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A numerical scheme for a model of drug delivery enhanced by light

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Abstract: In this paper, we study a numerical scheme for a nonlinear system of partial differential equations arising from the mathematical modeling of drug delivery enhanced by light. The system consists of diffusion-reaction equations for drug concentration and a diffusion equation for light propagation. Suitable initial conditions and Neumann-Dirichlet boundary conditions close the system. We establish that the numerical scheme is second-order supraconvergent in space in a discrete H^1-norm and first-order convergent in time in a discrete L^2-norm. Numerical experiments illustrate our convergence results.

keywords: Finite difference method; supraconvergence; drug delivery; numerical simulation.

MSC2020: 49-XX; 34-XX; 92-XX.

1 Introduction

In this paper we study a numerical scheme for the system of partial differential equations (1)-(3) where $D_I, D_d : \mathbb{R} \to \mathbb{R}$ are appropriate functions and $x \in \Omega$, $t \in (0, T]$. Let Ω be the set $\Omega = (0,1)^2$. We denote the boundary of Ω by the union of its edges: $\partial\Omega = \bigcup \Gamma_i, i = l, u, r, d$ (edges left, up, right and down). To complete our problem, we impose the initial and boundary conditions (4)-(6).

$$\begin{cases} \dfrac{1}{\beta}\dfrac{\partial I}{\partial t} = \nabla\cdot(D_I \nabla I) - \mu_a I, & (1) \\ \dfrac{\partial c_f}{\partial t} = \nabla\cdot(D_d \nabla c_f) + \gamma c_b I, & (2) \\ \dfrac{\partial c_b}{\partial t} = -\gamma c_b I, & (3) \end{cases}$$

$$\begin{aligned} I(x,0) &= 0, \quad c_f(x,0) = 0, \\ c_b(x,0) &= c_{b,0}(x), \ \ x \in \Omega, \end{aligned} \quad (4)$$

$$\begin{aligned} I(x,t) &= I_0(t), x \in \Gamma_l, t \in (0,T], \\ \nabla I(x,t)\cdot\eta &= 0, x \in \partial\Omega - \Gamma_l, t \in (0,T], \end{aligned} \quad (5)$$

$$\begin{aligned} \nabla c_f(x,t)\cdot\eta &= 0, x \in \partial\Omega - \Gamma_r, t \in (0,T], \\ c_f(x,t) &= 0, x \in \Gamma_r, \ t \in (0,T]. \end{aligned} \quad (6)$$

Drug delivery systems (DDS) have great potential for cancer treatment, in particular, those DDS that use near-infrared (NIR) light as an external stimuli to induce the drug release, since they allow not only spatio-temporal control of the drug but better penetretion in tissue [1]. We propose the model (1)-(6) to approximate the drug delivery dynamics from a polymeric matrix when light is used as enhancer. In equation (1), I is the light intensity. It is well known that light propagation through a scattering and absorbing medium can be described by the radiative

transfer equation (RTE) [3]. Depending on the magnitude of the absorption and scattering coefficients, μ_a and μ_s, respectively, different approaches can be considered to approximate the RTE. Following [2], we use the diffusion equation for light intensity (1), where D_I is the traditional light diffusion coefficient $D_I = 1/(3(\mu_a+\mu_s))$, term $\mu_a I$ symbolize the absorption of light and β is the speed of light in the medium.
It is assumed that drug molecules are initially linked to the polymeric chains and the links are broken due to energy absorption, that is, the cleavage of the links occur by light irradiation. Equation (2) approximates the dynamics of the free drug c_f and the function $\gamma c_b I$ represent conversion percentages of bound drug c_b into free drug that is allowed to be transported through the polymeric structure by diffusion. In (5) and (6), η denotes the unitary exterior normal.

