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OBSERVATION OF TRANSITION POINT IN CASE OF 3D QUANTITATIVE BRAIN TUMOR GROWTH MODEL BASED ON CELL PROLIFERATION AND DIFFUSION

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Abstract

The focus of this work was to develop a 3D mapping of brain tumor (glioma) growth based on cell proliferation and diffusion. In this mathematical model, we incorporated high resolution brain tissue maps (white and gray matter) from an anonymized pediatric patient and initialized the model with a single voxel seed point of tumor with a Gaussian distribution. We used this model to investigate the ratio of growth rate to the diffusion coefficient (ρ/D) which determines the proportion of tumor that is detectable. After expansion of the tumor growth model to three dimensions and solving the differential equations for our specific starting conditions, we performed several simulations to assess tumor growth patterns. After observing the performance of the model at varying time points across a one year time frame with different values for ρ/D, we ascertained that the tumor diffused more rapidly than the cell proliferated for a short period of time followed by an exponential growth in detectable tumor size. This growth pattern results in a transition point in the voxel-wise cell count with respect to time when the rate of diffusion and proliferation equilibrate and can in some cases result in the tumor becoming undetectable for a period of time.

Key Words*:* Proliferation, Diffusion, Tumor, Transition point.

Introduction

Glioma are major intracranial tumors that constitute more than 50% of all primary brain tumors and are one of the major causes of morbidity and mortality in the world [1]. They are thought to arise from the supporting glial cells of brain that have lost or ceased to respond to normal growth regulatory mechanism, presumably through mutations and/or altered

gene expression. One of the fundamental problems in treating glioma is their highly diffusive and infiltrative nature that makes it difficult to differentiate between healthy brain tissue and the tumor boundary as seen in various conventional imaging modalities [2]. In the tumor mass model [3], it is shown that tumor growth follows the 'universal' growth law curve which is exponential in nature. The basic rate of tumor growth can be calculated by deducting the tumor cell death from the rate of tumor cell birth [4]. A tumor growth model is proposed based on diffusion and cell proliferation [5].

Our hypothesis is that 3D diffusion mapping will provide a more sensitive method to better delineate tumor growth patterns by focusing on the extent of tumor invasiveness. The focus of our work is to develop a 3D mapping of brain tumor (glioma) growth based on cell proliferation and diffusion. The universal growth curve [3] gives us the idea for using exponential growth in our 3D model. The 3D growth model of PK Burgess et al. [6] incorporates tumor radius. A radius is defined there at which the glioma is usually fatal and then ρ and D are investigated as indicators of how long it may take the tumor to reach this critical radius. But actual tissue segmentation has not been used here for the image sets. Uniform diffusion properties have been assumed. The situation after the tumor has destroyed the underlying neuroanatomical structure has been observed but it has not been defined if it is in gray or white matter. However, in our 3D model, we have defined human brain as inhomogeneous considering two types of diffusion coefficients in gray and white matter. Also, we have considered a specific tumor cell density as a threshold of detection for MR images.

Method

We propose a 3D brain tumor growth model based on cell proliferation and diffusion that incorporates actual tissue mapping of white and gray matter from a pediatric subject. The tumor seed is assumed to be a Gaussian distribution with a mean of zero and a standard deviation of one (measured in millimetres). We begin by checking the performance of the model in 1D.

A. **The Mathematical Model**

Original works from Burgess et al. [6] Cruywagen et al. [7], Tracqui et al. [8] and Woodward et al. [9] develop a mathematical model of glioma growth based solely on cell proliferation and diffusion.

$$\frac{dc}{dt} = \nabla.(D\nabla c) + \rho c \qquad (1)$$

Where $c(x,t)$ is the number of cells, ρ (1/day) represents the net rate of growth of cells including proliferation and death (or loss), D (mm^2/day) is the diffusion coefficient of cells in brain tissue and ∇ represents the spatial gradient.

The diffusion term describes the active migration of the glioma cells using a simple Fickian diffusion where cells move from regions of higher to lower densities.

We propose to solve equation (1) through equations (2) and (3).

$$\frac{dc}{dt} = D\nabla^2 c + \rho c \qquad (2)$$

$$c = T(t)R(x, y, z) \qquad (3)$$

First, we assume that diffusion D is homogeneous in each region and c is the number of cells which is a function of time $T(t)$ and position $R(x, y, z)$.

