UFSM

CIÊNCIA e NATURA

ISSN 2179-460X
OPEN ACCESS

Ci. e Nat., Santa Maria, v. 46, n. spe. 1, e87204, 2024 • https://doi.org/10.5902/2179460X87204
Submitted: 03/21/2024 • Approved: 07/05/2024 • Published: 11/07/24

ERMAC e ENMC

Perturbative analysis of biological parameters for simulating glioblastoma multiforme using Swanson's model by the method of symmetries

Análise perturbativa dos parâmetros biológicos para simular o glioblastoma multiforme usando o modelo de Swanson através de um método de simetrias

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ABSTRACT

The present work aims to propose an exact solution through split and symmetries for a model used to simulate the growth rate of cancer cells in a specific region of the human body, it also intends to study the behavior of the tumor cell concentration rate by varying the diffusion and proliferation coefficients randomly within a specified interval. The model utilized to simulate the cell growth rate is the Swanson model, disregarding the term that follows the treatment and considering a constant diffusion coefficient by region. Attaining the exact solution of the Swanson model can aid in the treatment of specific cancer types, as implementing a more accurate model leads to a decrease in the destruction rate of healthy cells neighboring the cancerous cells.

Keywords: Swanson model; Exact solution; *Split*; Symmetries

RESUMO

O presente trabalho tem como objetivo propor uma solução exata via *Split* e simetrias para um modelo usado para simular a taxa de crescimento das células cancerígenas em uma região específica do corpo humano. Também pretende estudar o comportamento da taxa de concentração de células tumorais variando os coeficientes de difusão e proliferação de maneira randômica dentro de um intervalo especificado. O modelo utilizado para simular a taxa de crescimento celular é o modelo de Swanson, desconsiderando o termo referente ao tratamento e considerando um coeficiente de difusão constante por região. Alcançar a solução exata do modelo de Swanson pode auxiliar no tratamento de tipos específicos de câncer, pois a implementação de um modelo mais preciso pode levar a uma diminuição

na taxa de destruição das células saudáveis vizinhas às células cancerosas.

Palavras-chave: Modelo de Swanson; Solução exata; *Split*; Simetrias

1 INTRODUCTION

Cancer is an overarching concept that envelops a spectrum of over 100 distinct malignancies characterized by the chaotic proliferation of cells. This unregulated cell growth has the potential to infiltrate neighboring tissues or distant organs. Characterized by their rapid division, these cells often exhibit a high level of aggression and resist control, resulting in the development of tumors that possess the capacity to metastasize to remote areas within the body (INCA, 2023).

Among the various types of cancer, there are gliomas, which are highly invasive primary brain tumors that spread diffusely throughout the entire brain. Approximately 50% of all brain tumor types are gliomas, and the most aggressive subtype is known as glioblastoma multiforme (GBM), which has a life expectancy of six to twelve months (Hatzikirou et al., 2005).

Given the resistance and unspecified treatments against tumors, the most significant challenge lies in developing strategies that are more specific to tumor cells and less aggressive toward patients. This has led to the emergence of the concept of Boro Neutron Capture Therapy (BNCT), which represents a binary treatment modality for cancer. Formulations containing the chemical element Boron-10 (^{10}B) are introduced into the patient's bloodstream via intravenous or oral administration. These boron-based chemical compounds have the unique ability to accumulate in notably higher quantities within cancer cells compared to healthy cells. Consequently, this leads to elevated concentrations of ^{10}B specifically within tumors while maintaining lower levels in surrounding healthy tissues. Subsequently, the patient is positioned before a neutron beam emanating from a nuclear reactor. These neutrons exhibit a pronounced affinity for Boron-10, exhibiting a preferential tendency to interact with boron atoms over other atoms, substances, or cells in the human body. Given the predominant concentration of boron atoms in tumor cells, while a significant proportion of neutrons will specifically target cancerous cells, it's important to note that there will still be a degree of impact on healthy cells, albeit at a diminished level.

