise continuous function in $[0,1]$ such that $0 \le \sigma(x) \le \sigma_1$. Then, for every $t \ge 0$ and $0 \le x \le 1$, we have*

$$0 \le c(x,t) \le 1 - \frac{\cosh \lambda x}{\cosh \lambda} \le 1 - \frac{1}{\cosh \lambda} < 1, \quad \textit{where} \quad \lambda = \sqrt{\frac{3\sigma_1^{2/3}}{\alpha}}\,. \tag{2}$$

Moreover, $0 \le s(x,t) \le \sigma(x)$ is a non-increasing function of time, and strictly decreasing whenever it is not null. Finally, if σ is strictly positive in any subinterval in $[0,1]$, the equality $c(x,t) = 0$ holds only at the initial time $t = 0$, that is, the concentration c does never vanish at any point $x \neq 1$ and time, other than its requested initial condition.

Proof. Since $3(s^+)^{2/3} \ge 0$, the maximum principle (see Lemma 4 in the Appendix) applied twice, first to the equation for c, and then to the trivially obtained equivalent equation for $(1-c)$, immediately yields $0 \le c(x,t) \le 1$ for all (x,t).

Let now λ be defined as in (2), and

$$d(x,t) = 1 - \frac{\cosh \lambda x}{\cosh \lambda}, \qquad x \in [0,1].$$

The function d is non-negative, and monotonically decreasing in x, with $0 = d(1) \le d(x) \le d(0) < 1$. By direct inspection it is easy to verify that it satisfies the partial differential equation

$$d_t - \alpha d_{xx} + 3\sigma_1^{2/3} d = 3\sigma_1^{2/3},$$

with $d_x(0,t) = 0$ and $d(1,t) = 0$. Furthermore it holds

$$(d-c)_t - \alpha(d-c)_{xx} + 3\sigma_1^{2/3}(d-c) = 3\left(\sigma_1^{2/3} - (s^+)^{2/3}\right)(1-c) \ge 0, \quad \text{with}$$
$$(d-c)\Big|_{(x,0)} \ge 0, \quad (d-c)_x\Big|_{(0,t)} = 0, \quad \text{and} \quad (d-c)\Big|_{(1,t)} = 0.$$

Then again the maximum principle applies to the function $(d-c)$ and we obtain, for every (x,t),

$$c(x,t) \le d(x) \le d(0) < 1,$$

that is an upper bound for c which proves that the drug concentration in the dissolved phase does never reach its saturation value. In turn, this implies that $s_t < 0$ when $s > 0$. Since $s \leq 0$ implies $s_t = 0$, we infer that s can not become negative, and the second claim follows.

Finally, the fact that c cannot vanish at any time (different from $t = 0$) follows from the strong maximum principle, and the observation that $c_t(x, 0)$ is strictly positive whenever $\sigma(x) > 0$. □

By arguing as above, it is easy to show that, despite the lack of Lipschitz-continuity in the corresponding equation, for any fixed $c(x, t)$, there exists at most one solution of the Cauchy problem

$$s_t = -3(s^+)^{2/3}(1 - c), \quad s(x, 0) = \sigma(x).$$

Furthermore

$$s(x, t_0) = 0 \quad \Longrightarrow \quad s(x, t) = 0 \text{ whenever } t \geq t_0.$$

As we mentioned, existence, uniqueness, and much more information for system (1) will descend from an equivalent problem.

3.2. Equivalent parabolic problems

In this section we determine a single partial differential equation equivalent to the system (1). For the sake of brevity we initially consider a uniform initial datum $\sigma(x) \equiv \sigma_0 > 0$.

When $s(x, t) > 0$, the second equation in (1) can be rewritten as

$$\frac{1}{3}(s^+)^{-2/3} s_t = -(1 - c)$$

which, once integrated in time, yields

$$(s^+(x, t))^{1/3} = \sigma_0^{1/3} - t + \int_0^t c(x, \tau)\, d\tau.$$

This suggests to introduce a new unknown in the form of the previous right hand side,

$$u(x, t) = \sigma_0^{1/3} - t + \int_0^t c(x, \tau)\, d\tau.$$

Formal computations then show that u is a solution of

$$\begin{cases} u_t - \alpha u_{xx} = \sigma_0 - 1 - (u^+)^3 & 0 < x < 1,\ 0 < t < T \\ u(x, 0) = \sigma_0^{1/3} \\ u_x(0, t) = 0 \\ u(1, t) = \sigma_0^{1/3} - t. \end{cases} \tag{3}$$

As a consequence, it is natural to wonder whether (3) is (uniquely) solvable, and in such a case to prove that the relation between (c, s) and u is not only

formal. In particular, we aim at understanding whether the relation holds once we remove the condition $s(x,t) > 0$. As one can easily see, the key point in this direction is to prove higher regularity for u (roughly speaking, existence and continuity of second and third derivatives, possibly up to some part of the boundary). This plan is successfully addressed in the next section, and allows us to obtain existence, uniqueness and the actual solution of (1) by integrating (3).

