XLIII CILAMCE
21-25, November, 2022
FOZ DO IGUAÇU - PR - BRAZIL

Verification of the order of accuracy of the discretization error in the simulation of tumor growth

Jesika Maganin[1], Marcio Augusto Villela Pinto[2], Neyva Maria Lopes Romeiro[3]

[1]*Graduate Program in Numerical Methods in Engineering, Federal University of Paraná*
Centro Politécnico, Jardim das Américas, 81531-980, Curitiba, PR, Brazil
jesikamaganin@ufpr.br
[2]*Department of Mechanical Engineering, Federal University of Paraná*
Bloco IV do Setor de Tecnologia, Centro Politécnico, Jardim das Américas, 81531-980, Curitiba, PR, Brazil
marcio_villela@ufpr.br
[3]*Department of Mathematics, State University of Londrina*
Rodovia Celso Garcia Cid — PR 445 Km 380, 86.057-970, Londrina, PR, Brazil
nromeiro@uel.br

Abstract. In Engineering there are several problems to be studied, such as applications in biomedicine, which are typical problems in Computational Fluid Dynamics (CFD). To solve these problems, numerical methods are used regardless of complexity, geometry, physical parameters, boundary and initial conditions. Linear or nonlinear models can be considered to assess both temporal and spatial evolution. However, one of the main disadvantages of numerical methods is the determination of computational errors associated with their use, in which numerical solutions can be affected by truncation, iteration, rounding, and programming errors. Although numerical errors cannot be eliminated, they must be controlled or minimized. The discretization error is considered the most significant among the sources of numerical error, requiring its analysis. Therefore, this work aims to verify the accuracy of the discretization error of a one-dimensional model of tumour growth, using *a priori* and *a posteriori* estimates of numerical solutions. We predict the asymptotic behaviour of the discretization error in the *a priori* estimation. We estimate the magnitude of the error based on multiple meshes using the Richardson estimator in the *a posteriori* estimation. The model used in this work is described by a system of partial differential equations in a transient regime, with four variables involved in the process of tumour cell invasion, resulting in the description and evolution of cancer cell density, extracellular matrix (ECM) density, the concentration of matrix degradative enzymes (MDE) and tissue inhibitors of metalloproteinases (TIMP). To discretize the mathematical model, we used the finite difference method with Central Difference Scheme (CDS) for spatial discretization and the Crank-Nicolson method for temporal discretization. The nonlinear terms involved in the model were linearized by applying the Taylor series expansion. To advance in time, this discretization procedure results in the resolution of a set of algebraic equations to be solved with the aid of the iterative Gauss-Seidel method. The simulations are performed with Dirichlet boundary conditions. We use the manufactured solutions method for code verification and error analysis.

Keywords: Error analysis, Mathematical model, Numerical simulations.

1 Introduction

Mathematical models in Computational Fluid Dynamics (CFD) require using methods that provide accurate and reliable numerical solutions. As some of these models do not present a known analytical solution, we used numerical approximations to transform the continuous model into a discrete one. A widely used discretization method is the finite difference method (FDM). [1, 2].

The discretization of differential equations, using FDM, results in a system of algebraic equations whose resolution uses iterative methods, such as Gauss-Seidel. However, solutions can be affected by numerical errors. In this context, numerical verification procedures are addressed with the aim to identify the extent to which a mathematical model is adequately solved using a numerical method [3].

The main interest is the quantification of the numerical error (E) and the determination of its order of accuracy. Among the sources of error, the one resulting from discretization methods, or discretization error (Eh), was considered the most significant. As it is not always possible to obtain the analytical solution, we needed an estimate (Uh) for the Eh involved [3].

In this sense, verifying the order of accuracy of the numerical solution is the objective in this work. For that, two methods are discussed: error estimation *a priori* and error estimation *a posteriori*.

The *a priori* estimate of the order of accuracy we performed by deducing the asymptotic order based on the Taylor series. We used such an approach to verify the order of accuracy of numerical solutions effectively. To estimate *a posteriori* the magnitude of the order of discretization error, the Richardson error estimator was used.

