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Symmetry Methods Applied to a Mathematical Model of a Tumour of the Brain

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We use symmetry methods to study the model of growth of a tumour of the brain proposed by Wein and Koplow (Mathematical modeling of brain cancer to identify promising combination treatments, *Preprint, D Sloan School of Management, MIT*, 1999). The aim here is also to demonstrate the use of symmetries to obtain more complex and reliable models. We translate some of the results found into properties of the tumour of the brain.

1 Introduction

A brain tumour is a dynamic system in which cancer cells grow and spread eventually killing good cells in the brain by deprivation of space and nutrients. The tumour spreads along the periphery and often dies out in the Centre due to a lack of fuel (oxygen and nutrients from the blood). This behaviour has been compared to that of a fire [10]. To be able to destroy the tumour treatments must be able to move faster than the tumour spreads if the treatment is to destroy effectively the tumour. Tumours are known to grow extremely fast. In reference [15] the tumour growth is assumed to be uniform and we claim that an improvement to the assumption of uniformity can be made. Since there are many aspects that can be considered in this particular problem, we concentrate only on the treatment aspect of the problem.

2 Spatio-temporal model

We recall that brain-cancer cells grow very fast and, at any point in time, only a portion of them are replicating and most cancer treatments only kill cells during this active phase.

This means that, when determining the net tumour-cell kill rates, models need take this constraint into account. A small fraction of tumour cells (about one in a thousand) called clonogenic cells are capable of regrowing the entire tumour. What does this mean? If the tumour is not to grow back after treatment all these cells must be killed. A tumour such as glioblastoma multiforme has many billions of cells and no single treatment presently available is capable of such a high kill rate. Wein's paper [15] demonstrates this. For example a log cell kill rate would kill 90 % of the tumour cells. A two log treatment (such as radiation) would kill 99 % of the tumour cells etc. It is important for the treatment to have the ability to target tumour cells rather than healthy cells and to move through the brain to reach the periphery of the tumour. This does affect how well a particular treatment works. We consider the following model [15], known as the Burgess equation [1],

$$\frac{\partial n(r,t)}{\partial t} = D\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial n(r,t)}{\partial r}\right) + pn(r,t) - k_t n(r,t), \tag{1}$$

where

- $n(r,t)$ is the concentration of tumour cells at location r at time t,
- D is the diffusion coefficient (estimated at 0.0013 cm^2 per day for glioblastoma multiforme) which measures the invasiveness of the glioblastoma multiforme cells,
- p is the proliferation rate of the tumour,
- k_t is the (therapy-dependent) killing rate at time t and
- r measures the distance from the Centre (i.e. the origin of glioblastoma multiforme).

Under the rescaling $t = (p - k_t)T$, $R = (|p - k_t|D)^2 r$ we may write (1) in the parameter-free form

$$\frac{\partial n}{\partial t} = \frac{\partial^2 n}{\partial r^2} + \frac{2}{r}\frac{\partial n}{\partial r} + n, \tag{2}$$

in which we have reverted to lower case variables.

Equations (1) and (2) assume spherical symmetry. Without that assumption we have

$$\frac{\partial n}{\partial t} = \frac{\partial^2 n}{\partial r^2} + \frac{2}{r}\frac{\partial n}{\partial r} + \frac{1}{r^2}\frac{\partial^2 n}{\partial \theta^2} + \frac{1}{r^2}\cot\theta\frac{\partial n}{\partial \theta} + \frac{1}{r^2\sin^2\theta}\frac{\partial^2 n}{\partial \phi^2} + n \tag{3}$$

in which the dependent variable $n = n(t, r, \theta, \phi)$. This enables us to consider a growth of the tumour which does not possess spherical symmetry and thereby opens the possibility to deal with an initial boundary of the tumour which is not spherical. The assumption that the tumour is spherical on detection is restrictive, but it is a starting point. In this paper we accept this restriction and concentrate on treatment models of this problem and leave the extension to nonspherical symmetry to future work.

3 Lie point symmetries for the differential equation with general $K(x,t)$

Equation (2) may be written in the normal form

$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} + u \tag{4}$$

by the standard substitution $u(t,x) = rn(t,r)$, $x = r$. Here we consider the more general differential equation for a single cell type given by

$$\frac{\partial^2 u}{\partial x^2} - K(x,t)u - \frac{\partial u}{\partial t} = 0, \tag{5}$$

where $K(x,t)$ describes the temporal profile of the treatment and $K(x,t)u$ is the rate of removal of the tumour cells. In the model in reference [15] the treatment is allowed to be only a function of the time and we modify this to make it a function of both the position of the of the cancerous cells and time. This is a more realistic assumption.

