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DEVELOPING A NUMERICAL SIMULATION OF VASCULAR BRAIN TUMOR GROWTH USING 3-DIMENSIONAL PARTIAL DIFFERENTIAL EQUATIONS.

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Abstract
In this paper a model of vascular brain tumor is developed and solved using Adomian Decomposition Method (ADM). The model is developed as a set of partial differential equations giving the spatial-temporal changes in cell nutrients concentrations based on diffusion dynamics. The model predicts the volume of the tumor within certain time schedules. It is formulated in three dimensions whereby the tumor is assumed to be growing in radial symmetry. Under this algorithm, equation is decomposed into a series of Adomian polynomials. The model predicts the volume of the tumor at any time schedule after vascularization without necessarily imaging. Results obtained from the simulation of growth and dynamics of malignant brain tumor (GBM) compares well with those from medical literature hence, can provide clinical practitioners with valuable information on the potential effects of therapies in their exact schedules.
Keywords; Vascular tumor, volume of the tumor, Adomian Decomposition, and Diffusion dynamics.

1.Introduction

Adomian decomposition method for solving differential and integral equations, linear or non-linear was proposed by the American physicist called Adomian (1980). The method has been used to solve effectively and easily a large class of linear and non- linear ordinary and partial differential equations
It has the advantage of converging to the exact solution and can easily handle a wide class of both linear and non-linear differential and integral equations. The purpose of this paper is to apply this new and reliable method for solving ordinary and partial differential equation in providing a numerical simulation of vascular brain tumor growth.
It is fundamental to note that the development of a primary solid tumor begins with a single normal cell becoming transformed as a result of mutations in certain key genes. This transformed cell differs from a normal one in its escape from the body's homeostatic mechanisms, leading to inappropriate proliferation and a tendency to override apoptosis (cell death). An individual tumor cell has the ability over successive divisions to develop into a cluster of tumor cells. Further growth and proliferation leads to the development of an avascular tumor consisting of approximately 10^6 cells. A solid tumor may typically be detected only when it is approximately1cm in diameter. By then it contains approximately 10^9 cells. At this stage the cells feed on oxygen and other nutrients present in the local environment. A tumor which has developed to this stage is said to be vascularized. After the early stages of growth, the tumor's structure consists of an inner zone of necrotic cells (dead due to lack of nutrients) and an outer zone of living cells. This outer zone is further divided into a layer composed of non-proliferating cells and a layer largely composed of proliferating cells. The model analyzed here devises a method to provide a reasonably realistic discrete size of a tumor in different schedules.
For patients who are unable to undergo treatment immediately after scanning, medical practitioners can use the simulation to predict the size of the tumor in specific time schedules without further scanning.

2. Literature review

Since its introduction, the method has been attracting the attention of many mathematicians, physicist and engineers. It has an advantage of converging to the exact solutions and can easily handle a wide class of linear and non- linear differential and integral equations.

It has been the subject of extensive analytical and numerical studies. A large amount of literature has been developed concerning the method by applying it to large size of applications in applied sciences.

In his book, Adomian (1994) showed the possibility of obtaining explicit solutions of wide varieties of physically significant problems, e.g. He analyzed the mathematical models of the dynamics involved in population of bacteria, viruses, antigens or tumor cells. These models are usually nonlinear hence their solution generally begins by some form of linearization or perturbation. He found that the method is independent of linearization, perturbation as well as discretization hence greatly reducing the Cpu time.

Aminataei and Hosseini, (2007) compared the stability of Adomian decomposition method with other numerical methods. In comparison with the solution obtained by using the finite difference method, the conclusion was that Adomian decomposition method is weaker in stability than finite difference method but stronger in convergence. The general conclusion was that Adomian decomposition method, despite its greater efficiency in solving differential equations suffers certain weaknesses.

Emad *et al.*, (2012) developed a new straight forward approach for solving ordinary and partial second-order boundary value problems with Neumann boundary conditions. This approach depends mainly on a new definition of the differential operator and its inverse, which has been modified for Neumann boundary conditions. The effectiveness of the proposed approach is verified by several linear and nonlinear examples.
Significant research has also been done in the modeling of tumors using theoretical models and computer simulations. Previous modeling has been done on a range of tumor behaviors, including proliferative growth of tumor core.