In this article, we work with a continuous model of avascular tumour growth. Such a model was proposed by Anderson et al. [4], investigated and improved by Chaplain et al. [5] and Kolev and Zubik-Kowal [6]. However, in none of these works error analysis was performed, nor was the order of accuracy verified for the discretization error.

The model used in this work is composed of four partial differential equations (PDEs) and presents nonlinear terms. Such a model we discretized by the FDM with CDS in space and the Crank-Nicolson method for the time. We linearised the nonlinear terms by applying Taylor series expansion and used the Manufactured Solutions Method (MSM) for code verification and error analysis.

2 Mathematical model

The mathematical model developed in Kolev and Zubik-Kowal [6] describes the growth of generic solid tumours in the avascular stage, intending to analyze the interactions between the tumour and the surrounding tissue. The model presents four PDEs with the variables: density of cancer cells, the density of the extracellular matrix (ECM), the concentration of matrix-degrading enzymes (MDE) and the concentration of tissue inhibitors of metalloproteinases (TIMP) (known as endogenous inhibitor), denoted by n, f, m and u, respectively.

Considering the one-dimensional evolution, that is, $x \in \mathbb{R}$ and $t \in (0, t_f]$, the model is given by

$$\frac{\partial n}{\partial t} = \underbrace{d_n \nabla^2 n}_{\text{diffusion}} - \underbrace{\gamma \nabla.(n \nabla f)}_{\text{haptotaxis}} + \underbrace{\mu_1 n(1-n-f)}_{\text{proliferation}}, \tag{1}$$

$$\frac{\partial f}{\partial t} = - \underbrace{\eta m f}_{\text{degradation}} + \underbrace{\mu_2 f(1-n-f)}_{\text{renovation}}, \tag{2}$$

$$\frac{\partial m}{\partial t} = \underbrace{d_m \nabla^2 m}_{\text{diffusion}} + \underbrace{\alpha n}_{\text{production}} - \underbrace{\theta u m}_{\text{neutralization}} - \underbrace{\beta m}_{\text{decay}}, \tag{3}$$

$$\frac{\partial u}{\partial t} = \underbrace{d_u \nabla^2 u}_{\text{diffusion}} + \underbrace{\xi f}_{\text{inhibits production}} - \underbrace{\theta u m}_{\text{neutralization}} - \underbrace{\rho u}_{\text{decay}}. \tag{4}$$

Furthermore, the model establishes that the migration of tumour cells creates spatial gradients that direct the migration of invasive cells by a mechanism called haptotaxis, represented by γ. The constants d_n, d_m and d_u are the diffusion constants for the density of cancer cells, MDE and inhibitor, respectively. The tumor cell proliferation rate and the ECM growth rate are represented by μ_1 and μ_2, while η, α, θ, β, ξ and ρ are positive constants and their values can be seen in [7, 8].

In order to find an analytical solution to verify the code and perform the error analysis, we use the MSM. Manufactured solutions are exact solutions to a set of equations that have been modified with mandatory terms [9].

Thus, rewriting the Eqs. (1)-(4), coupled with the source terms, we have

$$\frac{\partial n}{\partial t} - d_n \Delta n + \gamma \nabla.(n \nabla f) - \mu_1 n(1-n-f) = f_n, \tag{5}$$

$$\frac{\partial f}{\partial t} + \eta m f - \mu_2 f(1-n-f) = f_f, \tag{6}$$

$$\frac{\partial m}{\partial t} - d_m \Delta m - \alpha n + \theta u m + \beta m = f_m, \tag{7}$$

$$\frac{\partial u}{\partial t} - d_u \Delta u - \xi f + \theta u m + \rho u = f_u. \tag{8}$$

The source terms f_n, f_f, f_m and f_u are obtained so that the Eqs.(5)-(8) satisfy the analytical solutions $n(x,t) =$

$m(x,t) = u(x,t) = e^t \sin(2\pi x)$ and $f(x,t) = e^{-t}\sin(2\pi x)$, given in [10]. Initial and boundary conditions are obtained using the analytical solutions.