Proposition 2 *Let (c,s) be a classical solution of* (1) *(in particular, c is twice differentiable in the space variable, once in the time variable, and continuous up to the boundary), and*

$$u(x,t) = \sigma_0^{1/3} - t + \int_0^t c(x,\tau)\,d\tau.$$

Then $s(x,t) = (u^+(x,t))^3$, and u solves (3).

On the other hand, let u be (the unique) solution of (3). *Then the pair*

$$s(x,t) = \left(u^+(x,t)\right)^3, \qquad c(x,t) = 1 + u_t(x,t)$$

is (the unique) solution of (1).

Proof. As regards the first part, it is trivial to see that u (defined in terms of c) verifies the initial and boundary conditions. By assumption, the function $\varphi(x,t) = (u^+(x,t))^3$ is C^1 in time up to 0, and $\varphi \geq 0$, so that we obtain

$$\varphi_t = 3\left(u^+\right)^2 u_t = -3\left(\varphi^+\right)^{2/3}(1-c).$$

Since $\varphi(x,0) = \sigma_0$, the remark at the end of the previous subsection implies that $\varphi \equiv s$. Finally, since equation (1) implies $c_t - \alpha c_{xx} = -s_t$, by straightforward calculations we obtain

$$\alpha u_{xx} = \int_0^t \alpha c_{xx}(x,\tau)\,d\tau = \int_0^t (c_t + s_t)\,d\tau = c + s - \sigma_0,$$

and therefore

$$u_t - \alpha u_{xx} = \sigma_0 - 1 - s.$$

Recalling the relation between s and u, the first part of the proposition follows.

On the other hand, by Proposition 3 below there exists exactly one solution u of (3), and the functions u_t, u_x, u_{tx} u_{xx}, u_{xxx}, u_{tt}, and u_{txx} are continuous up to the boundary (possibly except for the point $(x,t) = (1,0)$). This allows us to check, by direct evaluation, that c, s satisfy (1). □

For the sake of completeness, we report in Figure 2, the solution $u^+(x,t)$, corresponding to the test cases for the small diffusion regime, already discussed in Section 2.

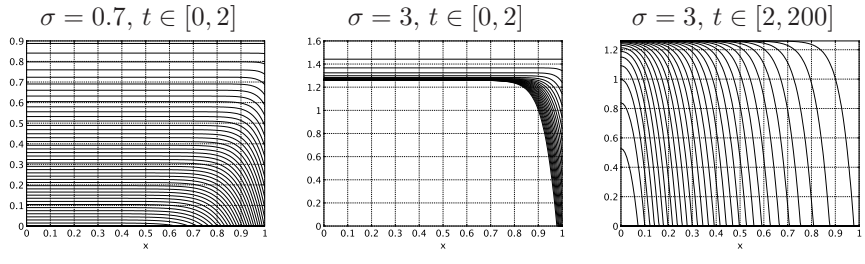


Figure 2: The solution $u^+(x,t)$ for the unsaturated loading $\sigma = 0.7$ (left), and saturated loading $\sigma = 3$ for the short time (middle) and long time scales (right).

By reasoning as above, one can also obtain another equivalent formulation of the problem, where all the boundary conditions are homogeneous. Indeed, if we let

$$v(x,t) = \int_0^t c(x,\tau)\,d\tau, \quad \text{then} \quad s(x,t) = \left[\left(\sigma_0^{1/3} - t + v\right)^+\right]^3,$$

and

$$\begin{cases} v_t - \alpha v_{xx} = \sigma_0 - \left[\left(\sigma_0^{1/3} - t + v\right)^+\right]^3 & 0 < x < 1,\ 0 < t < T \\ v(x,0) = 0 \\ v_x(0,t) = 0 \\ v(1,t) = 0. \end{cases} \tag{4}$$

