PROCEEDINGS OF SCIENCE

Waves and bifurcations in describing the proliferation of the brain tumors

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The paper reviews the mathematical models proposed for describing the proliferation of gliomas, the most common brain tumors, with strong dynamic invasiveness and proliferative growth. When the diffuse spreading through the brain and the heterogeneity of the tissue are considered, the growth of the tumor can be described by a reaction-diffusion equation, with the unknown quantity representing the concentration of the tumor cells. The long term expansion of the tumor can be simulated as a traveling wave, solution of the considered reaction-diffusion equation. An interesting connection between these waves and the bifurcation theory can be established

Keywords: glioma, tumor proliferation models, traveling waves, bifurcation theory.

11th International Conference of the Balkan Physical Union (BPU11),
28 August - 1 September 2022
Belgrade, Serbia

[*] Speaker

PoS(BPU11)282

1. Introduction. Medical data.

Gliomas are the most common primary brain tumors, appearing as a result of the chaotic growth of the cancer cells in the glial tissue of the brain. From medical point of view, the spreading is described using parameters as the variation of the density of infected cells, $u(\vec{r},t)$, or the "volume doubling time". The growth of glioma is determined by the superposition of two phenomena: **proliferation** of the cancer cells by repeated divisions, and **motility** or **diffusion,** consisting in a migration ("invasion") of the infected cells. Both the multiplication and the migration are extremely fast, without effects on the patient without obvious effects on the patient, which would allow early detection of the tumor. Because of that, gliomas are almost impossible to cure and have almost 100% fatality rate within approximately one year, even if extensive surgery, radiotherapy and chemotherapy are applied [1]. Based on the data collected by various research groups, the radial growth velocity starts from 2 mm/year for "low-grade" gliomas and it can reach a ten times higher velocity for "fast-grade" gliomas. Depending on their location on the brain, the tumors can be observed starting from a radius of $2-3$ cm and become fatal at 6 cm (fatal tumor burden) [2].

Considering the previous arguments and the experimental data, the mathematical models describing the growth rate of gliomas take into account the following two fundamental assumptions: the cell diffusion follows the classical Fick law, while the cell proliferation is linear. As we will see, expressed in terms of equations, these hypotheses will lead to a reaction-diffusion mathematical model for the growth rate of gliomas. The mathematical problem becomes well-posed considering as border conditions the limited volume of the brain, since gliomas never metastasizing from it.

The paper is structured as follows: after these introductive notes, in the second section various mathematical models proposed for the description of gliomas evolution will be reviewed. The third section, that represents the main section of the paper, will consider a generalized reaction-diffusion equation for describing gliomas growth and two specific methods for obtaining the solution in terms of traveling waves. The first method is based on the attached flow approach proposed in [3], while the second method is the classical first integrals approach [4]. This second method is considered because of its nice connections with the bifurcation theory, connections that can be very helpful in understanding the chaotic processes appearing during gliomas growth. The paper will end with a section of Conclusions, in which the main results reported in this paper will be synthesized.

2. Mathematical models on the growth and diffusion of gliomas

The growth and the diffusion of gliomas can be modeled assimilating the expansion process of the tumor's edges with the propagation of a traveling wave. An early stage attempt to describe gliomas growth was based on the assumption of the exponential law. It was a model inspired by the metastases in the lungs where the measurements show a growth at constant volume-doubling rates according to a simple exponential law, as it was noted by Collins and all in [5]. These models did not consider the motility (diffusion of the cells) and they are known as static models.

A second category of models took into consideration, in addition to the proliferative

growth of the tumor, the cellular motility. This more realistic dynamical models were based on the results of Steel [6], who noticed that there is an order of magnitude difference between the times involved in the definitions of cellular and gross kinetics: hours to a few days for individual cells, many days and even months for gross tumors.