Some of the earliest work in modeling of tumors using a three –dimensional cellular automaton on a cubic lattice was carried out by Dutching and Vogelsaenger (1985) for very small tumors. These automaton rules were designed to reflect nutritional needs for tumor growth. Other important factors, such as surrounding cells and mechanical pressure, however, remained unconsidered.

Chiocca *et al.*(2000) developed a three dimensional cellular automaton model which describes tumor as a function of time. The algorithm takes into account that growth starts out from a few cells, passes through a multi cellular tumor spheroid (MTS) stage and proceeds to the macroscopic stages. According to their work an idealized case of a tumor is essentially spherical within a small degree of randomness. However their algorithm gave simulation on only four designated time points i.e. spheroid stage, detectable lesion, diagnosis and death. As well their algorithm could not provide information about the rate of diffusion of the nutrients within the proliferative rim of the tumor.

Nicholson (2001) considered diffusion and related transport mechanisms in brain tissue. He highlighted the role of diffusion in brain function. According to him, the spaces between cells can be likened to the water phase of foam and many substances move within this complicated region. Diffusion in this space can be accurately modeled with appropriate modifications of classical equations. Besides delivering glucose and oxygen from the vascular system to the brain cells, diffusion also moves informational substances between cells, a process known as volume transmission. Diffusion is also essential to many therapies that deliver drugs to the brain.

Cheng (2005) developed a mathematical model for the quantitative description of the dynamics of avascular tumor growth. The model was formulated as a set of partial differential equations describing the spatial-temporal changes in cell concentrations based on reaction-diffusion dynamics and the law of mass conservation. His model was solved using standard finite difference techniques. He observed that even though the results compared well with those of experimental data, they could only be obtained at discrete points depending on the step sizes provided. This created a shortcoming since tumor growth is a dynamic process.

Friendman (2006) presented generic PDE models which governs the growth and development of tumors. He observed that the tumor region is a three dimensional region $\Omega(t)$ which varies with time (t).Within $\Omega(t)$ there

are several types of cells as well as several different chemicals such as oxygen and other nutrients. The densities of the cells and the concentration of the chemicals satisfy a system of partial differential equations. However a major difficulty in the analysis of the models was due to the fact that the region Ω(t) is one of the unknowns hence becoming a free boundary problem. As well being generic models he never specified the parameters and hence never obtained the simulation.

Friendman (2010) developed a partial differential equation model of the growth and response to treatment of prostate cancer. He considered existence and uniqueness of solutions for proven radially symmetric case. Finally, numerical simulations of a tumor growing in two dimensions with radial symmetry were carried out in order to evaluate the therapeutic potential of different treatment strategies. The simulations were able to reproduce a variety of clinically observed responses to treatment and suggested treatment strategies that may result in tumor remission, underscoring the model's potential to make a significant contribution in the field of prostate cancer therapeutics. He proved that for tumor cell growth rate the tumor radius was not consistent but had oscillator behavior.

Hillen and Painter, (2013); in their journal entitled Mathematical Modeling of Glioma growth; they presented a model of glioma invasion along the aligned neural fibre tracts. According to them, the invasion is facilitated by the directed movement of cells along the aligned neural fibre tracts that form a large component of the white matter. Diffusion Tensor Imaging (DTI) provides a window for visualizing this anisotropy and gaining insight on the potential invasive pathways. They demonstrated the results in a simple model for glioma growth exploiting both synthetic and genuine DTI datasets to reveal the potentially crucial role of anisotropic structure on invasion.

3. Methodology

Under this method, the model is separated into linear and nonlinear portions. The linear operator representing the linear portion of the equation is inverted and the inverse operator is then applied to the equation. Initial conditions for tumor growth and development in three dimensions are taken into consideration. The nonlinear portion is decomposed into a series of Adomian polynomials. This method generates a solution in the form of an infinite series which converges to accurate solutions.

3.1 Model formulation

The model for diffusion of nutrients within the tumor cells in three dimensions is;

$$\frac{\partial c}{\partial t} = Dc\Delta^2 C + f(x,y,z) \tag{1}$$

Subject to the initial condition

$$C(x,y,z,0) = 0$$

Whereby

D_C is the diffusion coefficient and $f(x,y,z)$ represents the nutrients concentration after the process of angiogenesis has taken place.