Equivalent formulations such as (3) or (4) can be determined also when the initial loading $\sigma(x)$ is not uniform. In fact, it is to be noted that in (4) we may simply replace σ_0 by a variable $\sigma(x)$, and all statements still hold. On the contrary, some extra-care is necessary if we want to generalize equation (3). In particular, such an equivalent problem can be easily obtained only if $\sigma^{1/3}$ is of class C^2. When this is the case, the partial differential equation in (3) is replaced by

$$u_t - \alpha(u - \sigma^{1/3})_{xx} = \sigma - 1 - (u^+)^3.$$

4. Solvability of the parabolic problem

We now prove that problem (3) has a unique solution, and we obtain further regularity for this solution. In order to comprise the case of a non constant $\sigma = \sigma(x)$, it is convenient to work with the equivalent formulation (4), involving

homogeneous boundary conditions. Then, we set

$$v(x,t) = u(x,t) - \sigma^{1/3}(x) + t = \int_0^t c(x,\tau)\,d\tau,$$
$$s(x,t) = \left[\Big(\sigma^{1/3}(x) - t + v(x,t)\Big)^+\right]^3,$$

so that v solves the initial-boundary value problem

$$\begin{cases} v_t - \alpha v_{xx} = \sigma - \left[\big(\sigma^{1/3} - t + v\big)^+\right]^3 & \text{in } Q_T \\ v(x,0) = 0 & \text{on } C \\ v_x(0,t) = 0 & \text{on } N \\ v(1,t) = 0 & \text{on } D, \end{cases} \tag{5}$$

where $Q_T = (0,1)\times(0,T)$, $C = [0,1]\times\{0\}$, $N = \{0\}\times[0,T]$, $D = \{1\}\times[0,T]$. By choosing $\sigma^{1/3}$ smooth enough, v has the same regularity properties as u. We now prove:

Theorem 3 *There exists exactly one solution $v \in C^{2,1}(Q_T)\cap C(\overline{Q_T})$ of (5). Moreover, v satisfies the following regularity properties:*

- *v_t, v_x $v_{tx} \in C(\overline{Q_T})$;*
- *v_{xx}, v_{xxx}, v_{tt} and v_{txx} are continuous in Q_T, uniformly up to N and to $C\cup D\backslash\{(1,0)\}$.*

Proof. We divide the proof into four steps.

1. *A priori bounds.* From the maximum principle (see appendix A) any smooth enough solution v of problem (5) satisfies $v \le v_\sigma$, where v_σ is the solution to the *linear* problem $v_t - \alpha v_{xx} = \sigma$ with the same (homogeneous) initial-boundary conditions. As in the proof of the estimates of Proposition 1, we assume that $0 \le \sigma(x) \le \sigma_1$. Then, again by the maximum principle, it is easily verified that $v_\sigma \le \frac{\sigma_1}{2\alpha}(1-x^2)$, so that any solution v to (5) satisfies

$$v(x,t) \le \frac{\sigma_1}{2\alpha}(1-x^2). \tag{6}$$

In particular, it follows that $v_t - \alpha v_{xx} \ge -\sigma_\alpha$ with $\sigma_\alpha = \sigma_1\big[(1+\frac{\sigma_1^{2/3}}{2\alpha})^3 - 1\big]$; thus, we also have the lower bound

$$v(x,t) \ge -\frac{\sigma_\alpha}{2\alpha}(1-x^2). \tag{7}$$

Finally, by denoting with $f(x,t)$ the term at the right hand side of the equation in (5), we have $-\sigma_\alpha \le f(x,t) \le \sigma$; hence, by standard calculations we get the uniform estimate

$$\|v\|_{L^2((0,T);H^1(0,1))} \le K_1\sqrt{T} \tag{8}$$

for every solution v.

2. *Local solvability.* Following a classical approach [2], one can reformulate problem (5) as an integral equation. Then, we consider the equation

$$v(x,t) = v_\sigma(x,t) - \int_0^t \int_0^1 \Theta(x,\xi,t-\tau) \left[\left(\sigma^{1/3} - \tau + v \right)^+ \right]^3 d\xi d\tau, \qquad (9)$$

where v_σ was defined in step 1 and

$$\Theta(x,\xi,t) = 2 \sum_{n=0}^{\infty} e^{-\alpha \left(n+\frac{1}{2}\right)^2 \pi^2 t} \cos\left[\left(n + \frac{1}{2} \right) \pi x \right] \cos\left[\left(n + \frac{1}{2} \right) \pi \xi \right].$$

Let $V = \{v \in H^1(0,1),\, v(1) = 0\}$. We first prove that (9) has a unique solution in the space $\mathcal{C}([0,T];V)$ for T small enough. To this aim, we consider the function

$$S[v](x,t) = s(x,t) = \left[\left(\sigma^{1/3}(x) - t + v(x,t) \right)^+ \right]^3, \quad \text{where } v \in \mathcal{C}([0,T];V). \qquad (10)$$