The real foundation of a mathematical model began in the early 1990s, with the researches presented in [7]. Considering the hypotheses presented above, they proposed to describe the proliferation and the invasion (diffusion) of gliomas through a conservative-diffusion equation of the form:

$$u_t = \nabla(\mathrm{A}\nabla \mathrm{u}) + \rho u \tag{1}$$

Here A is a constant diffusion coefficient, and ρ is another constant representing the net proliferation rate of the glioma cells. The choice of these two coefficients as constants is practically equivalent with considering that the brain tissue is homogenous. If, supplementary, we impose that the tumor is uni-focal, with a spherical symmetric growing, and we denote by x the radial direction, we conclude that (1) takes the form of a simpler $2D$ partial differential equation (PDE):

$$u_t = \frac{\partial}{\partial x}\left(A\frac{\partial u}{\partial x}\right) + \rho u = A\frac{\partial^2 u}{\partial x^2} + \rho u \tag{2}$$

Experimental measurements lead to the idea that the detectable tumor margin expands with a constant velocity v, that is given by twice the square root of the product ρA:

$$v = 2\sqrt{\rho A} \tag{3}$$

The relation (3) is known as the Fisher approximation.

Remark: The linear radial growth of tumor determines a cubic growth of the volume. Here is the major difference between this dynamic model and the static ones, where the infected cells have an exponential growth. The main effect is that now the volume-doubling time is not constant.

The weak point of the model described by (2) is that it considers the brain as homogeneous and isotropic. Practical investigations using the NRM technique show that, in reality, glioma cells migrate more quickly along blood vessels and fiber tracts. The brain has white and grey zones, with greater respectively smaller motilities. In the first instance, two different constants were considered as diffusion coefficients for the two zones. Later on the heterogeneity and anisotropy of the brain were included by switching to a model with $A = A(u)$ and $\rho = \rho(u)$ [8]. The new model is described by a full reaction-diffusion equation with variable coefficients. Keeping the idea of symmetric growth, one can write down this equation as the following $2D$ PDE:

$$u_t = \frac{\partial}{\partial x}\left(A(u)\frac{\partial u}{\partial x}\right) + \rho(u)u \tag{4}$$

It is the most current mathematical model used to describe the proliferation and diffusion of glioma cells before any medical intervention. Choosing appropriately $A(u)$ and $\rho(u)$, coefficients that strongly depend on the patient and can be determined through repeated measurements, the model allows making predictions related to the evolution of the tumor and to the life expectancy.

The model described by (4) can be improved, considering what is happening during and after the tumor's treatment. The treatment supposes a surgical resection, if it is possible, but anyway chemotherapy and radiotherapy. The influence of these interventions is expressed by introducing in the equation (4) of an additional function, $T(x,t)$, to describe the loss of tumor cells. The mathematical model becomes [7]:

$$u_t = \frac{\partial}{\partial x}(A(u)\frac{\partial u}{\partial x}) + \rho(u)u + T(x,t)u \tag{5}$$

This improved model allows not only predictions on the life expectancies but also determination of the favorable moments for the application of chemotherapy and radiotherapy procedures after the surgery. To get such information, we have to solve (5) and, from the form of its traveling wave solutions, to identify the moments when the resorption of the wave is maximal and the density of cancer cells becomes minimal.

3. The reaction-diffusion equation for the gliomas growth

3.1. A generalized reaction-diffusion equation

The equation (5) can be seen as a general diffusion-reaction equation of the form:

$$u_t = \frac{\partial}{\partial x}\left[A(u)\frac{\partial u}{\partial x}\right] + E(u) \tag{6}$$

Here $A(u)$ is the dissipative (diffusion) function, while $E(u)$ represents the reaction term. The equation (6) supports traveling wave solutions that can be obtained by passing to the "wave variable" $\xi = x - \lambda t$. By simple computations, denoting $u' = du/d\xi$, $u'' = d^2u/d\xi^2$, the equation (6) can be written as a nonlinear ordinary differential equation (NODE) of the form:

$$A(u)u'' + B(u)u'^2 + C(u)u' + E(u) = 0 \tag{7}$$

The identification of (5) with (7) requires:

$$B(u) = \frac{d}{du}A(u);\ C(u) = \lambda, E(u) = [\rho(u) - T(\xi)]u. \tag{8}$$