The 3D model is developed as follows.

$$c(x, y, z, t) = c_0 \frac{1}{\Pi^{3/2} G^3} . e^{-\frac{x^2+y^2+z^2}{G^2}} . e^{\rho t} \qquad (4)$$

where c_0 is the initial number of cells and

$$G^2 = a^2\left(1 + \frac{4Dt}{a^2}\right) \qquad (5)$$

where a is the standard deviation for the seed point.

When we differentiate number of cells with respect to time ,we get the following expression for transition point:

$t = \frac{1}{4D}\left(\frac{6D}{\rho} - a^2\right)$. Here, $D = D_w$ when the seed is in white matter and $D = D_g$ when seed is in gray matter.

We have assumed here that tumor growth occurs in two phases ([7]-[9]). In the first phase, the tumor cells only proliferate to form a small dense lesion and only at some later time the tumor cells begin to diffuse. The growth model is applied only in the second phase. Without this assumption, the model simulates the case of gliomatosis cerebri that is tumor cells can be found throughout the brain but no single bulk tumor is identifiable [5]. One special characteristic of the analysis is the use of a zero diffusion coefficient in all voxels not segmented as gray or white matter. This constrains the tumor from growing outside the head or into the ventricles.

B. Parameter Estimation

Parameter estimates in any realistic mathematical model are crucial. Doubling times for glioma have been estimated at 1 week to 12 months covering the range of high to low grade glioma [10]. To relate linear velocity of the detectable tumor margin, v, with the proliferation rate , ρ, and a random walk diffusion coefficient D, we used Fisher's approximation $D \approx \frac{v^2}{4\rho}$ ([6],[11]). This approximation comes from the observation that a population governed by growth and diffusion alone expands at a rate of $2\sqrt{\rho D}$ for a large period of time. The diffusion coefficients $D_w = \frac{v_w^2}{4\rho}$ and $D_g = \frac{v_g^2}{4\rho}$ are assigned the experimentally observed linear velocities v_g and v_w in gray and white matter, respectively ([7]-[9]). From the CT scans, the speed of advance of the tumor margin across the corpus callosum (white matter) is two to three times as fast as that in (predominately) gray matter. We therefore, estimate $v_w > 2.2v_g$ at 0.18 mm/day and $D_w > 5D_g$ at 0.22 mm^2/day. Parameter values are shown in Table I.

In our model, we have used empirically estimated parameters. We get the idea as to what the parameter values usually can be in case of high and low grade glioma from Swanson et al.'s model [5]. We also get the idea of the ratio between the diffusion coefficients of gray and white matter, but we considered two more empirical ideas for our estimation. First, we have used a pediatric brain which is structurally different than the adult one. So the diffusion coefficient will be smaller and the growth rate for the pediatric glioma should be faster than the adult glioma. Second, Swanson et al. [5] derived their parameters using contrast enhanced CT images, but our model is based on MR images. Therefore, detection threshold should be different in our case.

Table: Estimated parameter values.

	Swanson et al. [5]	**High grade glioma**	**Low grade glioma**
Doubling Time (days)	56	28	56
Growth rate, ρ(/day), corresponding to doubling time	0.012	0.036	0.018
Linear velocity of the detectable tumor margin in gray matter, v_g (mm/day)	0.08	0.046	0.018
Diffusion coefficient in gray matter, D_g (mm^2/day)	0.13	0.015	0.005
Linear velocity in white matter, v_w (mm/day)	0.176	0.08	0.03
Diffusion coefficient in white matter, D_w (mm^2/day)	0.65	0.045	0.015

Results

We investigated the performance of this model under several experimental conditions and reported those observed results. These investigations began with a simple 1D implementation to gain more experience with the affect and interaction of the variable parameters. Next, we implemented the full 3D version of the model in Matlab using an actual tissue map obtained from a pediatric patient treated for acute lymphoblastic leukaemia at St. Jude Children's Research Hospital, Memphis, Tennessee, USA. Diffusion and proliferation rates were chosen to model both high grade and low grade glioma and tested for seed points arising from both white matter and gray matter.

The first study conducted began with a 1D investigation of tumor cell density changes with time. In an early phase of growth, diffusion is the dominant factor for a period of time. After that time, the situation is reversed, with cell proliferation becoming the more dominant factor. Figures 1 and 2 demonstrate the results for 1D model experiment.