By the smoothness assumptions on $\sigma^{1/3}$ and recalling that v is continuous and bounded, it can be shown that $s \in \mathcal{C}([0,T];H^1(0,1))$. Besides, by (8),

$$\|s\|_{L^2((0,T);H^1(0,1))} \le K_2 \sqrt{T}, \qquad (11)$$

with the constant K_2 depending on $\|v\|_{\mathcal{C}([0,T];H^1(0,1))}$. Note that, if the estimates (6) and (7) hold, we can take K_2 independent of v. Finally, we have

$$s(1,t) = \left[\left(\sigma^{1/3}(1) - t \right)^+ \right]^3, \qquad (12)$$

so that $0 \le s(1,t) \le \sigma(1)$. Let us define

$$S_n(\tau) = \int_0^1 s(\xi,\tau) \cos\left[\left(n + \frac{1}{2} \right) \pi \xi \right] d\xi \qquad (13)$$

and

$$\tilde{S}_n(t) = \int_0^t e^{-\alpha \left(n+\frac{1}{2}\right)^2 \pi^2 (t-\tau)} S_n(\tau)\, d\tau. \qquad (14)$$

By denoting with $\Theta S[v](x,t)$ the integral term in (9), we now have

$$\Theta S[v](x,t) = 2 \sum_{n=0}^{\infty} \tilde{S}_n(t) \cos\left[\left(n + \frac{1}{2} \right) \pi x \right]. \qquad (15)$$

Since $s(\cdot,\tau) \in H^1(0,1)$, we can integrate by parts in (13), and we obtain

$$\left(n + 1/2\right) \pi S_n(\tau) = (-1)^n s(1,\tau) - \int_0^1 s_\xi(\xi,\tau) \sin\left[\left(n + \frac{1}{2} \right) \pi \xi \right] d\xi. \qquad (16)$$

Then, by (12) and by Hölder inequality, we get the bound

$$\big|\big(n+1/2\big)\pi S_n(\tau)\big| \le \sigma(1) + \frac{1}{2}\|s(\cdot,\tau)\|_{H^1(0,1)}. \tag{17}$$

By further applying the Hölder inequality in (14), we finally obtain

$$\begin{aligned}\big(n+1/2\big)\pi\big|\tilde{S}_n(t)\big| &\le \frac{\sigma(1)}{\sqrt{2\alpha}\big(n+1/2\big)\pi}\sqrt{t} \\ &\quad + \frac{1}{2}\left[\int_0^t e^{-2\alpha\left(n+\frac{1}{2}\right)^2\pi^2(\tau)}\,d\tau\right]^{1/2}\|s\|_{L^2(0,t;H^1(0,1))} \\ &\le K_3\frac{1}{\big(n+1/2\big)}\sqrt{t} + K_4\frac{\|s\|_{L^2(0,t;H^1(0,1))}}{\big(n+1/2\big)^{1-2\delta}}\,t^\delta,\end{aligned} \tag{18}$$

for any $\delta > 0$. By choosing $0 < \delta < 1/4$ in the above estimate and by using it in (15), together with (11), it follows that the operator given by the right hand side of (9):

$$v \mapsto v_\sigma - \Theta S[v],$$

maps a ball around v_σ in $\mathcal{C}([0,T];V)$ into itself for T small enough. We are now left with the Lipschitz estimate of $\Theta S[v]$ in $\mathcal{C}([0,T];V)$. By (10) and by standard calculations, we have $\big|S[v_1] - S[v_2]\big| \le L|v_1 - v_2|$, and

$$\big|\big(S[v_1] - S[v_2]\big)_x\big| \le L_1|(v_1-v_2)_x| + L_2|(v_2+\sigma^{1/3})_x|\,|(v_1-v_2)|,$$

where the constants L, L_1, L_2 only depend on the sup norm of v_1 and v_2. We can now repeat the previous estimates by replacing $S[v](x,t)$ with $\{S[v_1] - S[v_2]\}(x,t)$ (note that $\{S[v_1] - S[v_2]\}(1,t) = 0$). Then, we get

$$\begin{aligned}\|\Theta S[v_1] - \Theta S[v_2]\|_{\mathcal{C}([0,t];H^1(0,1))} \le \big[&M_1\|v_1 - v_2\|_{L^2(0,t;H^1(0,1))} \\ &+ M_2\|v_1 - v_2\|_{\mathcal{C}([0,t];H^1(0,1))}\big]t^\delta,\end{aligned}$$