3 Numerical Model

The solution of the mathematical model of interest, Eqs. (1) - (4), we obtain through the numerical approximation in each of its terms, using the FDM. The spatial terms of (1)-(4) were discretized using CDS. To discretize the temporal terms, we used the Crank-Nicolson method.

Applying the operators correctly and remembering that we are working with the one-dimensional model, we can rewrite Eq. (1), the equation referring to the variable n, as

$$\frac{\partial n}{\partial t} = d_n \frac{\partial^2 n}{\partial x^2} - \gamma\left(\frac{\partial n}{\partial x}\frac{\partial f}{\partial x} + n\frac{\partial f}{\partial x^2}\right) + \mu_1 n(1-n-f). \tag{9}$$

Considering one-dimensional problems, the domain $x \in \mathbb{R} : 0 \leq x \leq 1$ is partitioned into N_x points in the coordinate direction x creating a mesh with the points $x_i = (i-1)h_x$, where $i = 1, \ldots, N_x$ and $h_x = 1/(N_x - 1)$ is the length of each interval. We also consider $h_t = t_f/N_t$, where N_t is the number of steps in time. Approaching Eq. (9) using explicit method in time and CDS in space, at point i, at time level k we have:

$$\begin{aligned}\frac{N_i^{k+1} - N_i^k}{h_t} = d_n\left(\frac{N_{i-1}^k - 2N_i^k + N_{i+1}^k}{h_x^2}\right) - \gamma\left(\frac{N_{i+1}^k - N_{i-1}^k}{2h_x}\frac{F_{i+1}^k - F_{i-1}^k}{2h_x} + n\frac{F_{i-1}^k - 2F_i^k + F_{i+1}^k}{h_x^2}\right)\\ +\mu_1 N_i^k - \mu_1 (N_i^k)^2 - \mu_1 N_i^k F_i^k,\end{aligned} \tag{10}$$

where N and F are approximations for the variables n and f. Approaching Eq. (9) using time-implicit method and CDS in space, at point i, at time level $k+1$ we have:

$$\begin{aligned}\frac{N_i^{k+1} - N_i^k}{h_t} = d_n\left(\frac{N_{i-1}^{k+1} - 2N_i^{k+1} + N_{i+1}^{k+1}}{h_x^2}\right) - \gamma\left(\frac{N_{i+1}^{k+1} - N_{i-1}^{k+1}}{2h_x}\frac{F_{i+1}^{k+1} - F_{i-1}^{k+1}}{2h_x} + n\frac{F_{i-1}^{k+1} - 2F_i^{k+1} + F_{i+1}^{k+1}}{h_x^2}\right)\\ +\mu_1 N_i^{k+1} - \mu_1 (N^2)_i^{k+1} - \mu_1 N_i^{k+1} F_i^{k+1}.\end{aligned} \tag{11}$$

We can see that in Eq. (11) there is a quadratic term, which can be linearized using Taylor series expansion [8, 11]

$$(N^2)_i^{k+1} \simeq -(N^2)_i^k + 2N_i^k N_i^{k+1}. \tag{12}$$

Computing the average between the equations (10) and (11) we have the Crank-Nicolson method. In order to simplify the notation, the points of the computational mesh are labeled so that $P = (i,k)$, $E = (i+1,k)$, $W = (i-1,k)$, $P1 = (i,k+1)$, $E1 = (i+1,k+1)$ and $W1 = (i-1,k+1)$. Using the Crank-Nicolson method and the quadratic term of the Eq. (11) being linearized by (12), we can rewrite our system as

$$N_{P1} = \frac{a_P N_P + a_E N_E + a_W N_W + a_{E1} N_{E1} + a_{W1} N_{W1}}{a_{P1}}, \tag{13}$$