The traveling wave solutions of the equation (7) were extensively studied in [9] through an interesting approach, called the functional expansion method. Here we will analyze the equation (7) from the perspective of another method, the *attached flow*. The last one will allow connecting the traveling waves with the theory of bifurcation and will show what type of solutions are expected for various choices of the diffusion function $A(u)$ and of the reaction function $E(u)$. As we will comment below, the spread of gliomas as a traveling wave is completely different when (7) has, for example, periodic or rational solutions. The appearance of these types of solutions depends in turn on the values of the two parametric functions $A(u)$ and $E(u)$.

Remark: In its general form, the equation (7) includes many nonlinear equations of interest in physics, engineering and biomathematics. Specific examples of equations belonging to this class are the Schrodinger equation with cubic nonlinearity, the nonlinear Klein-Gordon equation, as well as Benjamin-Bona-Mahony, Korteweg de Vries, Burger, Chafee-Infante, Fisher type equations. Part of these equations can be exactly solved. They could be considered as auxiliary equations for other more complicated models with traveling wave solutions.

3.2. Glioma mathematical model in the attached flow approach

Let us come back to the equation (7), with $B(u)$ and $C(u)$ given by (8). We will also assume that the functions $A(u)$, $E(u)$ are non-vanishing polynomials, with the highest degrees $N(A)$, $N(B)$, $N(C)$, $N(E)$, and, respectively, with the minimal degrees $\{n(A), n(B), n(C), n(E)\}$ greater or equal to zero. A simple and classical approach for solving (7) supposes its reduction to two first order differential equations. As it is an autonomous equation, the reduction can be made by defining:

$$u' = f(u) \tag{9}$$

From (9), we have that:

$$u'' = \frac{df}{du}u' = \frac{df}{du}f \tag{10}$$

With (10), the equation (1) becomes a first order differential equation:

$$A(u)f(u)\frac{df}{du} + B(u)f(u)^2 + C(u)f(u) + E(u) = 0 \tag{11}$$

Practically, we reduce the solving of (7) to the solving of (11) with the constraint (9). The reduction was generated by a change of variable in which the dependent variable $u(\xi)$ from (7) takes the role of the independent one, the new dependent variables becoming the function $f(u)$, attached to the derivative $u'(\xi)$. This reduction procedure was called in [3] the *attached flow method.* The new variable is the quantity $f(u)$ called *flow* and it is a solution of (11).

We note that the equation (11) has the form of an Abel equation of the second kind [10] and it is not integrable for arbitrary coefficients. There are few exceptions when its solution can be written in an implicit form. Explicit solutions can be obtained in some specific cases, for example if $C(u) = 0$, when we have a degenerate case. How to get traveling waves of (7) by solving the Abel equation for various diffusion and reaction functions was extensively studied in [11]. The majority of the wave solutions are given here in a parametric form. The same class of solutions can be generated through the attached flow method in a simpler and explicit form. The method precisely avoids arriving at an Abel equation, proposing a forced decomposition of the reaction term $E(u)$ as:

$$E(u) = f(u)h(u) \tag{12}$$

The equation (11) takes the form:

$$A(u)\frac{df}{du} + B(u)f(u) + C(u) + h(u) = 0 \tag{13}$$

When and how (13) can be solved is extensively presented in [10].

3.3. The first integrals and the bifurcation theory

The reduction of the second order differential equation (7) to two first order equations is also achieved in another classical way, the first integral method [12], when we replace this equation with the system:

$$\begin{aligned} u'(\xi) &= v(\xi) \\ v'(\xi) &= b(u)v(\xi)^2 + c(u)v(\xi) + e(u), \end{aligned} \tag{14}$$

where

$$b(u) = \frac{B(u)}{A(u)}, c(u) = \frac{C(u)}{A(u)}, e(u) = \frac{E(u)}{A(u)}.$$

It is what we are usually doing passing from the Lagrangean to the Hamiltonian formalism.