where the constants M_1, M_2 depend on the sup norm of v_1, v_2 and M_2 also on the $L^2(0,t;H^1(0,1))$ norm of v_2. Note that M_1, M_2 are also uniformly bounded whenever v_1, v_2 satisfy (6), (7) and (8). By the previous discussion and by the fixed point theorem, we conclude that for small enough $T > 0$ there exists a unique solution $v \in \mathcal{C}([0,T];H^1(0,1))$ of (9). Moreover, by computing the term by term time derivative of (15) and using again (17) in the estimate of the derivatives of (14), one can show that v is a *weak solution* of (5), in the sense that $v_t \in \mathcal{C}((0,T),V')$ (V' being the dual space of V) and

$$< v', w > + \alpha\int_0^1 v_x w_x dx = \int_0^1 \{\sigma - S[v]\}w dx$$

for every $w \in V$ and every time $0 < t \le T$, with $S[v]$ given by (10); by same bound (17) it also follows that v_x is continuous on $\overline{Q}_T$. Next, we are going to show that the solution v has further regularity.

3. *Improved regularity and global solution.*

In order to gain more regularity, it is convenient to exploit a known theorem for weak solutions of parabolic problems [4], Chap. 7, Thm. 5, which applies to v considered as a (weak) solution to the *linear* problem $v_t - \alpha v_{xx} = f(x,t)$, where $f = \sigma - S[v]$ and v is the previously obtained local solution. By the boundedness of f, the regularity theorem implies $v_t \in L^2((0,T);L^2(0,1))$; then, by direct computation we get $f_t = -S[v]_t \in L^2(0,T;L^2(0,1))$, so that we also have $v_t \in L^\infty((0,T);L^2(0,1))$ by the same theorem. Thus, by differentiating (13) we find that the term $|S_n'(\tau)|$ is *bounded* in $(0,T)$. Now, by writing the derivative of (14) in the form

$$\tilde{S}_n'(t) = e^{-\alpha\left(n+1/2\right)^2\pi^2 t} S_n(0) + \int_0^t e^{-\alpha\left(n+\frac{1}{2}\right)^2\pi^2(t-\tau)} S_n'(\tau)\, d\tau, \qquad (19)$$

the last term is uniformly bounded by $K_5 \|S_n'\|_{L^\infty(0,T)}/(n+1/2)^2$. As a consequence, for every $t \in (0,T]$ we can differentiate term by term with respect to t the series at the right side of (15) obtaining a *continuous function*, and further weakly differentiate with respect to x obtaining a function in $L^2(0,1)$; but the same is true for the function v_σ at the right side of (9), so that we conclude

$$v \in \mathcal{C}^1((0,T];H^1(0,1)).$$

Now, the solution v has *enough regularity* to apply the maximum principle of appendix 1; hence, by the a priori bounds (6), (7), (8), the estimates obtained for the local existence are uniform (independent of the solution) and global existence follows by standard arguments.

4. *Higher regularity.*

We first prove that $v_t \in \mathcal{C}(\overline{Q}_T)$; note that, by the initial condition, $s(\xi,0) = \sigma(\xi)$. Hence, by evaluating (13) at $\tau = 0$ and by explicit calculations, it follows that

$$2\sum_{n=0}^{\infty} S_n(0) e^{-\alpha\left(n+1/2\right)^2\pi^2 t} \cos\left[\left(n+\frac{1}{2}\right)\pi x\right] = \partial_t v_\sigma(x,t), \qquad \forall\, t > 0.$$

Thus, by differentiating (9) with respect to t and taking account of (15) and (19), we get

$$v_t(x,t) = 2\sum_{n=0}^{\infty}\Big[\int_0^t e^{-\alpha\left(n+\frac{1}{2}\right)^2\pi^2(t-\tau)} S_n'(\tau)\, d\tau\Big] \cos\left[\left(n+\frac{1}{2}\right)\pi x\right]. \qquad (20)$$

By the estimate following (19), the series (20) converges uniformly in $\overline{Q}_T$, defining a continuous function v_t, with $v_t(1,t) = 0$; hence, by equation (5) (in weak form) we also find that the second derivative v_{xx} is continuous and bounded in Q_T. Note further that $v_t(x,0) = 0$, so that, by the initial condition, we obtain the continuity of v_{xx} in $Q_T \cup C$.

We remark that the previous analysis also implies $v_t \in \mathcal{C}([0,T];H^1(0,1))$. By (10), *the same is true for* s_t, so that we may integrate by parts the expression

$S_n'(\tau) = \int_0^1 s_t(\xi,\tau)\cos\left[\left(n+\frac{1}{2}\right)\pi\xi\right]d\xi$, and by estimates similar to those of step 2 (see (16)-(18)) we finally obtain

$$\int_0^t e^{-\alpha\left(n+\frac{1}{2}\right)^2\pi^2(t-\tau)}S_n'(\tau)\,d\tau \le K_6\frac{\|s_t(1,\cdot)\|_{\mathcal{C}([0,T])}+\|s_{tx}\|_{\mathcal{C}([0,T];L^2(0,1))}}{\left(n+\frac{1}{2}\right)^3},$$

which proves the continuity of v_{tx} in $\overline{Q}_T$ (take the x derivatives of the terms in (20)); then, $v_{xt} = v_{tx}$.