This investigation identified a transition point which could be defined as a function of the variable parameters. It was observed for the high grade model that the cell density in the seed voxel decreased for the first two days while diffusing to the surrounding voxels, and then began to increase again as proliferation became the dominant factor. This same pattern is seen for the low grade model but took a longer period of time.

Based on the findings of the 1D experiment, we conducted a study of this transition point. This transition point (days) is the point at which diffusion ceases to dominate the cell density in the seed voxel and cell proliferation becomes dominant. We performed two sets of experiments by initializing the seed voxel first in white matter and then in gray matter for both high and low grade glioma. The transition point in voxel-wise tumor cell density is longer in low-grade glioma than in high-grade reflecting the slower spread. The results of these experiments are shown in figures 3 and 4. We then conducted one final experiment to get a more continuous view of the relationship among growth rate, diffusion and transition points as shown in figure 9. These results tell us that when diffusion decreases, transition point also decreases and when growth rate decreases, transition increases. After obtaining a clearer understanding of the transition point and its relationship with diffusion and growth rate, we then implemented the full 3D version of the model using an actual tissue map obtained from a pediatric patient. Diffusion and proliferation rates were chosen to model both high grade and low grade glioma and tested for seed points arising from both white matter or gray matter. We initialized a 1 mm^3 Gaussian seed voxel in white matter of a segmented image and observed the growth of tumor (both high and low

grade) in serial time steps from three orthogonal views. Figures 5 and 6 demonstrate the results. Later we initialized a 1 mm^3 Gaussian seed voxel in gray matter of a segmented image and observed the growth of tumor (both high and low grade) in serial time steps from three orthogonal views. Figures 7 and 8 demonstrate the results.

Discussion

We have presented a 3D tumor growth model based on cell proliferation and diffusion which incorporated actual high resolution whole brain tissue maps. This model has produced results reflecting the density and spatial diffusion of tumors within the brain, which are consistent with clinical experiences. The characteristics of the model which resulted in three key observations were driven primarily by the careful selection of operational parameters for diffusion and proliferation rate. First, in the high-grade case, ρ / D results in a larger portion of the tumor remaining detectable relative to the low grade case. Second, high-grade glioma take less time to diffuse than low-grade. Third, detectable tumor was found to spread faster and to become larger when arising in white matter than gray matter. The growth pattern results in a transition point in the voxel-wise cell count with respect to time. The transition point occurs later in cases of low grade than that of high grade glioma. The existence of the transition point was an inherent characteristic of the form of the model while the temporal shifting of the transition point was a function of the parameter selection.

Conclusion

We have implemented a tumor growth model in 3D which used real patient 3D tissue maps from an MR imaging set. This use of real imaging from the patient will be important for future testing in actual brain tumor patients since their distribution of white and gray matter (D_w, D_g)will be different for each patient and needs to be based on actual imaging. Since our model is truly 3D, the results can be overlaid on patient imaging and viewed in orthogonal planes. The model we have implemented is a necessary and essential first step in any investigation of more elaborate tumor models.

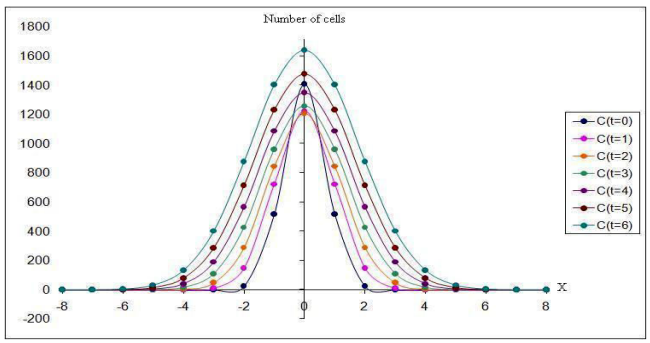


Fig. 1: Change of intensity and spread of cells with time (0-6 days). High grade glioma (ρ=0.036/day, Dw=0.045 mm2/day, Dg=0.015 mm2/day)