Suppose that the diffusion coefficients in (1) and (2) are bounded from below by a constant and are Lipschitz with Lipschitz constant L, i.e

$$D_{\rho,ii} \geq D_0 > 0 \quad \text{and} \quad |D_{\rho,ii}(x) - D_{\rho,ii}(\tilde{x})| \leq L|x-\tilde{x}|,\, x,\tilde{x}\in\mathbb{R}, i=1,2, \rho = I,d.$$

Let Λ be a sequence of vectors $H = (h,k)$ with $h = (h_1,\ldots,h_{N_1})$, $k=(k_1,\ldots,k_{N_2})$ with positive entries, such that $\sum_{i=1}^{N_1} h_i = \sum_{i=1}^{N_2} k_i = 1$, with $H_{max} = \max\{h_{max}, k_{max}\} \to 0$, where $h_{max} = \max_{i=1,\ldots,N_1} h_i$ and $k_{max} = \max_{i=1,\ldots,N_2} k_i$.

Let $\overline{\Omega}_H$ be a non-uniform partition of $\overline{\Omega}$ such that $\overline{\Omega}_H = \{(x_i,y_j), i=0,\ldots,N_1, j=0,\ldots,N_2\}$, where $x_i = x_{i-1}+h_i, i=1,\ldots,N_1, y_j = y_{j-1}+k_j, j=1,\cdots,N_2$, and and let $\Omega_H = \overline{\Omega}_H\cap\Omega$, $\partial\Omega_H = \overline{\Omega}_H \cap \partial\Omega$, and $\Gamma_{i,H} = \Omega_i \cap \partial\Omega_H, i=l,u,r,d$.

We introduce the finite difference operators $D_{\text{-}x} u_H(x_i,y_j) = \frac{u_H(x_i,y_j)-u_H(x_{i-1},y_j)}{h_i}$, $D_x^* u_H(x_i,y_j) = \frac{u_H(x_{i+1},y_j)-u_H(x_i,y_j)}{h_{i+\frac{1}{2}}}$, where $h_{i+\frac{1}{2}} = \frac{1}{2}(h_{i+1}+h_i)$, and the operators $\nabla_H u_H = (D_{\text{-}x}u_H, D_{\text{-}y}u_H)$, $\nabla_H^* u_H = (D_x^* u_H, D_y^* u_H)$, where $D_{\text{-}y}$ and D_y^* are the finite difference operators defined analogously to $D_{\text{-}x}$ and D_x^*.

In $W(\overline{\Omega}_H)$ we consider the following inner product $(u_H,v_H)_H = \sum_{(x_i,y_j)\in\overline{\Omega}_H} |\square_{ij}| u_H(x_i,y_j) v_H(x_i,y_j)$, where $\square_{ij} = [x_{i-\frac{1}{2}}, x_{i+\frac{1}{2}}] \times [y_{j-\frac{1}{2}}, y_{j+\frac{1}{2}}] \cap \overline{\Omega}$, and $u_H, v_H \in W(\overline{\Omega}_H)$. The norm induced by this inner product is denoted by $\|\cdot\|_H$.

We also use the notations $(u_H,v_H)_{x,+} = \sum_{(x_i,y_j)\in\overline{\Omega}_H-\Gamma_{l,H}} |\square_{x,ij}| u_H(x_i,y_j)v_H(x_i,y_j)$, $\|u_H\|_{x,+} = \sqrt{(u_H,u_H)_{x,+}}$, where $\square_{x,ij} = [x_{i-1},x_i]\times[y_{j-\frac{1}{2}}, y_{j+\frac{1}{2}}]\cap\overline{\Omega}$, and $u_H,v_H \in W(\overline{\Omega}_H - \Gamma_{l,H})$. Analogously, we define the notations $(u_H,v_H)_{y,+}$ and $\|u_H\|_{y,+}$ where $u_H, v_H\in W(\overline{\Omega}_H - \Gamma_{d,H})$.

