Random-walk Based Tractography Simulation for the growth of Brain Tumors

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Introduction:

A random walk based tractography model is proposed to simulate the growth of glioblostams multiforma (GBMs). The primary objective of our model is to investigate the growth of brain tumors and in particular the influence of the local diffusion tensor on tumor growth. The rationale to search for a model to adequately simulate the tumor growth has multiple components. It could allow us to better understand the physiology of the tumor growth. Furthermore, the degree and speed of tumor evolution could serve as a reference indicator for the tumor aggressiveness in a given patient; slower growing lesions may follow white matter tracts and therefore the local diffusion tensor more closely. Finally, predictive growth models might improve treatment planning by better defining the current or future tumor margins. Here, we propose a model and compare simulated results with observed growth of a GBM patient. We demonstrate the feasibility of the conceptual framework of the model; more evaluations are necessarily to demonstrate the model's robustness for future clinical applications.

Methods:

A. Random Walk Tractography Model:

We assume that at least a portion of tumor growth can be explained by the tendency of cancer cells to migrate along the water diffusion direction. We also know that water molecules' movement triggered by thermal energy can be described by a random walk model. In short, we and others hypothesize that the probability of a cancer cell to propagate in a given direction is at least proportional to the corresponding diffusion coefficient. Based on these ideas, the direction of a cancer cell diffusing in a non-homogeneous medium could be described as:

$$\mathbf{V}_{i+1} = \mathbf{V}_{i+1} + \beta \mathbf{d}_i$$

$$\mathbf{d}_i = \mathbf{D}^{\alpha}\mathbf{r}_i$$

where $\mathbf{r}_i$ is a random vector uniformly distributed over a unit sphere, $\mathbf{d}_i$ is a random vector defined on the unit sphere and distributed according to the local diffusion property, β is the step size and α is an anisotropy enhancing exponent. When α is large, the distribution will be centered around the principle eigenvector in which case the cancer migration direction will come close to the streamline tractography algorithm used for white matter fiber tracking. The model allows cancer cells to utilize the diffusion information at a local voxel and by introducing a random vector to the model, it also incorporates the Brownian motion nature of the migrating cancer cells. By tuning the step size, anisotropy enhancing exponent, we are able to adjust our model to better fit the observed tumor growth.

B. Imaging

Diffusion-weighted imaging data were acquired from a glioblostoma patient who participated in an IRB-approved Phase 2 study of cediranib using a 3 Tesla MRI system (TimTrio, Siemens Medical Solutions, Malvern, Pennsylvania). 60 slices of twice-refocused echo-planar diffusion-weighted images were acquired with TR 7500 ms, TE 84 ms, and a b-value of 700 s/mm^2 in 42 directions as well as 7 low b-value images (b ~ 0 s/mm^2) to allow reconstruction of the diffusion tensor at each voxel. Resolution was 2 mm isotropic, with a 128 × 128 matrix. Imaging time is 6:30. The patient underwent MRI on days -5, -1, +1 (at least 24 hours after the first administration of the antiangiogenic agent cediranib and before the second dose), +28, +56; in total 5 visits before and after cediranib treatment.

Results and Discussions:

Figure 1 shows Post-Contrast T1 weighted image for day +28 (left) and day +56 (right) respectively. Figure 2 demonstrates the result of the random walk simulation. Colored lines overlaid on DTI reference image (b=0) represent tumor boundary for two different simulation stage (the maximum steps allowed for the cancer cells). Blue line is tumor boundary used in the model as the starting seeds for tumor migration. The ventricles and dura are masked out before the simulation. Green and Red lines represent tumor margins after reaching 10 and 20 steps in the simulation respectively. Step Size (β) 0.75 was used. For each simulation, 150 random tests are preformed and their end points are saved as tumor boundary. The final tumor boundary also excludes the migrating paths that intercept with the tumor. Figure 2A and 2B are simulated with α = 1 and 5 respectively. α is the power to the diffusion matrix **D**. If α is small, the model allows more possible cancer cell trajectories deviating from the principle diffusion direction, whereas if α is large, the distribution is more aligned with the principle eigenvector in which the cancer cells will follow routes that come close to a classic main eigenvector-based fiber tracking. This effect could be shown in our simulation result where in Figure 2A (α = 1), the tumor boundary spreads more randomly than that in Figure 2B suggesting that cancer cells allow more random routes other than the principle diffusion vector provided in that voxel. It also provides possible explanations why there are fewer routes leading to the new tumor site, presumably due to the increased random deviation from the white matter tracts (e.g., some component of active invasion rather than simple diffusion). Higher α value will tighten the cell migration direction around the white matter tract. As shown in Figure 2B, more cells are able to take advantage of the diffusion along white matter to reach the new emerging tumor focus. In short, these early results suggest that this model has potential to predict tumor evolution that captures some important features of observed growth. We speculate that by tailoring the random parameters to best fit the model with the observed tumor growth for a larger group of patients, we will be able to find a set of random variables that best suits each individual patient, or perhaps a universal set that could best predict growth patterns over a larger patient database. We further speculate that training such models on a particular observed database may allow predictions that can be tested prospectively on new patients, with the eventual goal of allowing us to tailor therapy planning on an individual patient basis.

Conclusions:

We describe a conceptual approach to modeling complex evolution of tumor growth. The comparison of the simulated result with the follow-up MR image of a sample patient demonstrates the potential of the model. This initial, preliminary attempt to test the random walk based model requires further evaluation on more patient data to better understand its limitations and strengths; these evaluations are underway.

Reference:

P. Hagmann et el. DTI mapping of human brain connectivity: statistical fibre tracking and virtual dissection. NeuroImage 2003;19:545-554

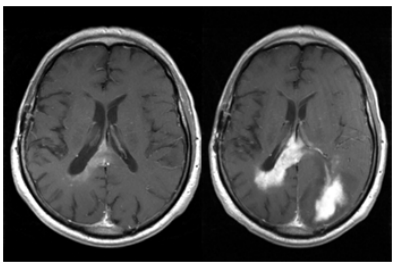

Figure 1: T1 weighted post-contrast image for day 28 (left) and day 56 (right) respectively in our GBM patient

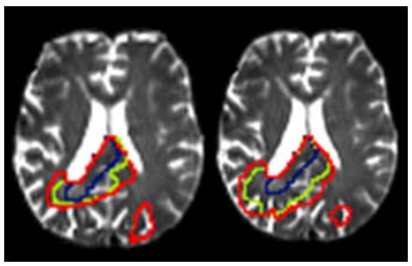

Figure 2: Blue line is tumor boundary used as the starting seeds for our model. Green and Red lines represent the end points of cancer cells after reaching 10 and 20 steps respectively in the simulation. For each simulation, 150 random tests are performed and their end points are saved as tumor boundary. The final tumor boundary also excludes the migrating paths that intercept with the tumor. Left and right panels are the results with α = 1 and 5 respectively where α is the power to the diffusion matrix **D**.