Upon interaction, a neutron collides with a boron atom, instigating a nuclear

reaction yielding a Lithium-7 (^7Li) atom alongside an alpha particle (constituting the nucleus of the chemical element Helium, He). Notably, in approximately 94% of these interactions, gamma rays are also emitted. This intricate process is formally represented as $^{10}B(n,\alpha)^7Li$ (Dalle, 1999).

Once this problem is presented, the aim of this study is to find an exact solution for the reaction-diffusion model proposed in Rockne et al. (2009), which describes the diffusion and proliferation of tumor cells and the impact of chemotherapy and radiotherapy treatments, employing symmetry-based methods as observed in the works of Beck (2009) and Sperotto (2007) and observe the behavior of this solution when we perturb the parameters D and ρ, which represent the diffusion and proliferation coefficients, respectively. The goal is to obtain an estimate of tumor concentration in space-time for a glioma-type brain tumor and examine the fluctuations in concentration based on changes in the diffusion and proliferation coefficients.

In this study, we will analyze the model while excluding the impact of treatment or therapy. Furthermore, we will consider a constant diffusion coefficient.

2 METHODOLOGY

2.1 The Swanson model

The equation based on the Swanson model without the tumor growth attenuation source term simulating therapy takes the following form:

$$\frac{\partial C}{\partial t} = \nabla \cdot (D(x,y,z)\nabla C) + \rho C\,, \tag{1}$$

with $x,y,z \in B, \quad t \geq 0, \quad C(x,y,z,0) = C_0, \quad n \cdot \nabla C \quad$ in $\quad \partial B$, where $C = C(x,y,z,t)$ represents the concentration of the cancerous tumor within cells per mm^3 per year, at position (x,y,z) in time t, where the domain B (brain) its closed and bounded, D it is the spatial diffusion coefficient with units of mm^2 per year, ρ represents the rate of cell proliferation per year, C_0 it is the initial distribution of tumor cells, $n \cdot \nabla C$ a zero-flux boundary condition that prevents cells from leaving the domain B at its boundary ∂B. With this, the term $\nabla(D(x,y,z)\nabla C)$ describes the net diffusion of glioma cells and ρC represents the proliferation rate of glioma cells. Since this model is a reaction-diffusion

differential equation describing net diffusion and the proliferation rate of cancerous cells, considering that in our study D is constant and two-dimensional Cartesian geometry, the model can be written as follows:

$$\frac{\partial C}{\partial t} = D\left(\frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2}\right) + \rho C\,. \tag{2}$$

In order to apply the proposed methodology in the upcoming session, the substitution is carried out as $C = \bar{C}e^{\rho t}$, ensuring the convergence of the geometric series that will form. In this case, we have:

$$\frac{\partial \bar{C}}{\partial t}e^{\rho t} + \rho \bar{C}e^{\rho t} = D\left(\frac{\partial^2 \bar{C}}{\partial x^2} + \frac{\partial^2 \bar{C}}{\partial y^2}\right)e^{\rho t} + \rho \bar{C}e^{\rho t}\,. \tag{3}$$

Simplifying the terms $\rho \bar{C}e^{\rho t}$, dividing both sides of the equation by $e^{\rho t}$, and recalling that D is constant throughout the domain, we find that Eq. (2) becomes:

$$\frac{\partial \bar{C}}{\partial t} = D\left(\frac{\partial^2 \bar{C}}{\partial x^2} + \frac{\partial^2 \bar{C}}{\partial y^2}\right)\,. \tag{4}$$

In order to solve Eq. (4) exactly, we seek methodologies to obtain a solution. Among the methodologies applied for this purpose, we have symmetry-based methods, which are a class of techniques used to solve partial differential equations (PDEs). They are based on the idea that the presence of symmetries in a PDE can be employed to simplify the solution. However, not all PDEs possess symmetries, and not all symmetries lead to exact solutions. It should be noted that these methods are a valuable tool, but not a universal solution for solving PDEs.

All variable changes that transform exact solutions of a particular differential equation into new solutions or equivalent solutions are referred to as Lie symmetries admitted by the equation, auto-Bäcklund transformations, or simply symmetries. Various exact techniques have been developed to obtain symmetries (Dattoli et al., 1998; Ibragimov, 1995; Zwillinger, 1992), such as the direct substitution method (Bluman and Kumei, 1989). However, at least one solution is necessary to initiate the process, which can be obtained through methods based on *split*, among other approaches.