By collecting the results proved so far, we conclude that $v_x \in W^{1,\infty}(Q_T)$; thus, v_x is *Lipschitz continuous* in $\overline{Q}_T$. Clearly, $v(x,t) = -\int_x^1 v_x(s,t)ds$ is also Lipschitz continuous; moreover, v_t and v_{xx} are continuous in Q_T and v solves problem (5) in the ordinary sense. By denoting as before with $f(x,t) = \sigma(x) - s(x,t)$ the right hand side of the equation in (5), we now have that f and f_x are Lipschitz functions in $\overline{Q}_T$, with $f(1,0) = 0$. By reflection about $x = 0$ and by the Neumann condition, we can take v as the solution of the Cauchy-Dirichlet problem

$$\begin{cases} v_t - \alpha v_{xx} = f(x,t) & -1 < x < 1,\ 0 < t < T \\ v(x,0) = 0 \\ v(-1,t) = v(1,t) = 0, \end{cases}$$

where $f(1,0) = f(-1,0) = 0$. We can now apply classical regularity results (interior and up to the boundary, see e.g., [8], chap. 3, sec. 5) to conclude that v_{xx}, v_{xxx}, v_t and v_{xt} are (Hölder) continuous in Q_T, uniformly in every domain whose closure is contained in $\overline{Q}_T\backslash\{(1,0)\}$. But this in turn implies that the same holds for f_t, f_{xx} and f_{xt}; thus, we further deduce that v_{tt} and v_{txx} are continuous in Q_T up to N and to $C \cup D\backslash\{(1,0)\}$.

Finally, uniqueness of the regular solution to problem (5) follows by the Lipschitz continuity of the map $v \mapsto S[v]$ (see [8], Chap. 7, Sect. 4). □

5. Numerical approximation of the problem

We briefly summarize here the numerical approximation techniques that have been applied in [1] to obtain the numerical simulations discussed throughout this work.

For simplicity, we refer to the following model problem

$$\begin{cases} u_t - \alpha u_{xx} = g(u) & -1 < x < 1,\ 0 < t < T \\ u(x,0) = u_0(x) & -1 < x < 1 \\ u(-1,t) = u(1,t) = 0 & 0 < t < T. \end{cases} \tag{21}$$

Due to the symmetry of the boundary conditions at $x = 0$ in (3), the restrictions to $(0,1)$ of (21) and (3) are equivalent.

We first discretize in space problem (21) by means of Lagrangian finite elements. Given a partition of $(-1,1)$ into equidistributed, non-overlapping

intervals $I_i,\ i = 1, \dots, N_h$ of length $h = 1/N_h$, we look for an approximate solution $u_h(x,t) \simeq u(x,t)$ such that

$$u_h(t) \in X^r_{h,0}(-1,1) = \big\{ v_h \in C^0([-1,1]) \ : v_h|_{I_i} \in \mathbb{P}^r(I_i),\ i = 1, \dots, N_h, \\ v_h(-1) = v_h(1) = 0 \big\},$$

$\mathbb{P}^r(I)$ being the space of polynomials of order $r \in \mathbb{N}$ on the interval I. Let $\{\varphi_i(x)\}_{i=1}^{N_h}$ be a Lagrangian basis of $X^r_{h,0}(-1,1)$, the problem to determine $u_h(t)$ is then equivalent to find a vector function $U(t) : (0,T) \to \mathbb{R}^{N_h}$ such that

$$\begin{cases} M\dot{U} + AU = G(U),\ 0 < t < T \\ U(0) = U_0, \end{cases} \tag{22}$$

where $U(t) = \{u_i(t)\}_{i=1}^{N_h}$ with $u_h(x,t) = \sum_{i=1}^{N_h} u_i(t)\varphi_i(x)$ and $M, A \in \mathbb{R}^{N_h \times N_h}$ are constant real matrices given by

$$M_{ij} = \int_{-1}^{1} \varphi_j \varphi_i dx, \quad A_{ij} = \alpha \int_{-1}^{1} \varphi_{x\,j} \varphi_{x\,i} dx$$

and $G(U) : \mathbb{R}^{N_h} \to \mathbb{R}^{N_h}$ is a nonlinear vector function such that

$$G_i(U) = \int_{-1}^{1} g(u_h)\varphi_i dx.$$

Provided that $u_0(x) \in L^2(-1,1)$, the initial state U_0 can be determined by projection, namely

$$U_0 = \{u_{h,0,i}\}_{i=1}^{N_h} \text{ with } \int_{-1}^{1} u_{h,0}\varphi_i dx = \int_{-1}^{1} u_0 \varphi_i dx,\ i = 1, \dots, N_h.$$

