Reaction and diffusion phenomena in modeling the proliferation of the brain tumors

R.Constantinescu, A.Pauna, M.Stoicescu
Department of Physics, University of Craiova, Romania

Abstract:

- *The proliferation of gliomas, common brain tumors, is given by two main mechanisms, invasiveness and proliferative growth. It can be mathematical described by a reaction-diffusion equation.*
- *The long term expansion of the tumor can be simulated as a traveling wave.*

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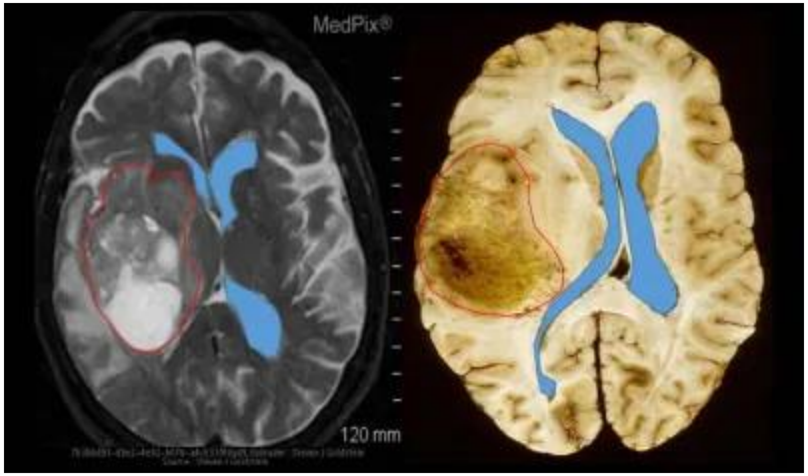
Introduction: medical data

- Gliomas arise from the supporting glial cells of the brain or their precursors and have 100% fatality rate within approximately one year, even after extensive surgery, radiotherapy and chemotherapy.
- They are almost impossible to cure because they grow and invade extensively before the patient notes any symptoms. Depending on their location on the brain, the tumors can be observed from a radius of 2 cm and become fatal at 6 cm ("fatal tumor burden").
- Gliomas grow with a constant radial velocity from 2 mm/year (low-grade gliomas) till ten times bigger (fast-grade gliomas).



Glioma (in red) pressing on the cerebral ventricles (in blue)

Hypothesis for a mathematical model

The mathematical models aim to describe the growth of glioma, predict the life expectation time and are based on the following facts:

- Two growth parameters are chosen: "Volume doubling time" and "Variation of the density of infected cells", $u(\vec{r},t)$
- The growth of gliomas is given by the superposition of two phenomena:
  - Proliferation, when the cells are stationary and multiply by repeated divisions, and
  - Motility or diffusion, consisting in a migration ("invasion") of the infected cells into the surrounding normal brain.
- The expansion process of the tumor's edges is assimilated with the propagation of a traveling wave.
- The cell diffusion follows the classical Fick law, while the growth due to the cell proliferation is linear.
- Gliomas can develop in a limited volume, metastasizing inside the brain.

Models on the gliomas' growth

I. Static models

- Are based on the models used for describing the metastases in the lungs.
- Do not consider the motility (diffusion of the cells) and describe the glioma growth on the base of an exponential law:

$$u = u(t) = U_0 e^{\rho t}$$

- They are known as static models because the volume-doubling time is constant.

II. Dynamical models with homogeneous tissue

- Clinical studies show difference between the times involved in the kinetics: hours to a few days for diffusion, days and even months for proliferation.

$$u_t = (u_t)_{diff} + (u_t)_{prolif} = \nabla(A\nabla u) + \rho u$$

Remarks on dynamical models with homogeneous tissue

1) The brain tissue is considered as homogenous, the tumor is uni-focal, with a spherical symmetric growing.
2) If we denote by *x* the radial direction, we have that:

$$u_t = \frac{\partial}{\partial x} \quad A\frac{\partial u}{\partial x} \quad + \rho u = A\frac{\partial^2 u}{\partial x^2} + \rho u$$

3) Measurements lead to the idea that the expansion velocity is constant:

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

4) The linear radial growth of tumor determines a cubic growth of the volume and the volume-doubling time is not constant.