Taking the diffusion coefficient to be $1/12$, then the exact model for simulation in three dimension is given as;

$$\frac{\partial c}{\partial t} = \frac{1}{12}(x^2 C_{xx} + y^2 C_{yy} + z^2 C_{zz}) + x^4 y^4 z^4 \tag{2}$$

Applying the inverse operator L^{-1} to both sides of equation (2) yields;

$$C(x,y,z,t) = x^4y^4z^4t + \frac{1}{12}L_t^{-1}(x^2C_{xx} + y^2C_{yy} + z^2C_{zz})$$

$$C_0(x,y,z,t) = x^4y^4z^4t \tag{3}$$

$$C_1(x^4y^4z^4t) = \frac{1}{12}L_t^{-1}\{x^2(C_0)_{xx} + y^2(C_0)_{yy} + z^2(C_0)_{zz}\}$$

$$= \frac{3}{2}x^4y^4z^4t^2 \tag{4}$$

$$C_2(x,y,z,t) = \frac{1}{12}L_t^{-1}\{x^2(C_1)_{xx} + y^2(C_1)_{yy} + z^2(C_1)_{zz}\}$$

$$= \frac{3}{2}x^4y^4z^4t^3 \tag{5}$$

$$C_3(x,y,z,t) = \frac{1}{12}L_t^{-1}\{x^2(C_2)_{xx} + y^2(C_2)_{yy} + z^2(C_2)_{zz})$$

$$= \frac{9}{8}x^4y^4z^4t^4 \tag{6}$$

$$C_4(x,y,z,t) = \frac{1}{12}L_t^{-1}\{x^2(C_3)_{xx} + y^2(C_3)_{yy} + z^2(C_3)_{zz}\}$$

$$= \frac{27}{40}x^4y^4z^4t^5 \tag{7}$$

$$C_5(x,y,z,t) = \frac{1}{12}L_t^{-1}\{x^2(C_4)_{xx} + y^2(C_4)_{yy} + z^2(C_4)_{zz}\}$$

$$= \frac{27}{80}x^4y^4z^4t^6 \tag{8}$$

$$C_6(x,y,z,t) = \frac{1}{12}L_t^{-1}\{x^2(C_5)_{xx} + y^2(C_5)_{yy} + z^2(C_5)_{zz}\}$$

$$= \frac{81}{560}x^4y^4z^4t^7 \tag{9}$$

$$C_7(x,y,z,t) = \frac{1}{12}L_t^{-1}\{x^2(C_6)_{xx} + y^2(C_6)_{yy} + z^2(C_6)_{zz}\}$$

$$= \frac{243}{4480} x^4 y^4 z^4 t^8 \tag{10}$$

$$C_8(x,y,z,t) = \frac{1}{12} L_t^{-1}\{x^2(C_7)_{xx} + y^2(C_7)_{yy} + z^2(C_7)zz\}$$

$$= \frac{81}{4480} x^4 y^4 z^4 t^9 \tag{11}$$

$$C_9(x,y,z,t) = \frac{1}{12} L_t^{-1}\{x^2(C_8)_{xx} + y^2(C_8)_{yy} + z^2(C_8)_{zz}\}$$

$$= \frac{243}{44800} x^4 y^4 z^4 t^{10} \tag{12}$$

$$c_{10}(x,y,Z,t) = \frac{1}{12} L_t^{-1}\{x^2(C_9)_{xx} + y^2(C_9)_{yy} + z^2(C_9)_{zz}\}$$

$$= \frac{729}{492{,}800} x^4 y^4 z^4 t^{11} \tag{13}$$

$$C_{11}(x,y,z,t) = \frac{1}{12} L_t^{-1}\{x^2(C_{10})_{xx} + y^2(C_{10})_{yy} + z^2(C_{10})_{zz}\}$$

$$= 0.000369825 x^4 y^4 z^4 t^{12} \tag{14}$$

$$C_{12}(x,y,z,t) = \frac{1}{12} L_t^{-1}\{0.013313717 x^4 y^4 z^4 t^{12}\}$$

$$= 0.0000853 x^4 y^4 z^4 t^{13} \tag{15}$$

$$C_{13}(x,y,z,t) = \frac{1}{12} L_t^{-1}\{0.0030724 x^4 y^4 z^4 t^{13}\}$$

$$= 0.00001839 x^4 y^4 z^4 t^{14} \tag{16}$$

$$C_{14}(x,y,z,t) = \frac{1}{12} L_t^{-1}\{0.00658371 x^4 y^4 z^4 t^{14}\}$$

$$= 0.00000366 x^4 y^4 z^4 t^{15} \tag{17}$$

In this model, ADM generates the solution in a series of the form;

$$C(x,y,z,t) = C_0(x,y,z,t) + C_1(x,y,z,t) + ----- C_{14}(x,y,z,t) ---- \tag{18}$$