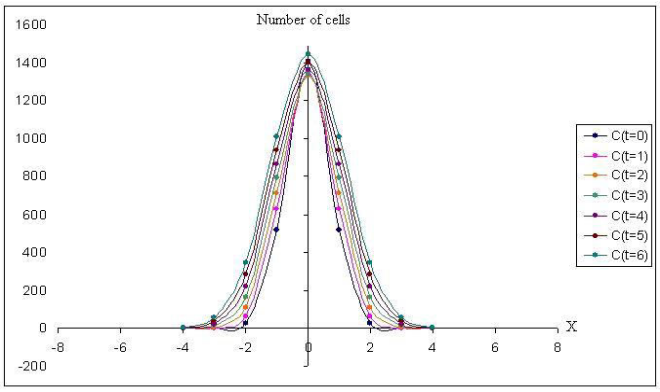
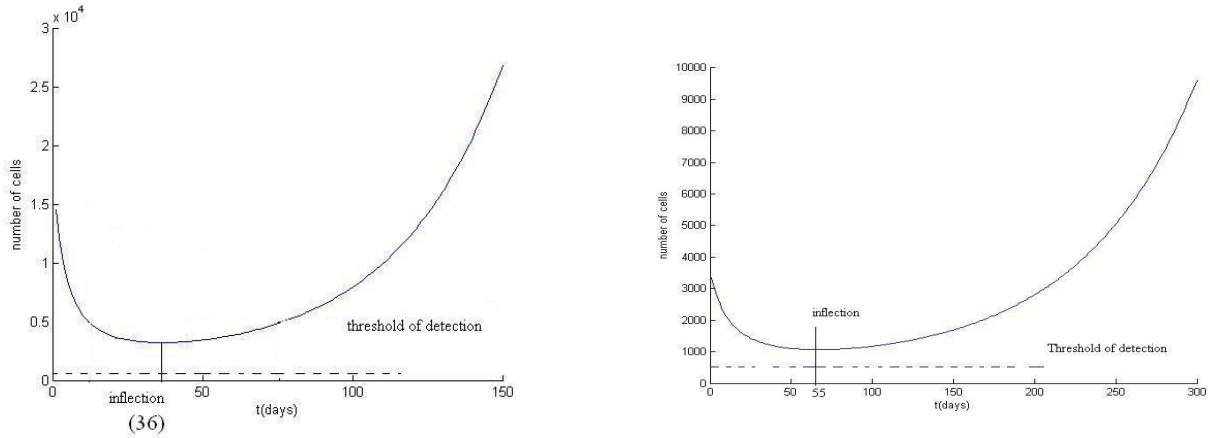
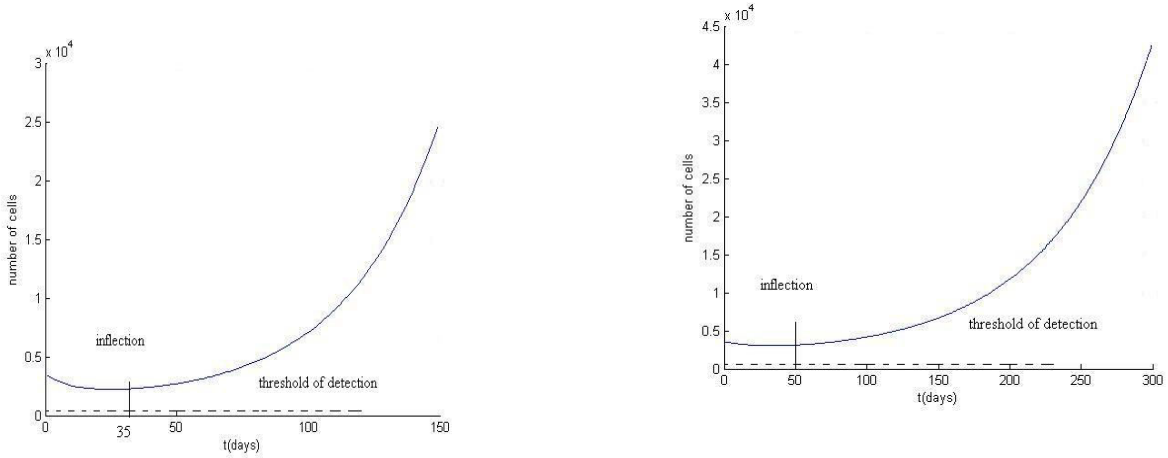


Fig. 2: Change of intensity and spread of cells with time (0-6 days). Low grade glioma (ρ=0.018/day, Dw=0.015 mm^2/day, Dg=0.005 mm^2/day)



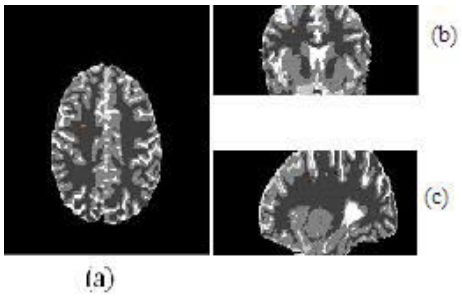
(a) (b)

Fig.3: Cell concentration of seed point (in white matter) as a function of time for a) high, b) low grade glioma.