The analysis of (5) for its Lie point symmetries has been established for a long time [4] (see also [5] and [13]). No matter the structure of $K(x,t)$ and there are always the homogeneity and solution symmetries, *videlicet*

$$\Gamma_h = u\partial_u \qquad \text{and} \qquad \Gamma_s = f(t,x)\partial_u, \tag{6}$$

where $f(t,x)$ and is any solution of (5). There are four possibilities for the structure of $K(x,t)$.

- Case I: $K(x,t)$ is an undifferentiated function. There is no symmetry additional to the two generic symmetries in (6).
- Case II: $K(x,t) = K(x)$. There is the additional symmetry

$$\Gamma_1 = \partial_t \tag{7}$$

which reflects the invariant of (5) under time translation. Since $[\Gamma_1, \Gamma_h]_{LB} = 0$, the Lie algebra of the finite symmetries is $2A_1$ Mubarakzyanov classification scheme [6–9].

- Case III: $K(x,t) = N\left(Ax+B\right)^2 + C + M/\left(Ax+B\right)^2$, where A, B, C, M and N are arbitrary constants and M and A are nonzero. This case can be reduced to the equivalence class

$$K_E(x) = \frac{\mu}{x^2} \tag{8}$$

by means of a suitable transformation [12]. With K as in (8) the additional symmetries are

$$\Gamma_1 = \partial_t, \qquad \Gamma_2 = 2t\partial_t + x\partial_x, \qquad \Gamma_3 = 4t^2\partial_t + 4tx\partial_x - \left(x^2 - 2t\right)u\partial_u \tag{9}$$

which have the Lie brackets $[\Gamma_1, \Gamma_2] = 2\Gamma_1$, $[\Gamma_2, \Gamma_3] = 2\Gamma_3$ and $[\Gamma_3, \Gamma_1] = -4\Gamma_2$ which is a representation of $sl(2,\mathbb{R})$. Since $[\Gamma_i, \Gamma_h] = 0$, $i = 0, 3$, the algebra of the finite symmetries is $sl(2,\mathbb{R}) \oplus A_1$.

- Case IV: $K(x) = Ax^2 + Bx + C$, where again A, B and C are arbitrary constants. This case can be reduced to the equivalence class

$$K_E = 0 \tag{10}$$

by the same transformation as used in Case III. The additional Lie point symmetries are those in (9) plus

$$\Gamma_4 = \partial_x, \qquad \Gamma_5 = 2t\partial_x - xu\partial_u \tag{11}$$

which have the Lie brackets $[\Gamma_4, \Gamma_5] = -\Gamma_4$. Consequently one needs to introduce Γ_h to close the algebra. Since $[\Gamma_4, \Gamma_h] = 0$ and $[\Gamma_5, \Gamma_h] = 0$, the algebra is $A_{3,1}$, commonly known as the Weyl algebra.

We note that the existence of the exceptional symmetries, Γ_1, $\Gamma_{2\pm}$ and $\Gamma_{3\pm}$, is directly related to the existence of Noether symmetries [11] for a Lagrangian of the form $\frac{1}{2}\left(\dot{x}^2 + 4K\right)$ [3].

Each of these cases, although Case I is trivial, is the representative of an equivalence class under point transformation. The essential point is that the number of Lie point symmetries additional to the generic symmetries, Γ_h and Γ_s, is limited to 0, 1, 3 or 5 for an equation of the form (5). To construct solutions using the symmetries viable forms of $K(x,t)$ are those for which the number of Lie point symmetries is 3 or 5, then we can use the method of construction employed by Lemmer *et al* [3] in the case of the time-dependent Schrödinger equation.

4 Similarity solutions of the Burgess equation

In the original model [15] equation (5) has the form

$$\frac{\partial u}{\partial t} - \frac{\partial^2 u}{\partial x^2} - (p - k_t)u = 0, \tag{12}$$

where we recall that the constants p and k_t representative proliferation rate and the killing rate respectively. Equation (12) is of Class IV and has the nontrivial Lie point symmetries

$$\begin{aligned}
&\Gamma_1 = \partial_t, \qquad \Gamma_2 = 2t\partial_t + x\partial_x + 2(p-k_t)tu\partial_u,\\
&\Gamma_3 = 4t^2\partial_t + 4tx\partial_x + \left[4(p-k_t)t^2 - 2t - x^2\right]u\partial_u,\\
&\Gamma_4 = \partial_x, \qquad \Gamma_5 = 2t\partial_x - xu\partial_u,
\end{aligned} \tag{13}$$

where we note the differences in Γ_2 and Γ_3 due to the presence of the term $(p-k_t)u$ (12). Any of these symmetries apart from Γ_1 are suitable symmetries for the construction of similarities solutions and, guided by the example of Lemmer *et al* [3] in a treatment of the time-dependent Schrödinger equation, we choose Γ_4. The invariants of Γ_4 are found from the solution of the associated Lagrange's system