Therefore from equation (3) to (17) the solution in a series form is given by;

$$C(x,y,z,t) = x^4y^4z^4(t + \frac{3}{2}t^2 + \frac{3}{2}t^3 + \frac{9}{8}t^4 + \frac{27}{40}t^5 + \frac{27}{80}t^6 + \frac{81}{560}t^7 + \frac{243}{4480}t^8 \ ----) \quad (19)$$

Where $C(x,y,z,t)$ is the level of nutrients concentration in three dimensions which determines volume of the tumor. Taking $x^4y^4z^4$ as the rate of diffusion of the nutrients and t as variable for time at selected points, then equation (19) generate the results given in the tables below.

4. Results and Discussion.

Taking $x^4y^4z^4 = 1.331cm^3/year$ as the rate of diffusion of nutrients in three dimensions, then results generated from equation (19) alongside the analytical ones are as tabulated.

Time in Days	***Experimental Radius(cm)***	***Analytical Volume (cm^3)***	***Simulation Volume (cm^3)***	***Error (cm^3)***	***% Error***
280	*1.05*	*4.85*	*3.99*	*0.86*	*17.7*
310	*1.20*	*7.24*	*5.22*	*2.02*	*27.9*
345	*1.30*	*9.21*	*7.11*	*2.10*	*22.8*
375	*1.50*	*14.14*	*9.22*	*4.92*	*34.8*
415	*1.65*	*18.82*	*12.99*	*5.83*	*31.0*
454	*1.85*	*26.53*	*18.08*	*8.45*	*31.9*
507	*2.20*	*43.41*	*28.18*	*15.23*	*35.1*
560	*2.50*	*65.48*	*43.78*	*21.70*	*33.1*
625	*3.00*	*113.14*	*74.99*	*38.15*	*33.7*

Table 1: Comparison between analytical and simulation volume at $x^4y^4z^4=1.331cm^3/year$

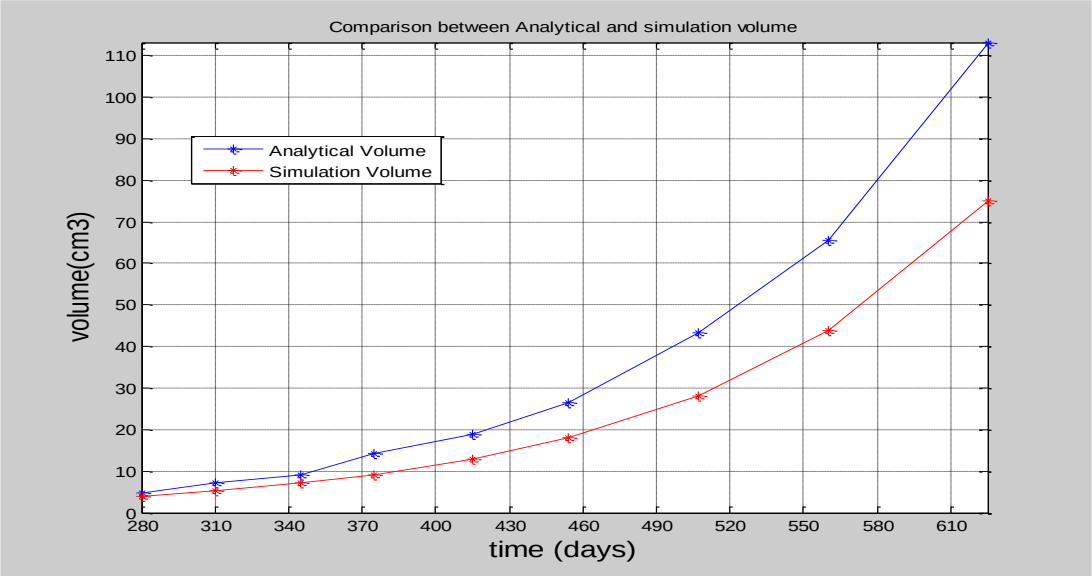

Fig.1: Analytical and simulation volume against time in days at $x^4y^4z^4=1.331cm^3/year$

Table 1 gives the comparison between analytical and simulation volume where the rate of diffusion in three dimensions is assumed to be $1.331cm^3/year$. The model provides unrealistic results as reflected at selected time points. It is observed that three dimensional model is not viable at this rate of nutrients diffusion.
Fig. 1 gives the plots of analytical and simulation volume where the red curve gives the simulation predictions while the blue curve gives the test case. As noted, there is no convergence at this stage of vascularization once the rate of diffusion of nutrients is $1.331cm^3/year$.