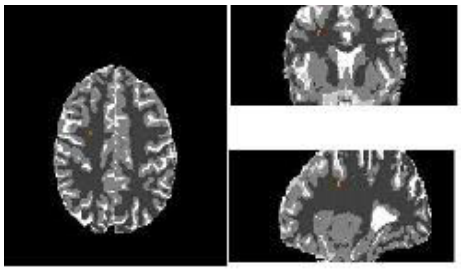


(a) (b)

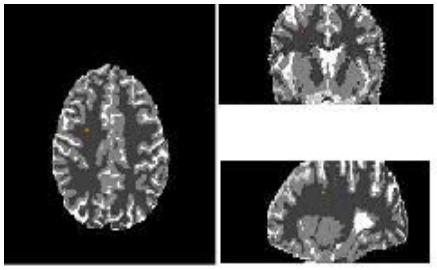
Fig.4: Cell concentration of seed point (in gray matter) as a function of time for a) high, b) low grade glioma.



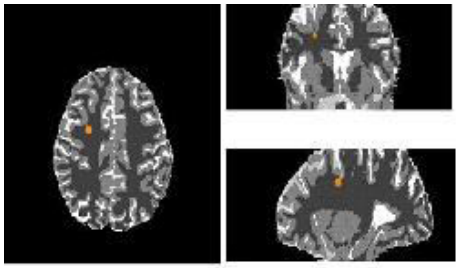
(I) t=0 day



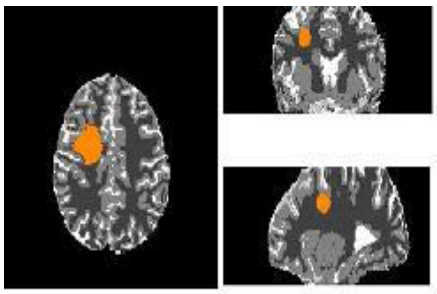
(II) t=10 days



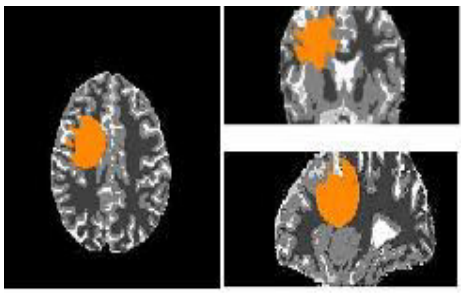
(III) t=25 days



(IV) t=75 days

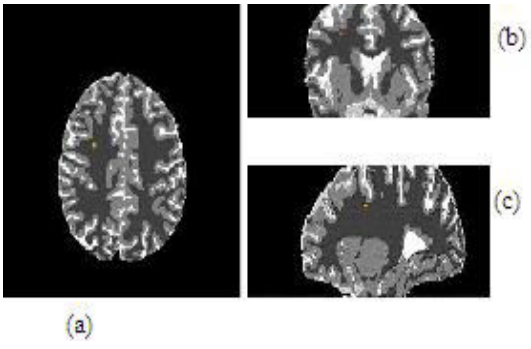


(V) t=150 days

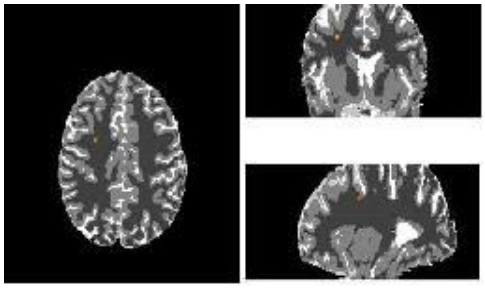


(VI) t= 365 days

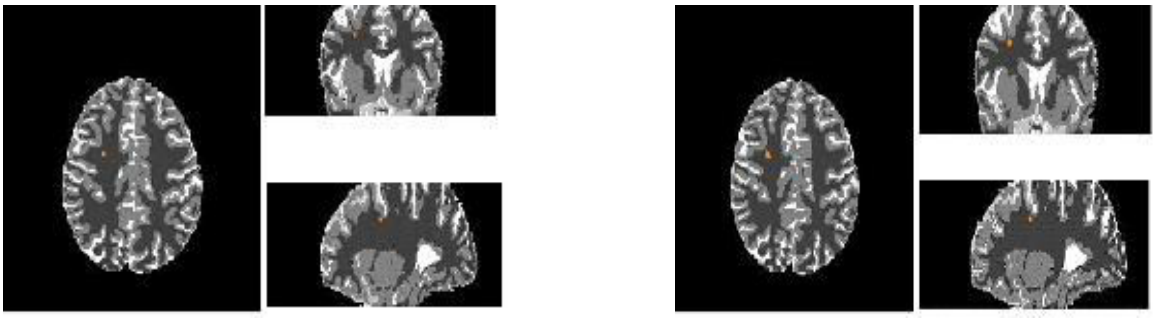