Problem (22) is called semi-discrete and is equivalent to a N_h-dimensional first-order Cauchy problem. We proceed with the time discretization of (22) by means of $(p+1)$-th order ($p = 0, 1, \dots, 5$) backward differentiation formulae (BDF). Given a sequence of equidistributed times t_n, characterized by a constant time step τ, we look for a sequence of vectors U_n such that

$$MU_{n+1} = M\Big(\sum_{j=0}^{p} a_j U_{n-j} \Big) + \tau b_{-1} \big(G(U_{n+1}) - AU_{n+1} \big) \tag{23}$$

where a_j, b_{-1} are constant coefficients that characterize this family of schemes and are uniquely determined by means of the constraints necessary to reach maximal order of accuracy. For further details we remand to [9].

Problem (23) requires to solve, at each time step, a N_h-dimensional system of nonlinear algebraic equations. Indeed, rearranging the terms of equation (23), we obtain $F(U_{n+1}) = 0$ where $F(V) : \mathbb{R}^{N_h} \to \mathbb{R}^{N_h}$ is

$$F(V) = \big(M + \tau b_{-1} A \big) V - \tau b_{-1} G(V) - M \sum_{j=0}^{p} a_j U_{n-j}.$$

The efficient solution of $F(V) = 0$ is not a trivial task. For this purpose, we apply the damped Newton method proposed in [3], which ensure robust and second-order convergence properties. For the sake of clarity, we briefly describe the damped Newton method below. Let $J_F(V)|_{ij} = \partial F_i/\partial V_j$ be the Jacobian matrix relative to $F(V)$. A straightforward computation shows that in our case

$$J_F(U) = \big(M + \tau b_{-1} A\big) - \tau b_{-1} J_G(U), \quad \text{with} \quad J_G(U)|_{ij} = \int_{-1}^{1} g'(u_h)\varphi_j\varphi_i dx.$$

Then, at the generic time step t_{n+1}, the solution of the problem $F(U_{n+1}) = 0$ is approximated by means of the following algorithm.

1. Define $V_0 = U_n$
2. Cycle for $k = 0, 1, 2, \ldots$
   - *a*) find W_{k+1} such that $J_F(V_k)W_{k+1} = -F(V_k)$
   - *b*) define $\lambda_0 = 1$ and E_0 such that $\|E_0\| = 1$
   - *c*) cycle for $m = 0, 1, 2, \ldots$
     1) compute $V_{m+1} = V_k + \lambda_m W_{k+1}$
     2) find E_{m+1} such that $J_F(V_k)E_{m+1} = -F(V_{m+1})$
     3) if $\|E_{m+1}\| \leq \min(\|E_m\|, tol)$ then go to (d)
        else reduce λ_m (e.g. $\lambda_{m+1} = \lambda_m/2$ and return to (i)
   - *d*) compute $V_{k+1} = V_k + \lambda_m W_{k+1}$
   - *e*) if $\|V_{k+1} - V_k\|/\|V_{k+1}\| \leq tol$ then go to (3)
     else return to (a)
3. Define $U_{n+1} = V_{k+1}$.

The damped Newton algorithm requires to solve at each iteration a linear system of equations defined by the matrix $J_F(V_k)$. This task is achieved by means of direct factorization methods, implemented in the library UMFPACK (see `http://www.cise.ufl.edu/research/sparse/umfpack`).

In order to verify if the numerical solution correctly captures the behavior of the problem at hand, we check that its sensitivity with respect to spatial and temporal resolution parameters, namely h and τ. Let us denote with $u_{h,1}(x,t)$ the numerical solution of (3) obtained by applying the present numerical scheme with linear finite elements ($r = 1$), a mesh characteristic size $h_1 = 1/120$ and a first order BDF scheme ($p = 0$, i.e. forward Euler) with a time step $\tau_1 = 10^{-3}$. Similarly, let $u_{h,2}(x,t)$ be the solution obtained by halving both h and τ, i.e. setting $h_2 = h_1/2$, $\tau_2 = \tau_1/2$. The numerical simulations obtained in the former case can be considered sufficiently accurate provided that the following test is satisfied with a sufficiently small tolerance,

$$\frac{\int_0^T \int_{-1}^1 \big(u_{h,1} - u_{h,2}\big)^2}{\int_0^T \int_{-1}^1 u_{h,1}^2} \leq \text{tol}$$

According to this criterion, the numerical results presented in the previous sections can be considered sufficiently accurate, because they satisfy the previous test with $\mathrm{tol} = 10^{-2}$.