The table below gives the results for three dimensional model at $x^4y^4z^4 = 2.0cm^3 / year$.

Taking $x^4y^4z^4 = 2.0cm^3 / year$ as the rate of diffusion of the nutrients in three dimensions, then results generated from equation (19) alongside the analytical ones are as tabulated.

Time in Days	***Experimental Radius(cm)***	***Analytical Volume (cm^3)***	***Simulation Volume (cm^3)***	***Error (cm^3)***	***% Error***
280	*1.05*	*4.85*	*5.99*	*1.14*	*23.5*
310	*1.20*	*7.24*	*7.85*	*0.61*	*8.43*
345	*1.30*	*9.21*	*10.69*	*1.48*	*16.1*
375	*1.50*	*14.14*	*13.85*	*0.29*	*2.05*
415	*1.65*	*18.82*	*19.53*	*0.71*	*3.77*
454	*1.85*	*26.53*	*27.17*	*0.64*	*2.41*
507	*2.20*	*43.41*	*42.35*	*1.06*	*2.44*
560	*2.50*	*65.48*	*65.77*	*0.29*	*0.44*
625	*3.00*	*113.14*	*112.68*	*0.46*	*0.41*

Table 2: Comparison between analytical and simulation volume at $x^4y^4z^4=2.0cm^3/year$

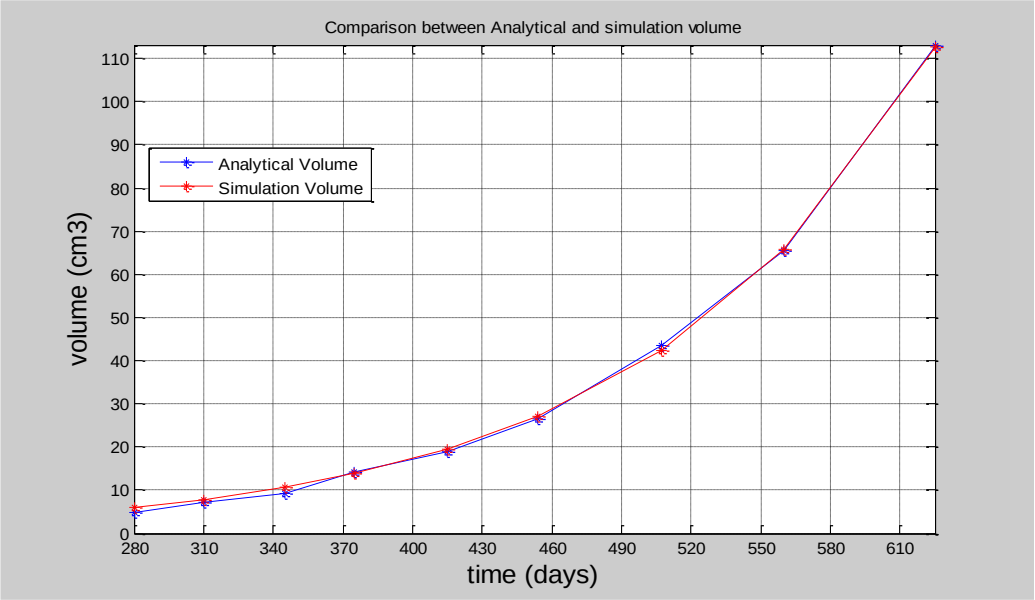

Fig.2: Analytical and simulation volume against time in days at $x^4y^4z^4=2.0cm^3/year$

Table 2 gives the comparison between analytical and simulation volume where the rate of diffusion of the nutrients is assumed to be $2.0cm^3$/year. It is observed that the simulation of this model provides very realistic results at most of the selected time points.

Fig. 2 gives the plots of analytical and simulation volume against time in days where the red curve gives the simulation predictions while the blue curve gives the test case. Simulation in this model gives very strong convergence at this rate of diffusion of the nutrients.

The table below gives the results for three dimensional model at $x^4y^4z^4 = 2.1cm^3 / year$.