The problem of solving (14) is clearly different from solving the system (9) and (11). In (14) the two variables u and v depend of ξ, while in (11) we have u as independent and $f(u)$ as dependent variables. For differential equations of order higher than two, the method leads to systems with more than two equations.

We will not insist on the traveling wave solutions of (14). These solutions strongly depend on the explicit form of the parametric functions $b(u)$, $c(u)$, $e(u)$, and, as we already mentioned, in the case of glioma's evolution they are very specific for each patient. The behavior of the tumor can be completely different for the various types of solutions supported by (14) and it is essential to know when a given type of solutions can appear. For example, we can have smooth solitary waves, kink or anti-kink solutions, periodic peakon solutions, or compactons. Each type of solution has to be managed differently.

Depending of that, the gliomas growth can evolve following periodic or singular orbits. Such interesting connections can be obtained using the theory of bifurcation. Practically, the system (10) represents a planar system with three parametric functions. Following the papers of Jibin Li, Guarong Chen and Wenguio Rui [13, 14], the following results can be established between the analytical expressions of the parametric functions $b(u)$, $c(u)$, $e(u)$ from (14) and the types of its traveling wave solutions:

(1) When $b(u)$, $c(u)$, $e(u)$ lead to a smooth homoclinic orbit to a saddle point of (14), the equation will accept a *smooth solitary wave* solution.

(2) When $b(u)$, $c(u)$, $e(u)$ lead to a smooth heteroclinic loop connecting two saddle points of (14), the equation will accept a pair *kink - anti-kink* wave solution.

(3) In specific conditions a homoclinic orbit can define a *pseudo-peakon* solution of (14).

(4) A *peakon* solution of (14) can be generated by a curve triangle connecting saddle points and surrounding a periodic annulus of a center, as a limiting curve of a family of periodic orbits.

(5) A *family of periodic peakons* can be generated by a family of periodic orbits.

(6) When $b(u)$, $c(u)$, $e(u)$ lead to a family of open orbits, then the solution of (14) can be a family of *compactons*.

As the parametric functions $b(u)$, $c(u)$, $e(u)$ are very different from one patient to another, it is therefore clear that the mathematical models describing the growth of glioma are very rich from the perspective of their velocity and form of growing.

4. Conclusions

The paper focused on some mathematical models for glioma, one of the most invasive forms of brain cancer. The invasiveness is the result of two distinct phenomena: diffusion of the infected cells and proliferation of the static cells by division. Due to the two factors, the diffu-

sion-reaction equations were found as adequate tools for describing the growth of the tumor. Clinical investigations made by computer tomography and by the magnetic resonance technique show that, at a long time scale, the proliferation and invasion of the tumor can be compared to the propagation of traveling waves in inhomogeneous and non-isotropic media. From medical point of view the main parameter measuring the tumor growth is the volume-doubling time, while the mathematical models describe the variation of the tumor cells density.

Many mathematical models based on diffusion-reaction were proposed over the years, part of them considering the growth in itself, part of them simulating also the effects of surgical resection, radiotherapy and chemotherapy. The key issue of the simulations is to determine the traveling wave velocity and to make predictions on the life expectancies. The main mathematical difficulty in the direct solving of the corresponding diffusion-reaction equations is related to the fact that they lead to Abel equations, integrable in only a few cases. We mentioned two specific approaches that prevent such an outcome and allow finding explicit solutions. One of them, the first integrals method, also allows classifying the solutions following a bifurcation investigation. Many other approaches can be also used for investigating the integrability of the nonlinear systems. Part of such approaches is based on the extended or on the point-like symmetries of the system [15, 16]. A nice review of the methods that allow finding analitic solutions of various nonlinear models is offered in [17]

The main conclusion is that a large variety of behaviors can appear in glioma's propagation. Even if the same equation is used for describing it, the effective evolution is determined by very specific factors intimately related to the particularities of each patient. These factors are included in the mathematical model as parametric functions and determine the existence of solitary waves, kink waves or periodic waves, as solutions of the diffusion-reaction equation.

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