Fig.5 (I)-(VI): High-grade glioma (ρ=0.036/day, D_w =0.045mm^2/day, D_g =0.015 mm^2/day) from three orthogonal views while seed voxel was initiated in white matter. a) transverse, b) coronal , c) sagittal plane.



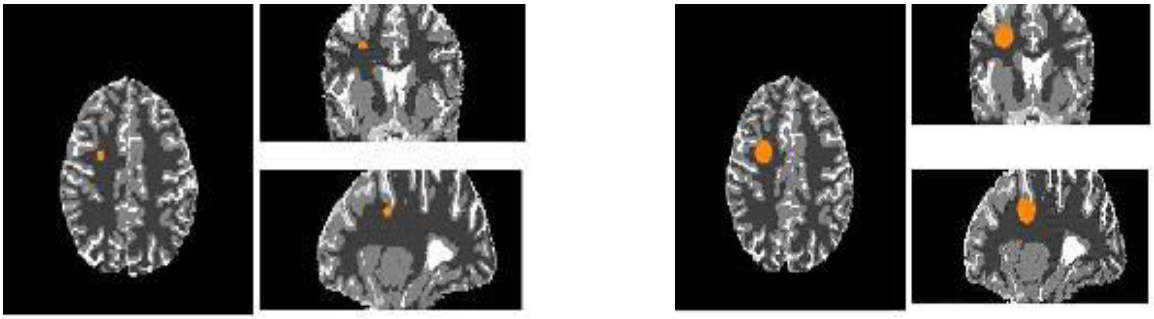
(I) t=0 day



(II) t=10 days

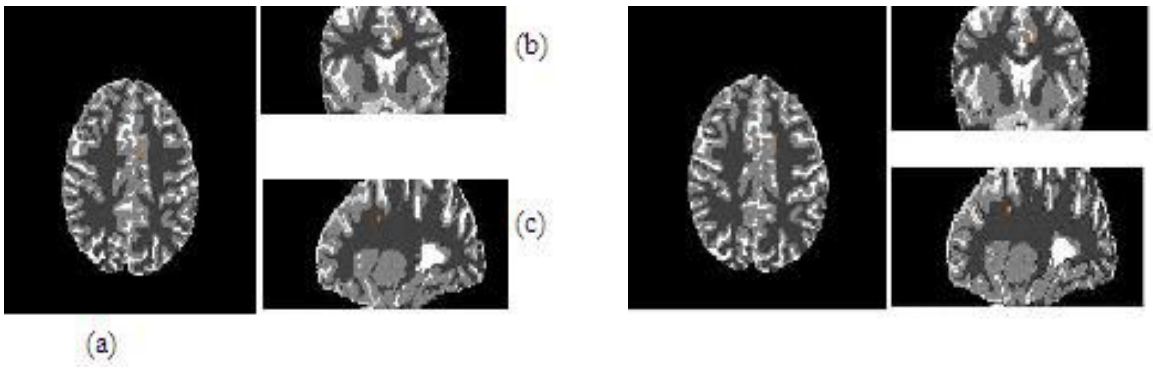


(III) t=25 days (IV) t=75 days



(V) t=150 days (VI) t=365 days

Fig.6 (I)-(VI): Low-grade glioma (ρ=0.018/day, D_w =0.015mm^2/day, D_g =0.005 mm^2/day) from three orthogonal views while seed voxel was initiated in white matter. a) transverse, b) coronal , c) sagittal plane.