where,

$$a_{P1} = -2\mu_1 N_i^k + (\frac{2\gamma}{h^2} - \mu)F_i^{k+1} - \frac{2}{h_t} - \frac{\gamma(F_{i+1}^{k+1} + F_{i-1}^{k+1})}{h_x^2} + \mu - \frac{2d_n}{h_x^2},$$
$$a_P = \frac{2}{h_t} - \frac{2d_n}{h_x^2} - \frac{\gamma(F_{i+1}^k - F_i^k + F_{i-1}^k)}{h_x^2} + \mu(1 - F_i^k),$$
$$a_E = -\frac{\gamma}{4h_x^2}(F_{i+1}^k - F_{i-1}^k) + \frac{2d_n}{h_x^2},$$
$$a_W = \frac{d_n}{h_x^2} + \frac{\gamma}{4h_x^2}(F_{i+1}^k - F_{i-1}^k),$$
$$a_{E1} = -\frac{\gamma}{4h_x^2}(F_{i+1}^{k+1} - F_{i-1}^{k+1}) + \frac{d_n}{h_x^2},$$
$$a_{W1} = \frac{\gamma}{4h_x^2}(F_{i+1}^{k+1} - F_{i-1}^{k+1}) + \frac{d_n}{h_x^2}.$$

The discretizations of the variables f, m and u are made analogously.

4 Numerical verification

The objective of numerical verification is to determine the extent to which a mathematical model is adequately solved using a numerical method. A challenge in simulation is the level of accuracy. Although numerical errors from simulations cannot be eliminated, they must be controlled or minimized.

The numerical error (E) can be defined as the difference between the analytical solution (Φ) of a variable of interest and its numerical solution (ϕ). Among the sources of numerical error, the discretization error (Eh) is the most significant [11] and can be defined by

$$Eh = c_0 h^{p0} + c_1 h^{p1} + c_2 h^{p2} + c_3 h^{p3} + \ldots = \sum_{V=0}^{\infty} c_V h^{p_V}, \tag{14}$$

where the coefficients $c_j, j = 0, 1, 2, 3, \ldots$ are real numbers obtained as a function of the dependent variable of the problem and its derivatives, but are independent of h. The true orders, p_V, are the exponents of h and are integers following the relationship $1 \le p_0 < p_1 < p_2 < p_3 \ldots$. The smallest exponent, p_0, is called asymptotic order, known in the literature as order of accuracy and denoted by P_A. When $h \to 0$, the term $c_0 h^{p0}$ in Eq. (14) is the main component of Eh [12].

You can calculate P_A through effective (P_E) and/or apparent orders (P_U), depending on the type of solution available. For this, the numerical solutions ϕ_F, ϕ_C and ϕ_{SC} obtained in the fine (given by h_F), coarse (h_C) and super coarse (h_{SC}), respectively, generated with refining ratio $q = \frac{h_C}{h_F} = \frac{h_{SC}}{h_C}$ [3].

$$P_E = \frac{log[\frac{E(\phi_C)}{E(\phi_F)}]}{log(q)}, \qquad P_U = \frac{log(\frac{\phi_C - \phi_{SC}}{\phi_F - \phi_C})}{log(q)}. \tag{15}$$

Note that the effective order (P_E) depends on the knowledge of the analytical solution.

When the analytical solution ϕ is unknown, the discretization error cannot be calculated. So, the concept of uncertainty (U) is used. The uncertainty of a numerical solution is calculated by the difference between the estimated analytical solution (ϕ_∞) for a variable of interest and its numerical solution (ϕ) [3], that is,

$$U(\phi) = \phi_\infty - \phi. \tag{16}$$

To estimate the discretization error, Richardson's error estimator based on the apparent and asymptotic orders were used because it is widely reported in the literature, thereby serving as a reference estimator [13]. The Richardson's error estimators are given by

$$U_{Ri}(P_U) = \frac{(\phi_F - \phi_C)}{(q^{P_U} - 1)}, \qquad U_{Ri}(P_A) = \frac{(\phi_F - \phi_C)}{(q^{P_A} - 1)}. \tag{17}$$

5 Results

Considering $x \in [0, \pi/6]$ and final time $t_f = 0.5$, we use the variable of interest, the central point of the domain in the last time step.