2.2 The Symmetry-based Method

In order to find exact solutions for Eq. (4), it is written as:

$$Lf = 0\,, \tag{5}$$

where L is a linear operator that can be decomposed as $L = A - B$, where A and B are also linear differential operators that commute, i.e., $AB = BA$. This leads to an equation expressed as:

$$Af = Bf\,. \tag{6}$$

Applying the left inverse operator of A, denoted as A^{-1}, to both sides of Eq. (6), we have:

$$A^{-1}Af = A^{-1}Bf\,. \tag{7}$$

Thus, Eq. (5) results, after incorporating the null space of the operator A, in the following expression:

$$f = A^{-1}Bf + h(A)\,. \tag{8}$$

Note that $h(A)$ is the null space of A, represented by the set of solutions to the equation $Ah(A) = 0$. Rearranging the terms containing the function f results in:

$$\left[I - A^{-1}B\right] f = h(A)\,, \tag{9}$$

which solving for f using the inverse $[I - A^{-1}B]^{-1}$, becomes:

$$f = \left[I - A^{-1}B\right]^{-1} h(A) + h(I - A^{-1}B)\,. \tag{10}$$

If we observe, we can rewrite the inverse of the operator appearing in Eq. (10) as a

geometric series in the following manner:

$$\frac{1}{I - A^{-1}B} = \sum_{k=0}^{\infty} \left(A^{-1}B\right)^k . \tag{11}$$

Taking into account the restriction referring to the norm of the operator $A^{-1}B$ in relation to the convergence of the series, $|A^{-1}B| < 1$. Then, The solution is derived in the following form:

$$f = \sum_{k=0}^{\infty} \left(A^{-1}B\right)^k h(A) + h(I - A^{-1}B) . \tag{12}$$

In order to attain a solution for the given Eq. (12), it becomes imperative to select a function that will work as a possible proposed solution for the series transformation, in the form $\eta_0 \in h(A) \cap h(I - A^{-1}B)$, where $h(I - A^{-1}B)$ represents the null space of $A^{-1}B$. Note that the term $h(I - A^{-1}B)$ is redundant, as it stems from:

$$(A^{-1}B)h(I - A^{-1}B) = 0 . \tag{13}$$

After choosing this η_0, in order to transform the series solution into a finite sum, we will derive the functions belonging to the null space of a finite power n of the operator $A^{-1}B$, that follow as a truncated series.

$$f = \sum_{k=0}^{n} \left(A^{-1}B\right)^k \eta_0 , \tag{14}$$

which is always an exact solution, since all terms beyond n are automatically null. For this reason, no questions regarding convergence arise over the development of the proposed formulation.

2.3 The structure of η_0 through the split method

To ascertain a specific solution for Eq. (4), and thereby determine the foundational function for the solution structure of η_0, we will employ a mathematical technique known as the split method.

The fundamental concept of the method is to decompose the original partial differential equation (PDE) into several sub-PDEs, each of which can be solved

independently. This decomposition is achieved by separating the differential operator of the original equation into its constituent components. Essentially, it involves breaking down the target equation into a system typically comprised of two auxiliary differential equations. This approach simplifies the development of resolution algorithms that require only basic calculus knowledge, primarily involving partial differentiation and integration.

In order to find an η_0 that fulfills the predetermined conditions, we will rewrite the operators A and B as follows:

$$\begin{cases} A = \dfrac{\partial(\cdot)}{\partial t} \\ \\ B = D\left(\dfrac{\partial^2(\cdot)}{\partial x^2} + \dfrac{\partial^2(\cdot)}{\partial y^2}\right) \end{cases} \tag{15}$$

and, consequently,

$$A^{-1} = \int (\cdot) dt\,. \tag{16}$$

The resolution involves equating each half of the original equation to a source, which can initially be constant or even zero, and then solving the resulting system. To break down the differential equation into a system of two equations, we start by bringing together its terms to put it in the form $Af = Bf$, where A and B are differential operators. One of these operators is chosen to be easily invertible and to have its null space known. The criterion for separation is being intentionally simplified here, suitable for desirable conditions for a split to be executed without excessively restricting the resulting solution space.