Models with heterogeneity and anisotropy

- The RMN investigations show that 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 variable coefficients:

$$u_t = \frac{\partial}{\partial x}[\ A(u)\frac{\partial u}{\partial x}]\ + \rho(u)u$$

- More elaborated models take into consideration what is happening during the tumor's treatment, by surgery, chemotherapy or radiotherapy:

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

A general reaction-diffusion equation

- The previous equation can be seen as a general diffusion-reaction equation:

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

- This equation accepts traveling wave solutions that can be obtained by passing to the "wave variable“:

$$\xi = x - vt; \quad u' = du/d\xi; \quad u'' \quad d^2u/d\xi^2,$$

$$A(u)u'' + B(u)u'^2 + C(u)u' + E(u) = 0$$

$$B(u) = \frac{dA}{du}; \; C(u) = v.$$

- The equation from above is an Abel equation of the second kind and it is not integrable for arbitrary coefficients . Some traveling waves in parametric form can be found.

Glioma's waves through the attached flow method

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Article

Solving Nonlinear Second-Order Differential Equations through the Attached Flow Method

Carmen Ionescu and Radu Constantinescu *

Department of Physics, University of Craiova, 13 A.I.Cuza, 200585 Craiova, Romania
* Correspondence: rconsta@central.ucv.ro

Abstract: The paper considers a simple and well-known method for reducing the differentiability order of an ordinary differential equation, defining the first derivative as a function that will become the new variable. Practically, we attach to the initial equation a supplementary one, very similar to the flow equation from the dynamical systems. This is why we name it as the "attached flow equation". Despite its apparent simplicity, the approach asks for a closer investigation because the reduced equation in the flow variable could be difficult to integrate. To overcome this difficulty, the paper considers a class of second-order differential equations, proposing a decomposition of the free term in two parts and formulating rules, based on a specific balancing procedure, on how to choose the flow. These are the main novelties of the approach that will be illustrated by solving important equations from the theory of solitons as those arising in the Chafee–Infante, Fisher, or Benjamin–Bona–Mahony models.

Keywords: nonlinear differential equations; attached flow; Chafee–Infante equation; Fisher equation; Benjamin–Bona–Mahony equation

MSC: 34A34; 34C20; 35B08; 35C08; 35G20

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1. Introduction

The nonlinear evolutionary phenomena in the real world are commonly modeled either through nonlinear ordinary differential equations (NODEs), when we speak about one-dimensional dynamics, or through nonlinear partial differential equations (NPDEs), in the case of multi-dimensional processes. Many approaches for dealing with NPDEs, based on analytical or numerical methods [1–4], were proposed and are currently used by specialists. Some of them, such as the inverse scattering method [5,6], Lax operators [7], Hirota biliniarization [8–10], Lie symmetry theory [11–13], or ghost fields method [14–16], are general approaches for investigating and solving NPDEs. There are also more direct approaches, suitable for investigating specific classes of solutions, such as solitary and traveling wave solutions. From this last category belong the methods that look for solutions expressed by specific functions, such as sine–cosine [17], hyperbolic [18], or elliptic functions [19], as well as more elaborate methods, such as G'/G [20], Kudryashov [21], functional expansion [22], and so on [23]. All these methods have, as common features, the reduction of NPDEs to NODEs, by switching to a single coordinate—the wave variable. So, at the end, we arrive at the key issue of solving NODEs.

How to solve NODEs is not a trivial problem. This type of equation can accept many classes of solutions and there is not a clear algorithm on how to obtain them. Many alternative approaches have been proposed, and, mainly, these approaches can be divided into two categories: direct solving methods, based on reduction procedures, and approaches looking for solutions in the form of various expansions, either in terms of predefined functions, or, more generally, of known solutions of an auxiliary equation.

This paper refers to one of the direct solving methods suggested in the math textbooks [24,25] for the autonomous NODEs in which the independent variable does not

appear explicitly. It is quite a simple prescription for reducing the differentiability order that consists of attaching to the first derivative of the dependent variable a sort of "flow", a function that will be seen as a new variable. Finding the flow allows us to find the initial unknown variable by integrating the flow equation. It is an approach similar but still different from what is performed in the "first integrals" approach, when the "generalized velocities" become independent variables and the initial equation transforms into a system of two differential equations of decreased orders. Despite its simplicity, the recipe is not easy to be applied, because it is not always clear how to integrate the reduced equation in the flow variable. This paper makes an exhaustive analysis of how these difficulties can be overcome for a quite general class of second-order NODEs with polynomial coefficients. The main idea is related to how the flow should be attached so that the flow equation could be integrated. Based on a forced decomposition of the free term and on balancing requests, we will be able to formulate general rules and algorithms, as well as to effectively solve some equations belonging to the considered class. These two elements, the decomposition of the free term and a balancing analyze, represent in fact the original proposals of our approach.

The paper is organized as follows: after the introduction, we point out the class of equations on which we focus on. The difficulties in solving it and our prescriptions to overcome them will be underlined in Section 3. The Section 4 illustrates how these prescriptions work effectively on some specific equations, very important in the soliton theory. Models such as Benjamin–Bona–Mahony, Chafee–Infante, Fisher, or Dodd–Bullough are considered. Some concluding remarks and comments on the advantages and also on the limits of the attached flow method ends the paper.