We can check from Table 1, the discretization error varying h_x and h_t, considering $q = 2$ and all four variables of the mathematical model n, f, m and u.

Table 1. Discretization error varying h_x and h_t.

h_x	h_t	$Eh_n(\phi)$	$Eh_f(\phi)$	$Eh_m(\phi)$	$Eh_u(\phi)$
5.2360e-02	2.5000e-02	3.1510e-04	9.1596e-05	2.5889e-04	1.0022e-05
2.6180e-02	1.2500e-02	7.8884e-05	2.2952e-05	6.4869e-05	2.4858e-06
1.3090e-02	6.2500e-03	1.9728e-05	5.7412e-06	1.6226e-05	6.2020e-07
6.5450e-03	3.1250e-03	4.9324e-06	1.4355e-06	4.0572e-06	1.5497e-07
3.2725e-03	1.5625e-03	1.2331e-06	3.5889e-07	1.0143e-06	3.8738e-08
1.6362e-03	7.8125e-04	3.0828e-07	8.9724e-08	2.5359e-07	9.6842e-09

The discretization error is given in Fig. 1. We can see that the smaller the size of h_x and h_t (represented in Fig. 1 simply by h), the smaller the discretization error.

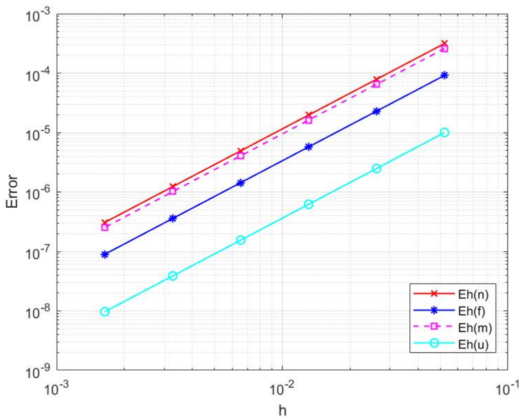

Figure 1. Discretization error *versus* h (representing the h_x and h_t of Table 1) for the variables *n*, *f*, *m* and *u*.

Then we perform the calculation of the effective (P_E) and apparent orders (P_U), in order to verify *a posteriori* of the numerical solutions, that P_U and P_E tend monotonically to P_A when $h \to 0$. This can be seen in Table 2, and corroborated by Fig. 2.

Table 2. Effective (P_E) and apparent (P_U) orders for each variables *n*, *f*, *m* and *u*.

	n		*f*		*m*		*u*	
h_x	P_U	P_E	P_U	P_E	P_U	P_E	P_U	P_E
5.2360e-02								
2.6180e-02		1.9980		1.9966		1.9967		2.0114
1.3090e-02	1.9975	1.9995	1.9958	1.9991	1.9959	1.9991	2.0142	2.0028
6.5450e-03	1.9994	1.9998	1.9989	1.9997	1.9989	1.9997	2.0036	2.0007
3.2725e-03	1.9998	1.9999	1.9997	1.9999	1.9997	1.9999	2.0009	2.0001
1.6362e-03	1.9999	1.9999	1.9999	1.9999	1.9999	1.9999	2.0002	2.0000

The other objective of this work is to calculate the uncertainty of numerical solutions, which is an estimate of the discretization error (Eh). The Table 3 presents the uncertainty using the Richardson estimator (U_{RI}, Eq. 17) with the apparent P_U and asymptotic orders P_A for the variable *n* . Similarly, we perform the uncertainty calculation based on P_A and P_U using U_{RI} in the other variables (*f*, *m* and *u*). Similar results were achieved.