The split technique is based on employing the solution obtained from one step (k) as a source for the subsequent step $(k+1)$. In this way, we can derive several exact solutions using a process that takes the form:

$$\begin{cases} Af_{k+1} = f_k \\ Bf_{k+1} = f_k \end{cases}, \tag{17}$$

where the functions f_k represent the exact solutions of the original equation. For the

iterative process to be applicable to the equations generated by the split, it's necessary to verify the commutativity between A and B, i.e., if $[A, B] = 0$. Based on the choice made in Eq. (15), it's evident that $[A, B] = 0$. Therefore, since the coefficients of A and B commute, one can proceed with $k = 0$.

$$\begin{cases} Af_1 = f_0 \\ Bf_1 = f_0 \end{cases}, \tag{18}$$

by choosing $f_0 = 0$ and recognizing that the operator A is invertible and its null space is known, it becomes feasible to find a solution for the equation related to operator A by integrating it with respect to time and adding the corresponding null space. Consequently, we have a function f_1 defined as:

$$f_1 = g_1(x, y)\,. \tag{19}$$

The next step involves applying the solution (19) to the equation related to operator B, resulting in:

$$D\left(\frac{\partial^2}{\partial x^2}g_1(x, y) + \frac{\partial^2}{\partial y^2}g_1(x, y)\right) = 0\,. \tag{20}$$

To solve this equation, we apply a new split,

$$\begin{cases} \dfrac{\partial^2}{\partial x^2}g_1(x, y) = 0 \\ \\ \dfrac{\partial^2}{\partial y^2}g_1(x, y) = 0 \end{cases}. \tag{21}$$

By integrating the first equation of the system (21) twice with respect to the variable x and solving for $g_1(x, y)$, we arrive at an expression with the format:

$$g_1(x, y) = a_1(y)x + b_1(y)\,, \tag{22}$$

replacing Eq. (22) into the second equation of the system (21), we have:

$$a"_1(y)x + b"_1(y) = 0\,. \tag{23}$$

The only way to satisfy this equation is by setting $a"_1(y) = 0$ and $b"_1(y) = 0$. Consequently, these functions become:

$$a_1(y) = c_1 y + c_2 \qquad e \qquad b_1(y) = c_3 y + c_4\,, \tag{24}$$

which provides a solution in the form:

$$f_1 = g_1(x, y) = c_1 xy + c_2 x + c_3 y + c_4\,. \tag{25}$$

Once this solution is found, the process is applied once again, this time introducing the Eq. (25) as the new source. Thus, for $k = 1$, we have:

$$\begin{cases} \dfrac{\partial}{\partial t} f_2 = c_1 xy + c_2 x + c_3 y + c_4 \\ \\ D\left(\dfrac{\partial^2}{\partial x^2} f_2 + \dfrac{\partial^2}{\partial y^2} f_2\right) = c_1 xy + c_2 x + c_3 y + c_4 \end{cases}. \tag{26}$$

By integrating the first Eq. of (26) with respect to t, we obtain:

$$f_2 = g_2(x, y, t) = c_1 xyt + c_2 xt + c_3 yt + c_4 t + g_3(x, y)\,. \tag{27}$$

In order to solve the second Equation of (26), a new split is performed, resulting in the system:

$$\begin{cases} D\left(\dfrac{\partial^2}{\partial x^2} f_2\right) = \dfrac{1}{2}\left(c_1 xy + c_2 x + c_3 y + c_4\right) \\ \\ D\left(\dfrac{\partial^2}{\partial y^2} f_2\right) = \dfrac{1}{2}\left(c_1 xy + c_2 x + c_3 y + c_4\right) \end{cases}, \tag{28}$$

which, upon rearranging the terms, becomes:

$$\begin{cases} \dfrac{\partial^2}{\partial x^2} f_2 = \dfrac{1}{2D}\left(c_1 xy + c_2 x + c_3 y + c_4\right) \\ \\ \dfrac{\partial^2}{\partial y^2} f_2 = \dfrac{1}{2D}\left(c_1 xy + c_2 x + c_3 y + c_4\right) \end{cases} . \tag{29}$$