For $u_H = (u_{H,1},u_{H,2}), v_H = (v_{H,1}, v_{H,2})$, where $u_{H,1}, v_{H,1} \in W(\overline{\Omega}_H - \Gamma_{l,H})$, $u_{H,2}, v_{H,2} \in W(\overline{\Omega}_H - \Gamma_{d,H})$, we take $(u_H,v_H)_{H,+} = (u_{H,1},v_{H,1})_{x,+} + (u_{H,2},v_{H,2})_{y,+}$ and $\|u_H\|_+ = \sqrt{(u_H,u_H)_{H,+}}$.
The diffusion coefficients D_I and D_d are diagonal matrices with entries $D_{I,ii}, D_{d,ii}$, for $i=1,2$. We take D_d as a function of c_f, then, to approximate this nonlinear coefficient we use the average operators $M_h u_H(x_i,y_j) = \frac{1}{2}\big(u_H(x_i,y_j)+u_H(x_{i-1},y_j)\big)$, being M_k defined analogously. By $D_d(M_H u_H)$ we denote the diagonal matrix with diagonal entries $D_{d,11}(M_h u_H)$ and $D_{d,22}(M_k u_H)$.

To discretize the light intensity equation (1) and the boundary conditions (5) we need to consider the auxiliary point $x_{N_1+1} = x_{N_1} + h_{N_1}$, $y_{N_2+1} = y_{N_2}+k_{N_2}$ and $y_{-1} = -y_1$ and the fictitious points $\Gamma_{i,H}^{(I)}$, for $i=d,u,r$, see (7). Similarly, to discretize the free drug concentration equation (2) and the boundary condition (6) we need to introduce the auxiliary point $x_{-1} = -x_1$ and the fictitious points $\Gamma_{i,H}^{(c)}$, for $i=l,d,u$.

$$\begin{array}{ll} \Gamma_{d,H}^{(I)} = \{(x_i,y_{-1}), i=1,\ldots,N_1\}, & \Gamma_{l,H}^{(c)} = \{(x_{-1},y_j), j=0,\ldots,N_2\}, \\ \Gamma_{u,H}^{(I)} = \{(x_i,y_{N_2+1}), i=1,\ldots,N_1\}, & \Gamma_{d,H}^{(c)} = \{(x_i,y_{-1}), i=0,\ldots,N_1-1\}, \\ \Gamma_{r,H}^{(I)} = \{(x_{N_1+1},y_j), j=0,\ldots,N_2\}, & \Gamma_{u,H}^{(c)} = \{(x_i,y_{N_2+1}), i=0,\ldots,N_1-1\}. \end{array} \tag{7}$$

Let $W^*_{I,H}$ and $W^*_{c,H}$ be the space of grid functions defined in $\overline{\Omega}_H \cup (\cup_{i=d,r,u}\Gamma^{(I)}_{i,H})$ and $\overline{\Omega}_H \cup (\cup_{i=l,d,u}\Gamma^{(c)}_{i,H})$, respectively. Moreover, let $W_b(\overline{\Omega}-\Gamma_{r,H})$ be the space of grid functions defined in $\overline{\Omega}-\Gamma_{r,H}$.

2 Results and discussion

In the time domain $[0,T]$ we define the uniform grid $\{t_m, m=0,\cdots,M\}$, with $t_0=0$, $t_M=1$ and $t_{m+1}=t_m+\Delta t$, for $m=0,\cdots,M-1$.

We consider that the fully-discrete approximation $I^m_H \in W^*_{I,H}$, $c^m_{f,H} \in W^*_{c,H}$, $c^m_{b,H} \in W_b(\overline{\Omega}_H - \Gamma_{r,H})$ are solution of the system

$$\begin{cases} D_{\text{-}t}I^m_H = \nabla^*_H \cdot ((D_I(M_H I^m_H)\nabla_H I^{m+1}_H)) + G(I^m_H) & \text{in } \overline{\Omega}_H - \Gamma_{l,H} \quad (8)\\ D_{\text{-}t}c^m_{f,H} = \nabla^*_H \cdot ((D_d(M_H c^m_{f,H})\nabla_H c^{m+1}_{f,h})) + F(I^m_H, c^m_{f,H}, c^m_{b,H}) & \text{in } \overline{\Omega}_H - \Gamma_{r,H} \quad (9)\\ D_{\text{-}t}c^m_{b,H} = S(I^m_H, c^m_{f,H}, c^m_{b,H}) & \text{in } \overline{\Omega}_H - \Gamma_{r,H} \quad (10)\end{cases}$$

$$\text{with} \quad \begin{aligned} I_H(t_m) &= R_H I_i(t_m) \text{ on } \partial\Omega_{l,H},\ \nabla^{(I)}_H I_H(t_m)\cdot\eta = 0 \text{ on } (\partial\Omega_H - \Gamma_{l,H}) \times (0,T],\\ c_{f,H}(t_m) &= 0 \text{ on } \Gamma_{r,H}\times(0,T],\ \nabla^{(c)}_H c_{f,H}(t_m)\cdot\eta = 0 \text{ on } (\partial\Omega_H - \Gamma_{r,H})\times(0,T].\end{aligned} \quad (11)$$