2. Class of Equations to Be Investigated

To fix ideas, we consider the case when a dependent variable $u(\xi)$ evolves following an autonomous second order differential equation of the form $\Delta(u,\ u',\ u'') = 0$, where $u' = \frac{du}{d\xi}$, $u'' = \frac{d^2u}{d\xi^2}$. Moreover, we suppose that this equation can be solved for the highest derivative and brought to the form:

$$u'' = \Delta(u, u') = b(u)u'^2 + c(u)u' + e(u). \tag{1}$$

The coefficients $b(u)$, $c(u)$, $e(u)$ are considered as polynomials that could include negative powers of u. For convenience, these powers can be eliminated by bringing to the same denominator, the previous equation becoming:

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

The relation (2) describes in fact the most general form of equation generated when a 2-dimensional nonlinear diffusion equation is reduced to an ODE, using the wave transformation $\xi = x \pm \lambda t$. This is the type of equations we investigate in this paper, considering $A(u)$, $B(u)$, $C(u)$ and $E(u)$ as arbitrary polynomials that could consist in many monomials of positive degrees in u. Constant polynomials are accepted as "zero degree" terms. Practically, we have:

$$A(u) = \sum_{i=n(A)}^{N(A)} a_i u^i;\ B(u) = \sum_{i=n(B)}^{N(B)} b_i u^i;\ C(u) = \sum_{i=n(C)}^{N(C)} c_i u^i; E(u) = \sum_{i=n(E)}^{N(E)} e_i u^i. \tag{3}$$

In these relations $\{a_i,\ b_i,\ c_i,\ e_i\}$ are real constants, $\{N(A),\ N(B),\ N(C),\ N(E)\}$ denote the maximal degrees in u, while $\{n(A),\ n(B),\ n(C),\ n(E)\}$ denote the minimal degrees in u of the respective polynomials. All of them are considered integer numbers, positive or greater than zero.

Even if, as we mentioned, $A(u)$, $B(u)$, $C(u)$ and $E(u)$ are considered as polynomials, simpler cases, when part of them are vanishing or take the form of monomials, may occur.

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Ideas on the attached flow method

The attached flow method aims to solve an equation of the form:

$$A(u)u'' + B(u)u'^2 + C(u)u' + E(u) = 0$$

It can be written as an Abel equation with a change of variable of the form:

u'=f(u)

To avoid solving the Abel equation, the attached flow method proposes a forced decomposition of the reaction term:

$$E(u) = f(u)h(u)$$

The equation to be solved becomes a first order equation with two unknown variables:

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

This equation was solved in the cited paper by using special graduation rules.

Gliomas' growth through the functional expansion method

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Article

Solutions of the Bullough–Dodd Model of Scalar Field through Jacobi-Type Equations

Rodica Cimpoiasu, Radu Constantinescu and Alina Streche Pauna *

Department of Physics, University of Craiova, 13 A.I. Cuza Street, 200585 Craiova, Romania; rodica.cimpoiasu@edu.ucv.ro (R.C.); rconsta@central.ucv.ro (R.C.)
* Correspondence: streche.alina.z6e@student.ucv.ro (A.S.P)

Abstract: A technique based on multiple auxiliary equations is used to investigate the traveling wave solutions of the Bullough–Dodd (BD) model of the scalar field. We place the model in a flat and homogeneous space, considering a symmetry reduction to a 2D-nonlinear equation. It is solved through this refined version of the auxiliary equation technique, and multiparametric solutions are found. The key idea is that the general elliptic equation, considered here as an auxiliary equation, degenerates under some special conditions into subequations involving fewer parameters. Using these subequations, we successfully construct, in a unitary way, a series of solutions for the BD equation, part of them not yet reported. The technique of multiple auxiliary equations could be employed to handle several other types of nonlinear equations, from QFT and from various other scientific areas.

Keywords: scalar field theory; Bullough–Dodd equation; multiple auxiliary equations; traveling wave solutions

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1. Introduction

A model of a scalar field, $u(x^\mu)$, in Quantum Field Theory (QFT) can be described through a Lagrangian density of the form:

$$\mathcal{L} = \frac{1}{2}(\partial_\mu u)^2 - V(u). \tag{1}$$

Depending on the choice of the potential $V(u)$, the model can represent many types of physical situations. For example, the inflation phenomena in the early Universe is obtained when we choose a potential expressed through a tachyonic field. A tachyonic nonstandard Lagrangian of the DBI-type was proposed in [1]. It has the potential to be a multiplicative factor and a square root of derivatives as a "kinetic" term:

$$\mathcal{L}(u, \partial^\mu u) = -V(u)\sqrt{1 + g_{\mu\nu}\partial^\mu u \partial^\nu u}. \tag{2}$$

This is a particularly attractive model of K-inflation, defined by the local action for a scalar field minimally coupled to Einstein gravity, useful, as we said, in describing the very early stage of the Universe.