$$\frac{\mathrm{d}t}{0} = \frac{\mathrm{d}x}{1} = \frac{\mathrm{d}u}{0} \tag{14}$$

and are

$$v = t \qquad \text{and} \qquad w = u \tag{15}$$

so that we may set

$$u = f(t) \tag{16}$$

and substitute it into (12) to obtain

$$f(t) = \exp\left[(p-k_t)\,t\right], \tag{17}$$

where we omit the multiplicitive constant of integration. Hence

$$u_0 = \exp\left[(p-k_t)\,t\right], \tag{18}$$

where we use the subscript zero to denote the basic solution. We use the property that symmetries map solutions into solutions and apply Γ_5 to the solution surface for u_0, *videlicet*

$$\Sigma_0 = u^{-1}\exp\left[(p-k_t)\,t\right] \tag{19}$$

to obtain

$$u_1 = x\exp\left[(p-k_t)\,t\right]. \tag{20}$$

Similarly we obtain

$$u_2 = \left(2t + x^2\right)\exp\left[(p-k_t)\,t\right], \qquad u_3 = \left(6tx + x^3\right)\exp\left[(p-k_t)\,t\right], \qquad \ldots. \tag{21}$$

Equally we could commence with Γ_5 to obtain a basic solution and use Γ_4 to create further solutions from the solution surface. We find that

$$\begin{aligned}
&v_0 = t^{-1/2}\exp\left[(p-k_t)\,t - \frac{x^2}{4t}\right], \qquad v_1 = -\frac{x}{2t^{3/2}}\exp\left[(p-k_t)\,t - \frac{x^2}{4t}\right],\\
&v_2 = t^{-1/2}\left(\frac{x^2}{4t^2} - \frac{1}{2t}\right)\exp\left[(p-k_t)\,t - \frac{x^2}{4t}\right], \qquad \ldots.
\end{aligned} \tag{22}$$

We note that we can use Γ_2 and Γ_3 to generate solutions in the same way and that they also act as ladder operators on the solutions obtained by the other symmetries.

We recall that intensity of cells is essentially given by $n = u/x$ so that the number of cells within a sphere of radius X is

$$N_X = 4\pi \int_0^X x^2 \mathrm{d}x\, n(x,t) = 4\pi \int_0^X xu(x,t)\,\mathrm{d}x. \tag{23}$$

A feature of the solutions is the critical nature of the value of the expression $p-k_t$. If $p-k_t > 0$, the number of cells increases exponentially with time which is one of the salient properties of glioblastoma multiforme and the reason for its generally fatal outcome. By the time the tumour is large enough to be detected the number of cells is proliferating at a prodigious rate.

In the case that $p-k_t < 0$ the solutions indicate a rapid drop in the number of cells. However, the assumption of a constant killing rate is not a good one. In the case of chemotherapy the efficacy of the chemical decreases with time, usually in an exponential fashion. Thus we should replace k_t with something like $k\exp[-\sigma t]$. The number of nontrivial symmetries is unchanged. They are

$$\begin{aligned}
&\Lambda_1 = \partial_t + ku\exp\left[-\sigma t\right]\partial_u, \qquad \Lambda_2 = 2t\partial_t + x\partial_x + 2t\left[p - k\exp\left[-\sigma t\right]\right]u\partial_u,\\
&\Lambda_3 = 4t^2\partial_t + 4tx\partial_x - \left[2t + x^2 - 4t^2\left(p - k\exp\left[-\sigma t\right]\right)\right]u\partial_u,\\
&\Lambda_4 = \partial_x, \qquad \Lambda_5 = 2t\partial_x - xu\partial_u.
\end{aligned} \tag{24}$$

In the same fashion as above we obtain the two families of solutions

$$\begin{aligned}
&u_0 = \exp\left[pt + \frac{k}{\sigma}\,\mathrm{e}^{-\sigma t}\right], \qquad u_1 = x\exp\left[pt + \frac{k}{\sigma}\,\mathrm{e}^{-\sigma t}\right]\\
&u_2 = \left(2t + x^2\right)\exp\left[pt + \frac{k}{\sigma}\,\mathrm{e}^{-\sigma t}\right], \qquad \ldots,\\
&v_0 = t^{-1/2}\exp\left[pt + \frac{k}{\sigma}\,\mathrm{e}^{-\sigma t} - \frac{x^2}{4t}\right], \qquad v_1 = -\frac{x}{2t^{3/2}}\exp\left[pt + \frac{k}{\sigma}\,\mathrm{e}^{-\sigma t} - \frac{x^2}{4t}\right],\\
&v_2 = t^{-1/2}\left(\frac{x^2}{4t^2} - \frac{1}{2t}\right)\exp\left[pt + \frac{k}{\sigma}\,\mathrm{e}^{-\sigma t} - \frac{x^2}{4t}\right], \qquad \ldots.
\end{aligned}$$