Define $D^{(I)}_{\eta_x}u_H(x_i,y_j) = \frac{1}{2}\big(D_{I,11}(M_h u_H(x_{i+1},y_j))D_{\text{-}x}u_H(x_{i+1},y_j) + D_{I,11}(M_h u_H(x_i,y_j))D_{\text{-}x}u_H(x_i,y_j)\big)$, for $(x_i,y_j)\in\Gamma_{r,H}$ and $D^{(I)}_{\eta_x}u_H(x_i,y_j)=0$, for $(x_i,y_j)\in\partial\Omega_H-\Gamma_{r,H}$.

Similarly $D^{(I)}_{\eta_y}u_H(x_i,y_j) = \frac{1}{2}\big(D_{I,22}(M_k u_H(x_i,y_{j+1}))D_{-y}u_H(x_i,y_{j+1}) + D_{I,22}(M_k u_H(x_i,y_j))D_{-y}u_H(x_i,y_j)\big)$, for $(x_i,y_j)\in\Gamma_{u,H}\cup\Gamma_{d,H}$ and $D^{(I)}_{\eta_y}u_H(x_i,y_j)=0$, for $(x_i,y_j)\in\partial\Omega_H-(\Gamma_{u,H}\cup\Gamma_{d,H})$.

The boundary operators $D^{(c)}_{\eta_x}$ and $D^{(c)}_{\eta_y}$ are defined analogously. Let $\nabla^{(j)}_{H,\eta}$ be defined by $\nabla^{(j)}_{H,\eta} = (D^{(j)}_{\eta_x}, D^{(j)}_{\eta_y})$, for $j=I,c$.

Notice that system (8)-(11) is an IMEX (implicit-explicit) scheme. In example 1, we illustrate numerically the convergence rates in time and space for $c_{f,H}$ and $c_{b,H}$, however, we remark that I_H behaves in the same manner. Example 2 shows the numerical solution of c_f for different values of $I_0(t)$ in the system (1)-(6) as well as the release rate of c_f.

Example 1 *Let* $\overline{\Omega}=[0,1]\times[0,1]$ *and* $t\in[0,1]$*. In system* (1)-(3) *we consider the functions with* $D_I(c_f)=0.5\beta$, $D_d(c_f)=1+c_f^2$*. We set the parameters* β,γ *and* μ_a *equal to* 1.

The functions $g_I(x,t)$, $g_f(x,t)$ *and* $g_b(x,t)$ *were added to the right hand side of equations* (1), (2) *and* (3)*, respectively, such that, the exact solution of the problem is* $I(x,t)=\exp(t)\sin(xy)(x-1)(y-1)$, $c_f(x,t)=\exp(t)(x^2-x)(y^2-y)$ *and* $c_b(x,t)=\exp(t)x\cos(xy)$*. We solved this example using the IMEX scheme* (8)-(10).

For the approximations $c_{f,H}$ and $c_{b,H}$, define the numerical error on a random mesh H, respectively as $\text{Error}^2_{f,H} = \max_{m=1,\ldots,M}\|E^m_{f,H}\|^2_h + \Delta t\sum_{k=1}^m \|D_{\text{-}x}E^m_{f,H}\|^2_+$ and $\text{Error}^2_{b,H} = \max_{m=1,\ldots,M}\|E^m_{b,H}\|^2_h$.