In this paper, we investigate the model generated by the potential:

$$V(u) = pe^u - \frac{q}{2}e^{-2u}. \tag{3}$$

It is known as the *Bullough–Dodd model* [2], and its spectrum consists of a single massive particle. In the context of QFT, in the perturbative approach, the model has to be linearized in order to generate a quantum model. At the classical level, in the $2D$ space, it can be seen as a nonlinear integrable model, belonging to the class of affine Toda field

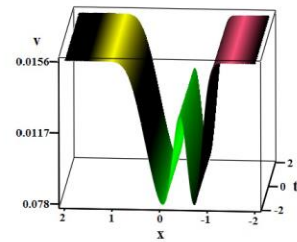

Figure 3. The numerical evolution of the W-shaped soliton wave solution (45) with $\phi(\xi) = \frac{2H_0\cosh\left(\frac{\sqrt{-4H_0H_2}}{2}\xi\right)}{\sqrt{-6H_0H_2}\sinh\left(\frac{\sqrt{-4H_0H_2}}{2}\xi\right) \mp \sqrt{-2H_0H_2}\cosh\left(\frac{\sqrt{-4H_0H_2}}{2}\xi\right)}$ at parametric choices $H_2 = -4c = -4k = -4H_1 = -68H_0 = -8$.

4.2. *Classes of Solutions Related to (23)*

By choosing some other appropriate values for the parameters $h_i, i = \overline{0,4}$ appearing in the general elliptic Equation (5), we can derive some new classes of traveling wave solutions for the studied model (18).

Case VI : Let us assume that the parameters α and β exist so that the parameters h_i, $i = \overline{0,4}$ from (23) appear in the form:

$$h_0 = h_1 = 0, h_2 = 1, h_3 = -\frac{2\beta}{\alpha}, h_4 = 0. \tag{47}$$

The compatibility requirement between Equations (23) and (47) imposes the fulfillment of the following constraint conditions:

$$b = -\frac{3\beta a}{\alpha}, \omega = -\frac{3ap}{k}, q = -pa^3, \forall p, \forall a, \forall k, \forall \alpha, \forall \beta. \tag{48}$$

Taking into consideration the known solution of the auxiliary ODE (5) under the conditions (47), we can generate for the master Equation (18) with $q = -pa^3$ a four-parameter family of soliton solutions:

$$v(x, t) = a\left[\frac{1 - 2\,\mathrm{sech}\left(kx - \frac{3ap}{k}t\right)}{1 + \mathrm{sech}\left(kx - \frac{3ap}{k}t\right)}\right]. \tag{49}$$

Case VII Let us use, instead of (47), some quite similar values of the parameters, namely:

$$h_0 = h_1 = 0, h_2 = -1, h_3 = \frac{2\beta}{\alpha}, h_4 = 0. \tag{50}$$

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Explicit solutions through the functional expansion method

We look for solutions of the wave propagation equation of the form:

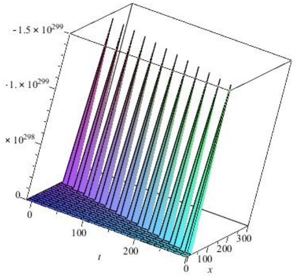
$$u = \sum_{n=0}^{m} P_n(G)(G'(\xi)^n$$

as functions of the solutions of the Riccati equation. The explicit solution that we found for gliomas growth is:

$$u = P_2 C^2 (\exp(\alpha\xi))^2 + \frac{3}{4} P_4^2 C^4 (\exp(\alpha\xi))^4$$

The graphical representation of the solution for the choice of parameters

$$P_i, C = const, \beta = 0, k = \frac{1}{4\alpha^2}, P_4 = \frac{3}{4} P_2^2, P_1 = 0, P_3 = 0, P_0 = 0, v = \frac{1}{2\alpha}$$



Conclusions

•The high invasiveness of glioma is the result of two distinct phenomena:

Diffusion of the infected cells, and

Proliferation of the static cells by division.

The diffusion-reaction equations are adequate for describing the growth of the tumor.

• Computer Tomograph and Magnetic Resonance Techniques 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.

• 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.

• Specific techniques as functional expansion and attached flow from the dynamical systems theory allow finding and classifying traveling wave solutions of nonlinear PDEs.

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THANK YOU !