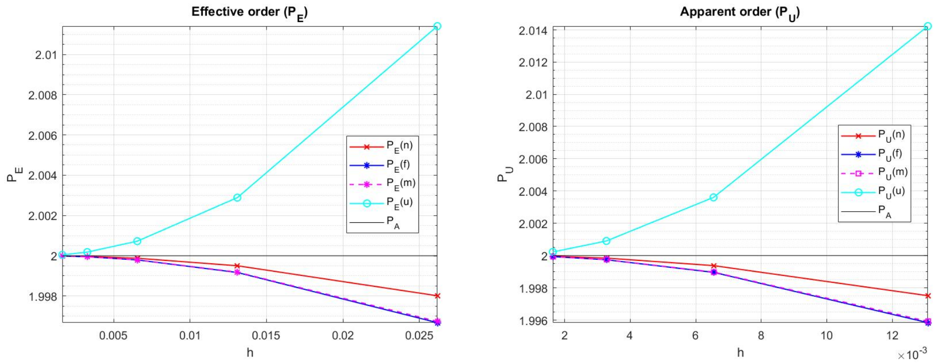

Figure 2. Effective and apparent orders, with $P_A = 2$.

Table 3. Numerical uncertainty based on asymptotic (P_A) and apparent orders (P_U) using Richardson's estimator on variable n.

h_x	h_t	ϕ	$U_{Ri}(P_U)$	$U_{Ri}(P_A)$
5.2360e-02	2.5000e-02	1.644507		
2.6180e-02	1.2500e-02	1.644271		-7.8740e-05
1.3090e-02	6.2500e-03	1.644212	-1.9764e-05	-1.9719e-05
6.5450e-03	3.1250e-03	1.644197	-4.9346e-06	-4.9318e-06
3.2725e-03	1.5625e-03	1.644193	-1.2332e-06	-1.2331e-06
1.6362e-03	7.8125e-04	1.644192	-3.0829e-07	-3.0828e-07

For all analyzed variables (*n*, *f*, *m* and *u*), we found that the error estimate decreased with the increase in the number of nodes in the mesh. This estimate reached 10^{-7} for the variable *n* and 10^{-9} for the variable *u*.

To ensure that the error estimate is reliable, Marchi and Silva [3] showed that

$$\frac{U_{RI}(P_A)}{Eh} < 1 < \frac{U_{RI}(P_U)}{Eh}, \text{ when } P_U \to P_A \text{ monotonically with values less than } P_A, \tag{18}$$

$$\frac{U_{RI}(P_U)}{Eh} < 1 < \frac{U_{RI}(P_A)}{Eh}, \text{ when } P_U \to P_A \text{ monotonically with values greater than } P_A. \tag{19}$$

Therefore, we can see in the Table 4 the ratio between the Richardson estimator (for P_A and P_U) and the truncation error.

Table 4. Ratio between the uncertainty (U) and the truncation error (Eh) in the variable n.

h_x	$U_{Ri}(P_A)/Eh$	$U_{Ri}(P_U)/Eh$
5.2360e-02		
2.6180e-02	0.998168	
1.3090e-02	0.999541	1.001834
6.5450e-03	0.999885	1.000458
3.2725e-03	0.999971	1.000114
1.6362e-03	0.999992	1.000028

We can see from Eqs. (18)-(19) and confirmed by Table 4, that the ratio between the estimator and the truncation error for the variable *n* approaches 1, with mesh refinement. The same happened with the other variables (*f*, *m* and *u*). This can be seen in Fig. (3).

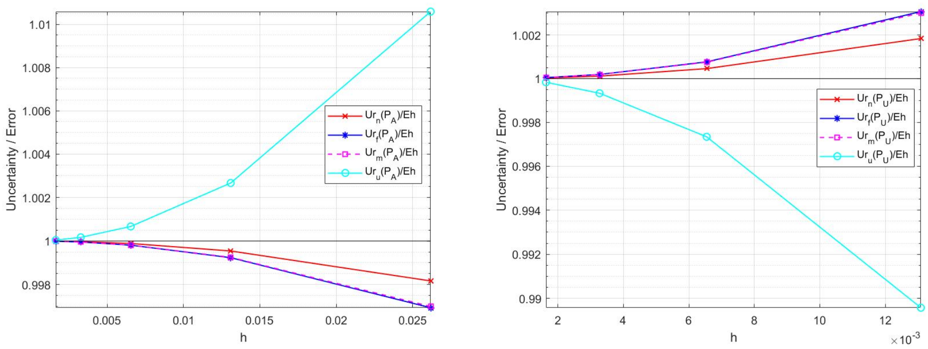

Figure 3. Ratio between the uncertainty (U) and the truncation error (Eh) in the variables n, f, m, u.