The second derivative we get:

$$\frac{\partial^2}{\partial x^2} f_2 = \frac{\partial^2}{\partial x^2}\left(g_3(x,y)\right) = \frac{1}{2D}\left(c_1 xy + c_2 x + c_3 y + c_4\right) \tag{30}$$

and

$$\frac{\partial^2}{\partial y^2} f_2 = \frac{\partial^2}{\partial y^2}\left(g_3(x,y)\right) = \frac{1}{2D}\left(c_1 xy + c_2 x + c_3 y + c_4\right) . \tag{31}$$

Note that by integrating $\frac{\partial^2}{\partial x^2} g_3(x,y)$ twice with respect to x, results in:

$$g_3(x,y) = \frac{1}{2D}\left(\frac{c_1}{6}x^3 y + \frac{c_2}{6}x^3 + \frac{c_3}{2}x^2 y + \frac{c_4}{2}x^2 + a_2(y)x + b_2(y)\right) , \tag{32}$$

which, by replacing the value of $g_3(x,y)$ in $\frac{\partial^2}{\partial y^2} g_3(x,y)$ becomes:

$$\frac{\partial^2}{\partial y^2} g_3(x,y) = \frac{1}{2D}\left(a_2^{"}(y)x + b_2^{"}(y)\right) = \frac{1}{2D}(c_1 xy + c_2 x + c_3 y + c_4) . \tag{33}$$

The Eq. (33) is solved by setting $a_2^{"}(y) = c_1 y + c_2$ and $b_2^{"}(y) = c_3 y + c_4$, which, upon integrating with respect to y twice, stay with:

$$a_2(y) = \frac{c_1 y^3}{6} + \frac{c_2 y^2}{2} + c_5 y + c_6 \quad and \quad b_2(y) = \frac{c_3 y^3}{6} + \frac{c_4 y^2}{2} + c_7 y + c_8 . \tag{34}$$

Upon replacing the derived values of $a_2(y)$ and $b_2(y)$ into Eq. (32), it follows that $g_3(x,y)$ takes the following form:

$$g_3(x,y) = \frac{1}{2D}\left[c_1\left(\frac{x^3 y + x y^3}{6}\right) + c_2\left(\frac{x^3 + 3xy^2}{6}\right) + c_3\left(\frac{3x^2 y + y^3}{12}\right) + c_4\left(\frac{x^2 + y^2}{2}\right) + c_5 xy + c_6 x + c_7 y + c_8\right] . \tag{35}$$

Replacing $g_3(x, y)$ into Eq. (27), we find that f_2 results in:

$$f_2 = g_2(x, y, t) = c_1xyt + c_2xt + c_3yt + c_4t + \frac{1}{2D}\left[c_1\left(\frac{x^3y + xy^3}{6}\right) + c_2\left(\frac{x^3 + 3xy^2}{6}\right) + c_3\left(\frac{3x^2y + y^3}{6}\right) + c_4\left(\frac{x^2 + y^2}{2}\right) + c_5xy + c_6x + c_7y + c_8\right]. \tag{36}$$

As can be observed, Eq. (36) is a solution for Eq. (4), and consequently, for Eq. (2).

2.4 Results and Discussion

Once the concentration of tumor cells in a specific location is obtained, the focus shifts to studying how the concentration of tumor cells will vary when randomly selecting values for the cell diffusion coefficient (D) and the cell proliferation coefficient (ρ). In order to investigate the model's sensitivity to changes in the diffusion and proliferation coefficients, these parameters are perturbed by a 10% margin from their reference values.