A. A maximum principle

Lemma 4 *Let* $\gamma \in C\left([0,T];L^1(0,1)\right)$ *and let* $f \in C^1\left((0,T];H^1(0,1)\right) \cap C\left([0,T];L^2(0,1)\right)$ *satisfy*

$$\partial_t f - \partial_{xx} f + \gamma f \geq 0,$$

with initial condition $f(x,0) \geq 0$, *and boundary conditions* $\partial_x f(0,t) = 0$, $f(1,t) \geq 0$. *Then* $f(x,t) \geq 0$ *for every* t.

Proof. By assumption we can write $|\gamma(x,t)| \leq k + \gamma_1(x,t)$, where k is constant and $|\gamma_1|_1 < 1$. Let

$$\rho(t) = \frac{1}{2}\int_0^1 |f^-(x,t)|^2\,dx.$$

We obtain that $\rho \in C^1((0,T]) \cap C([0,T])$ and $\rho(0) = 0$. By testing the equation with f^- and integrating by parts we obtain

$$\begin{aligned}\rho'(t) &= -\int_0^1 f^-\partial_t f\,dx \leq -\int_0^1 \left(f^-\partial_{xx} f + \gamma|f^-|^2\right)\,dx \\ &\leq -|\partial_x f^-|_2^2 + k|f^-|_2^2 + |\gamma_1|_1|f^-|_\infty^2 \leq (-1+|\gamma_1|_1)\,|\partial_x f^-|_2^2 + k|f^-|_2^2 \\ &\leq 2k\rho(t)\end{aligned}$$

(recall that, since $f^-(1,t) = 0$, $|f^-|_\infty \leq |\partial_x f^-|_2$ for any t). Then we deduce that $\rho(t) \leq e^{2kt}\rho(0)$ and the lemma follows. □

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References

[1] P. Biscari, S. Minisini, D. Pierotti, G. Verzini and P. Zunino: *Controlled release with finite dissolution rate*, to appear on SIAM J. Appl. Math.

[2] J.R. Cannon: *The one-dimensional heat equation*, Addison-Wesley Pub. Co. (Reading, Ma.), 1984.

[3] P. Deuflhard: *A modified Newton method for the solution of ill-conditioned systems of nonlinear equations with application to multiple shooting*, Numer. Math. **22** (1974), 289-315.

[4] L.C. Evans: *Partial differential equations*, (Graduate Studies in Mathematics **19**, AMS) 1998.

[5] L. Formaggia, S. Minisini, and P. Zunino: *Modeling erosion controlled drug release and transport phenomena in the arterial tissue*, Math. Mod. Meth. Appl. Sci. **20** (2010), 1759-1786.

[6] G. Frenning: *Theoretical investigation of drug release from planar matrix systems: effects of a finite dissolution rate*, J. Control. Release **92** (2003), 331-339.

[7] G. Frenning: *Theoretical analysis of the release of slowly dissolving drugs from spherical matrix systems*, J. Control. Release **95** (2004) 109-117.

[8] A. Friedman: *Partial differential equations of parabolic type*, Prentice-Hall, Inc. (Englewood Cliffs, N.J.) 1964.

[9] E. Hairer and G. Wanner: *Solving ordinary differential equations II*, Springer Series in Computational Mathematics **14**, Springer-Verlag, Berlin, 2nd ed., 1996.

[10] T. Higuchi: *Rate of release of medicaments from ointment bases containing drugs in suspension*, J. Pharm. Sci. **50** (1961), 874-875.

[11] T. Higuchi: *Mechanisms of sustained action medication: theoretical analysis of the rate of release of solid drugs dispersed in solid matrices*, J. Pharm. Sci. **52** (1963), 1145-1149.

[12] R. Langer: *New methods of drug delivery*, Science **249** (1990), 1527-1533.

[13] P. Macheras and A. Iliadis: *Modeling in biopharmaceutics, pharmacokinetics, and pharmacodynamics*, Interdisciplinary Applied Mathematics **30**, Springer, New York, 2006.

[14] S.N. Rothstein, W.J. Federspiel, and S.R. Little: *A unified mathematical model for the prediction of controlled release from surface and bulk eroding polymer matrices*, Biomaterials **30** (2009), 1657-1664.

[15] J.S. Soares and P. Zunino: *A mixture model for water uptake, degradation, erosion and drug release from polydisperse polymeric networks*, Biomaterials **31** (2010), 3032-3042.