The numerical rate of convergence for $c_{f,H}$ is given by $\text{Rate}_{f,H} = \log_2\left(\dfrac{\text{Error}_{f,H}}{\text{Error}_{f,\frac{H}{2}}}\right)$, where $\frac{H}{2}$ denotes the mesh obtained by halving the step sizes of the mesh H. The time step is chosen small enough (of the order of H^2_{max}) so that the spatial error dominates the time error. The results are presented in table 1.

T	Δt	Error$_{\Delta t,f}$	Rate$_{\Delta t,f}$	Error$_{\Delta t,b}$	Rate$_{\Delta t,b}$
4	$\times 10^{-2}$	1.3384×10^{-2}	–	6.8469×10^{-3}	–
8	$\times 10^{-3}$	3.8365×10^{-3}	0.9013	1.4678×10^{-3}	1.1109
16	$\times 10^{-3}$	1.0211×10^{-3}	0.9548	3.3167×10^{-4}	1.0729
32	$\times 10^{-4}$	2.6236×10^{-4}	0.9802	7.7990×10^{-5}	1.0442
64	$\times 10^{-5}$	6.6167×10^{-5}	0.9936	1.8721×10^{-5}	1.0293

M	N_1	N_2	H_{max}	Error$_{f,H}$	Rate$_{f,H}$	Error$_{b,H}$	Rate$_{b,H}$
82	12	12	1.1039×10^{-1}	7.2627×10^{-5}	-	1.2644×10^{-5}	-
328	24	24	5.5195×10^{-2}	2.7008×10^{-6}	2.3745	5.6640×10^{-7}	2.2402
1312	48	48	2.7598×10^{-2}	1.6714×10^{-7}	2.0071	3.8612×10^{-8}	1.9374
5251	96	96	1.3799×10^{-2}	1.0367×10^{-8}	2.0055	2.5305×10^{-9}	1.9658
21007	192	192	6.8994×10^{-3}	6.4455×10^{-10}	2.0038	1.6203×10^{-10}	1.9826
84030	384	384	3.4497×10^{-3}	4.0165×10^{-11}	2.0021	1.0251×10^{-11}	1.9912

Table 1: Time errors (on the left) for c_f and c_b. Space errors and convergence rates for c_f and c_b (on the right).

Example 2 *This example illustrate the behavior of the drug delivery system in the domain* $\Omega \times [0, T]$. *The initial conditions are* $c_b(x, 0) = 1$ *for* $0 \leq x \leq 0.25$, $c_b(x, 0) = 0$ *for* $x \geq 0.25$ *and* $c_f(x, 0) = 0$, $I(x, 0) = 0$ *for* $x \in \Omega$. *In figure 1, the values of* c_f *are plotted for different values of* $I(x, t) = I_0(t)$, $x \in \Gamma_l$, $t \in [0, T]$, *with* $T = 60s$. *Figure 2 shows the* c_f *release rate for a bigger time domain with* $T = 3600s$. *For both figures the parameters values are* $\beta = 2.0689 \times 10^{10} cm/s$, $\mu_a = 4cm^{-1}$, $\mu_s = 13cm^{-1}$, $D_I = 1/(3(mu + mu_s))$, $D_d = 4 \times 10^{-4} cm^2/s$.

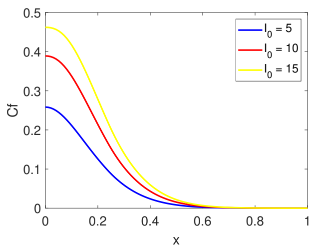

Figure 1: Free drug c_f for diferent I_0 values

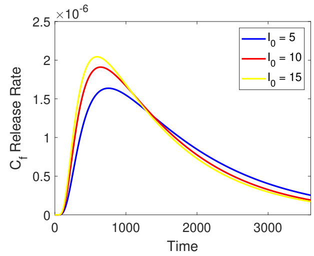

Figure 2: c_f release rate for $T = 1h$.

3 Conclusions and Future work

We consider an IMEX time scheme combined with a nonuniform finite difference method for a non-linear system modeling light-enhanced drug delivery. We state and numerically illustrate that our method is first-order convergent in time and exhibits supraconvergence in space. By supraconvergence, we mean that the error is second-order convergent in a discrete H^1-norm despite the truncation error being first order in the L^∞-norm.

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