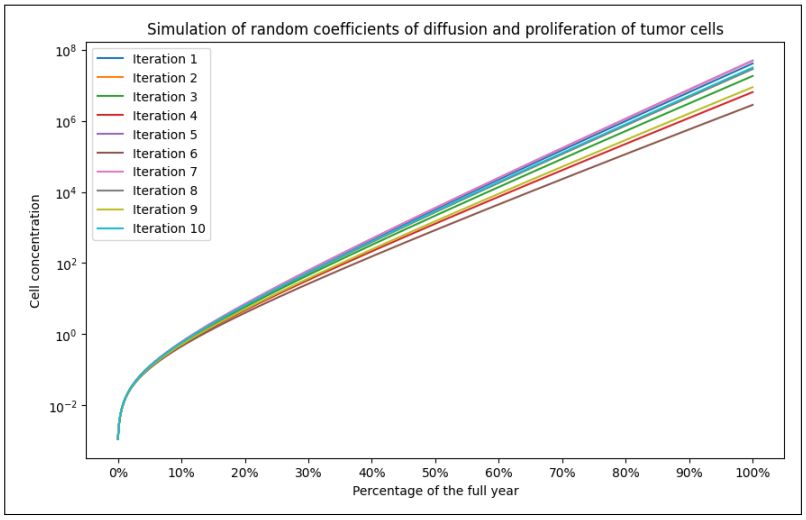
This selection is aimed at simulating scenarios where tumor cells could exhibit fluctuations in their rates of growth and spread. Such variations may arise from factors including treatment responses or alterations in the tumor microenvironment conditions.

Iterations were performed in which the diffusion and proliferation coefficients were randomly chosen within the defined perturbation range. Then, tumor cell concentrations are calculated for different time values, considering the exact solution of the model proposed in this work. The results are plotted in graphs that show the behavior of the concentrations over time, highlighting the influence of disturbances on the coefficients. For the analysis of the results, four time intervals were selected for a more detailed study: from 10%, 30%, 70% and 100% of the complete year. These ranges were chosen to investigate how tumor cell concentrations vary at different stages of growth, where significant changes can occur.

In conclusion, we can claim that the methodology employed has proven to be suitable and successful for solving the proposed model, as it yielded an exact solution to a problem that has historically been addressed numerically over the years. Consequently, the further exploration of this study holds significant importance, as it opens the door to extending the proposed methodology to the complete model,

including the treatment term, while also considering the spatial dependence of the biological parameters. Through observation, it is evident that despite the relatively small variation in cell diffusion and proliferation coefficients, around ±10%, this has had a significant impact on the development of the tumor cell concentration rate.

Figure 1 – Random coefficients of diffusion and proliferation



Caption: Simulation of random coefficients of diffusion and proliferation of tumor cells

Table 1 – Concentration rate

Iteration	D (mm^2)	ρ $(year^{-1})$	10%	30%	70%	100%
1	1.3916	17.537	0.6450	64.17	16×10^4	70×10^5
2	1.3679	17.183	0.6217	57.61	12×10^4	51×10^5
3	1.3132	16.727	0.5929	50.13	93×10^3	33×10^5
4	1.4636	15.682	0.5318	36.45	44×10^3	13×10^5
5	1.5556	17.729	0.6580	68.06	18×10^4	84×10^5
6	1.5639	14.854	0.4880	28.32	24×10^3	62×10^4
7	1.4615	17.714	0.6569	67.73	18×10^4	82×10^5
8	1.4220	17.187	0.6220	57.69	12×10^4	51×10^5
9	1.4690	16.002	0.5498	40.18	55×10^3	17×10^5
10	1.4571	17.274	0.6276	59.24	13×10^4	55×10^5

Caption: Concentration rate results for random D and ρ at one-year intervals.

This underscores the importance of ongoing research into treatments that can effectively control these coefficients.

As a future perspective, it is anticipated that favorable outcomes will be achieved

in extending the methodology to the complete model, including the term that accounts for the BNCT treatment.

ACKNOWLEDGEMENTS

The first author acknowledges the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES) for the financial support provided.

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How to cite this article

Caurio Jr., J. L. de M.; Ribeiro, A. A.; Petersen, C. Z.; Tumelero, F. (2024). Perturbative analysis of biological parameters for simulating glioblastoma multiforme using Swanson's model by the method of symmetries. *Ciência e Natura*, Santa Maria, v. 46, spe. 1, e87204. https://doi.org/10.5902/2179460X87204