in which we note the first similarity to the solutions listed in (21) and (22) and from which we see that the concentration of the tumor cells increases with time for both series of solutions and eventually decreases with radial distance in the second series. The assumption of a constant kill rate in space is suspect since the inner cells are more crowded and the supply of nutrients is not as great as on the surface of the tumour. From our discussion of the symmetries available for different $K(x,t)$ we can see that there are several possibilities which maintain a rich supply of Lie point symmetries. For example, we take $K(x,t) = px - k$, with both p and k constant for simplicity although they both could be time-dependent. Equation (12) now has the five nontrivial Lie point symmetries

$$\begin{aligned}
&\Delta_1 = \partial_t, \qquad \Delta_2 = 2t\partial_t + \left(x - 3pt^2\right)\partial_x + t\left(3px - 2k - p^2t^2\right)u\partial_u,\\
&\Delta_3 = 4t^2\partial_t + 4t\left(x - pt^2\right)\partial_x - \left(4kt^2 + x^2 + 2t - 6pt^2x\right)u\partial_u,\\
&\Delta_4 = \partial_x + ptu\partial_u, \qquad \Delta_5 = 2t\partial_x + \left(pt^2 - x\right)u\partial_u
\end{aligned} \tag{25}$$

and from Δ_4 and Δ_5 we obtain, in the manner described above, the solutions

$$\begin{aligned}
&u_0 = \exp\left[ptx + \frac{1}{3}p^2t^3 - kt\right], \qquad u_1 = \left(x + pt^2\right)\exp\left[ptx + \frac{1}{3}p^2t^3 - kt\right],\\
&u_2 = \left[2t + \left(x + pt^2\right)^2\right]\exp\left[ptx + \frac{1}{3}p^2t^3 - kt\right], \qquad \ldots,
\end{aligned}$$

$$
\begin{aligned}
v_0 &= t^{-1/2}\exp\left[\frac{1}{2}ptx - kt - \frac{1}{12}p^2t^3 - \frac{x^2}{4t}\right],\\
v_1 &= -\frac{1}{2}t^{-1/2}\left(pt + \frac{x}{t}\right)\exp\left[\frac{1}{2}ptx - kt - \frac{1}{12}p^2t^3 - \frac{x^2}{4t}\right],\\
v_2 &= \frac{1}{4}t^{-1/2}\left[\left(pt + \frac{x}{t}\right)^2 - \frac{2}{t}\right]\exp\left[\frac{1}{2}ptx - kt - \frac{1}{12}p^2t^3 - \frac{x^2}{4t}\right], \qquad \ldots
\end{aligned} \tag{26}
$$

from which we can infer the first set of solutions increases with no bound for both t and x and the second series of solutions tends to zero for large t and x.

5 Conclusion

We conclude that the therapy-dependent killing rate K need not be a function of time only but of both position and time. This is an improvement to the model of Wein & Koplow [15]. The symmetry analysis of the model yields some interesting properties, i.e., the symmetries are ladder operators and can be used to map solutions into solutions of the model. Several aspects of the problem remain unanswered from a mathematical point of view and, as additional therapies are developed, definitions of parameters in the model will be helpful in planning the dose and timing of these therapies which are currently limited by the tolerance of normal brain for XRay-irradiation and hematopeotic tissues for chemotherapies. In addition to this one may ask how much the diffusion constant D varies from one glioma to another and how the cell concentration or cell type contributes independently to D. In his book on Mathematical Biology Murray [10] remarks that the prediction of tumour response to therapy is a goal which mathematical models could help to reach.

In the treatment of HIV-AIDS the use of recombinant viruses has been proposed [14] and numerical simulations suggest that such viruses are very effective in reducing the viral load of the HIV and reasonably effective in restoring the number of healthy cells. Effectively the recombinant virus controls the evolution of the disease although it does not provide a cure. In the case of a tumour such as glioblastoma multiforme the development of a viral therapy could remedy the problem of exponential decay of the therapeutic agent. Now there are two coupled equations, one for the growth of the number of cancer cells and one for the growth of the number of viruses. A model for such a system is a generalisation of the Burgess equation (1) such as

$$
\begin{aligned}
\frac{\partial n_1}{\partial t} &= D_1\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial n_1}{\partial r}\right) + (p_1 - k_2n_2)\,n_1,\\
\frac{\partial n_2}{\partial t} &= D_2\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial n_2}{\partial r}\right) + (p_2 - k_1n_1)\,n_2
\end{aligned} \tag{27}
$$

in which n_1 and n_2 represent the densities of the tumour cells and viruses, p_1 and p_2 their proliferation rates and k_1 and k_2 the killing rates for cells/virus. Such models are to be the subject of further investigation.

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