Taking $x^4y^4z^4 = 2.1cm^3 / year$ as the rate of diffusion of the nutrients in three dimensions then results generated from equation (19) alongside the analytical ones are as tabulated.

Timein Days	***Experimental Radius(cm)***	***Analytical Volume (cm^3)***	***Simulation Volume (cm^3)***	***Error (cm^3)***	***% Error***
280	*1.05*	*4.85*	*6.29*	*1.44*	*29.7*
310	*1.20*	*7.24*	*8.23*	*0.99*	*13.7*
345	*1.30*	*9.21*	*11.22*	*2.01*	*21.8*
375	*1.50*	*14.14*	*14.55*	*0.41*	*2.9*
415	*1.65*	*18.82*	*20.50*	*1.68*	*8.9*
454	*1.85*	*26.53*	*28.53*	*2.00*	*7.5*
507	*2.20*	*43.41*	*44.46*	*1.05*	*2.4*
560	*2.50*	*65.48*	*69.08*	*3.6*	*5.5*
625	*3.00*	*113.14*	*118.31*	*5.17*	*4.6*

Table 3: Comparison between analytical and simulation volume at $x^4y^4z^4=2.1cm^3/year$

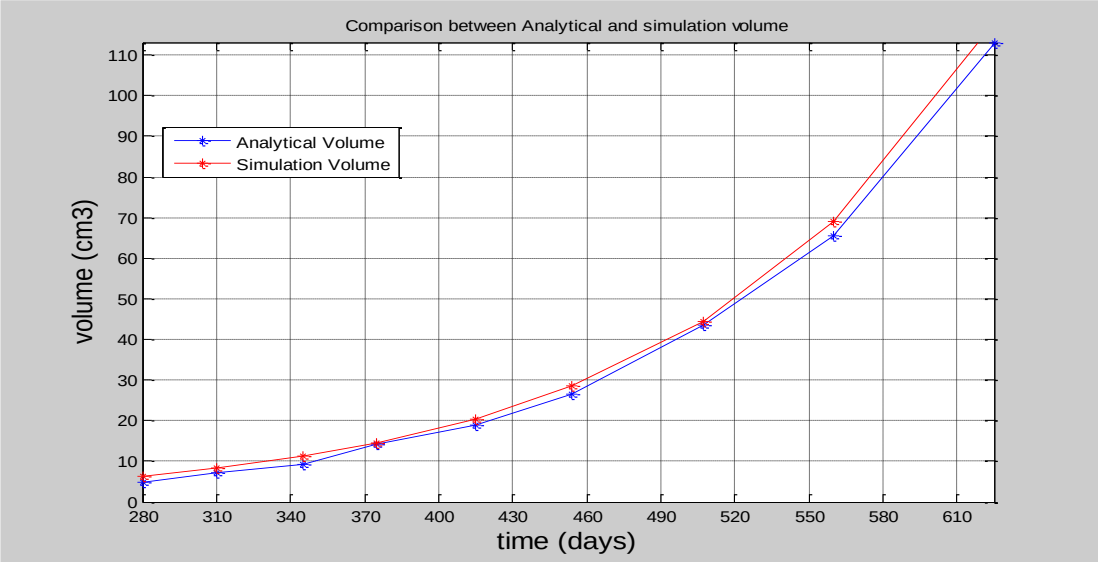

Fig.3: Analytical and simulation volume against time in days at $x^4y^4z^4$=2.1cm^3/year

Table 3 gives the comparison between analytical and simulation volume where the rate of diffusion of the nutrients is assumed to be 2.1cm^3/year. It is observed that any attempt to raise the rate of diffusion will increase the volume at selected time points. This confirms that the only viable rate of diffusion in this model is 2.0cm^3/year.

Fig. 3 gives the plots of analytical and simulation volume against time, where the red curve gives the simulation predictions while the blue curve gives the test case. Simulation in this model fails to converge owing to high rate of diffusion.

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5.0 Conclusion

Results obtained from the simulation predict the growth and dynamics of malignant brain tumor (GBM) proliferation at selected time points. They compare well with the analytical data obtained from experimental radius which is obtained from the medical literature, hence can lead to insights within cancer research and into complex bio systems related to this field. Quantitative results from the present model will provide clinical practitioners with valuable information of how the tumor grows and specifically be able to approximate the volume of the tumor in different time schedules. This will help in future therapeutic strategies to be manipulated in managing the disease.

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