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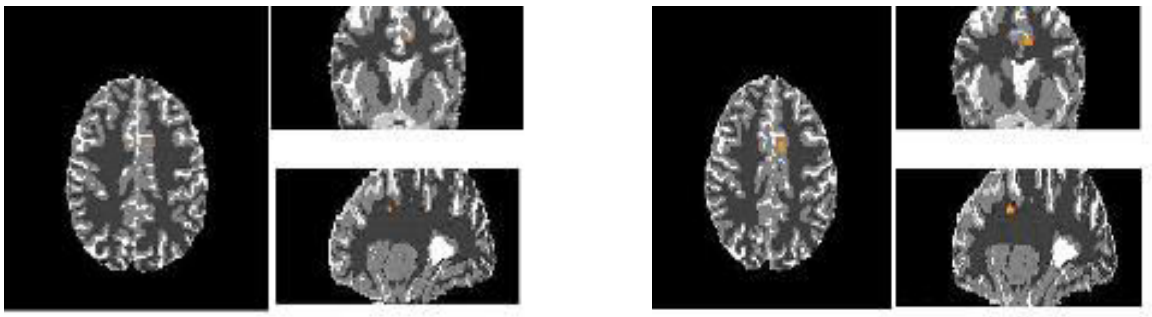

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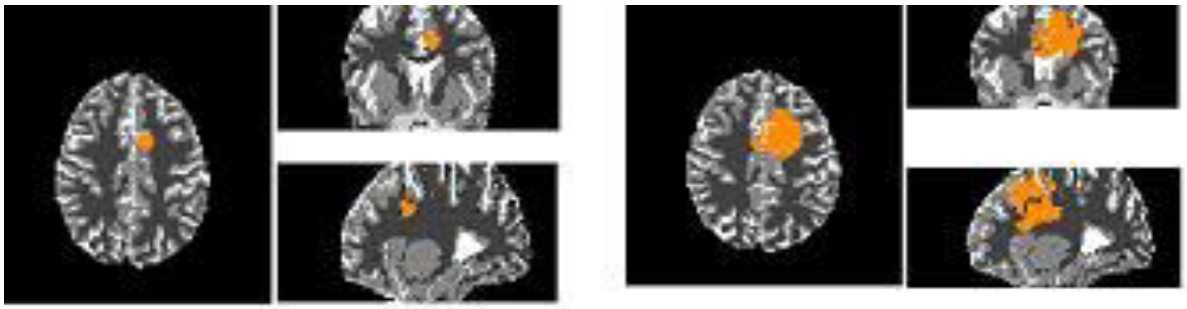
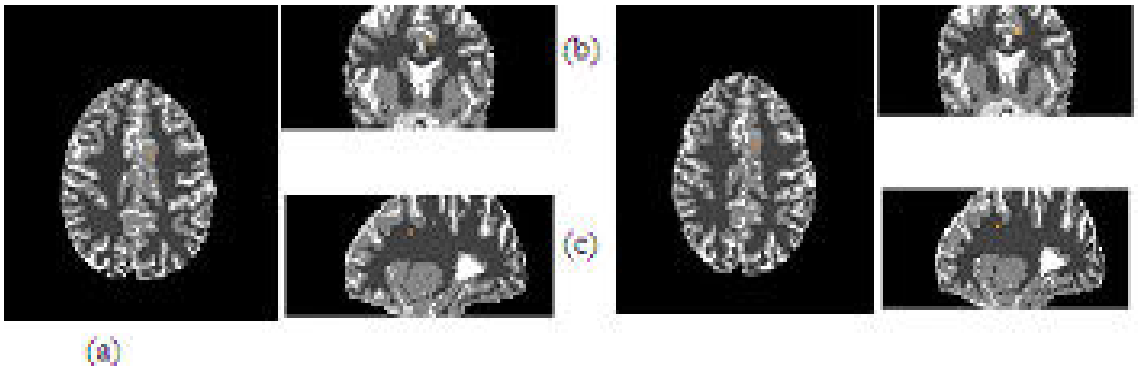


(V) T=150 DAYS (VI) T=365 DAYS

Fig.7 (I)-(VI): High-grade glioma (ρ=0.036/day, D_w=0.045mm^2/day, D_g=0.015 mm^2/day) from three orthogonal views while seed voxel was initiated in gray matter. a) transverse, b) coronal , c) sagittal plane.