6 Conclusions

In this paper, we check the errors for a tumour growth model using the central differencing scheme in space and the Crank-Nicolson in time, in order to discretize the set of PDEs. Due to the discretization process, numerical solutions are affected by numerical errors. An analysis of the truncation error was presented, verifying that the effective and apparent orders of the discretization error converge to the asymptotic order. We also verified that the numerical uncertainty, or error estimate, using the Richardson estimator, was considered reliable.

Acknowledgements. The present work was carried out thanks to UEL and UFPR for the opportunity to study.

Authorship statement. The authors hereby confirm that they are the sole liable persons responsible for the authorship of this work, and that all material that has been herein included as part of the present paper is either the property (and authorship) of the authors, or has the permission of the owners to be included here.

References

[1] G. H. Golub, J. M. Ortega, and others. *Scientific computing and differential equations: an introduction to numerical methods*. Academic press, 1992.
[2] R. H. Pletcher, J. C. Tannehill, and D. Anderson. *Computational fluid mechanics and heat transfer*. CRC press, 2012.
[3] C. H. Marchi and A. F. C. d. Silva. Unidimensional numerical solution error estimation for convergent apparent order. *Numerical Heat Transfer: Part B: Fundamentals*, vol. 42, n. 2, pp. 167–188, 2002.
[4] A. R. Anderson and others. Mathematical modelling of tumour invasion and metastasis. *Computational and mathematical methods in medicine*, vol. 2, n. 2, pp. 129–154, 2000.
[5] M. A. Chaplain. Mathematical modelling of tissue invasion. *Cancer modelling and simulation*, 2003.
[6] M. Kolev and B. Zubik-Kowal. Numerical solutions for a model of tissue invasion and migration of tumour cells. *Computational and mathematical methods in medicine*, vol. 2011, 2011.
[7] L. G. López, C. A. Ruiz, and A. P. Castaño. Numerical simulation of tumor growth and cell migration in 1D and 2D. *Revista Argentina de Bioingeniería*, vol. 22, n. 1, pp. 60–66, 2018.
[8] J. Maganin. Simulation of a mathematical model of tumor growth in the breast using finite difference method. Master's thesis, State University of Londrina - Department of Mathematics, Londrina, Pr, Brazil, 2020.
[9] A. P. d. S. Vargas. Richardson multi extrapolation and 1st and 2nd order, mixed and Crank-Nicolson schemes on 2D advencement-diffusion and Fourier equations, 2013.
[10] S. Ganesan and S. Lingeshwaran. Galerkin finite element method for cancer invasion mathematical model. *Computers & Mathematics with Applications*, vol. 73, n. 12, pp. 2603–2617, 2017.
[11] C. J. Roy and W. L. Oberkampf. A comprehensive framework for verification, validation, and uncertainty quantification in scientific computing. *Computer methods in applied mechanics and engineering*, vol. 200, n. 25-28, pp. 2131–2144, 2011.
[12] C. H. Marchi and A. Silva. Multi-dimensional discretization error estimation for convergent apparent order. *Journal of the Brazilian Society of Mechanical Sciences and Engineering*, vol. 27, n. 4, pp. 432–439, 2005.
[13] C. H. Marchi, C. D. Santiago, and C. A. R. d. Carvalho Jr. Lid-driven square cavity flow: A benchmark solution with an 8192× 8192 grid. *Journal of Verification, Validation and Uncertainty Quantification*, vol. 6, n. 4, 2021.