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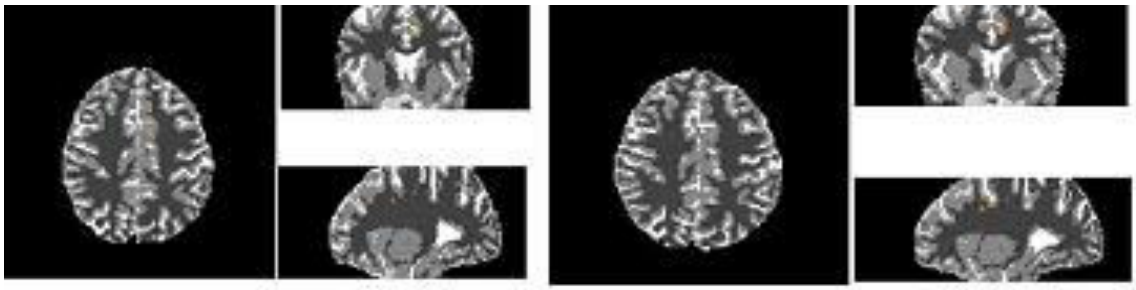

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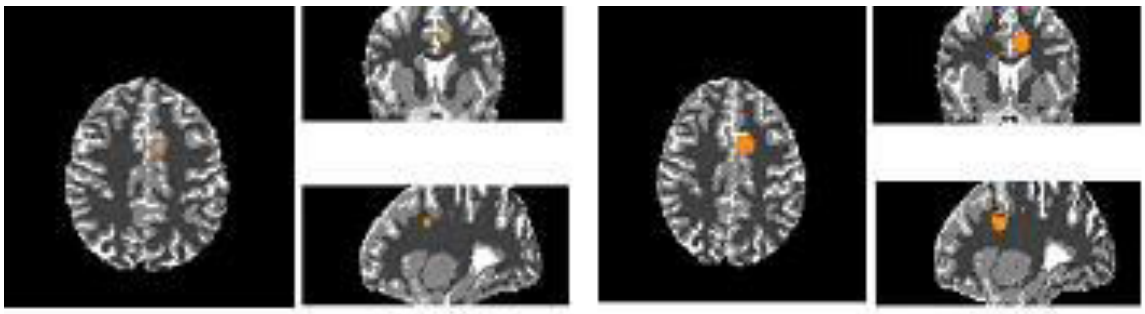

(V) t=150 days (VI) t=365 days

Fig.8 (I)-(VI): Low-grade glioma (ρ=0.018/day, D_w=0.015mm^2/day, D_g=0.005 mm^2/day) from three orthogonal views while seed voxel was initiated in gray matter. a) transverse, b) coronal , c) sagittal plane.

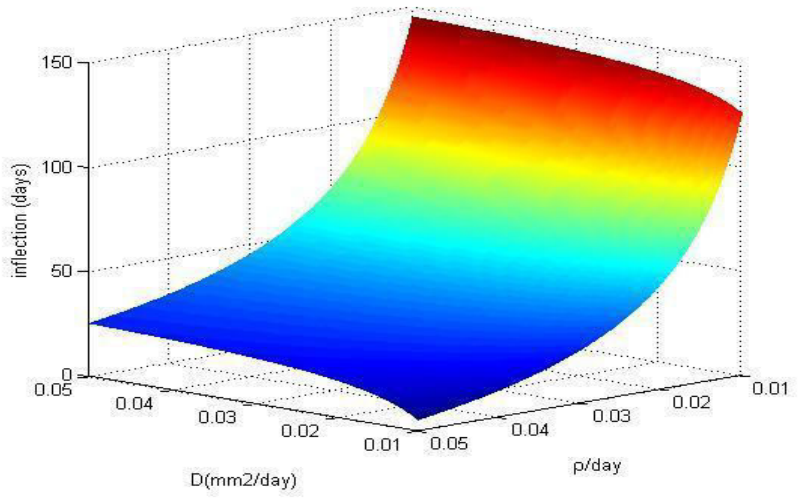

Fig.9: The relationship among proliferation (ρ), Diffusion (D) and transition (inflection) point.

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