The effect of fiber affinity on predicted cancer cell migration based on MR-DTI

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Purpose: The current methods of determining Stereotactic Radiotherapy (SRT) treatment margins needed to encompass microscopic spread for primary brain cancer are often inadequate as recurrences/secondary tumors often occur at the boundary of treatment margin. We developed a pseudo-random walk model of tumor cell migration constrained by the local diffusion environment determined using MR Diffusion Tensor Imaging (DTI) to predict the microscopic spread of gliomas. Our hypothesis is that paths of elevated water diffusion along the white matter tracts provide a preferred path for migration of glioma cells and we have shown previously that the areas of higher cell concentration predicted by the model coincide with the direction of tumor recurrence. In the current study we determine the effect of model parameters: spread of the direction of migration and step-size on the predictions of the model.

Materials and Methods: The current analysis was performed using the DTI data of three volunteers obtained on a 3.0T Siemens scanner using an EPI sequence with 70 serial axial images of voxel dimension 2.0×2.0×2.0 mm; TR 10.1 s; TE 100 ms; 60 diffusion encoding directions; b value of 1200 s/mm^2 and 10 reference (b=0) scans. In all the simulations, the contrained-random walk model was initiated with 250 cells in each tumor surface voxel and each walk had 150 steps. The affinity of cells for fibers was modeled by varying the spread of the direction of migration of the cancer cell about the Principal Diffusion Direction (PDD, $\Delta\Theta\&\Delta\Phi$). The chemotactic factors that force the cancer cells to migrate away from the tumor mass and inhibit migration backwards was modeled by forcing cells to move along the fiber tract along a direction away from the primary tumor. To model isotropic spread of tumor cells, Θ and Φ were chosen randomly in the range of 0 to 180^o thereby removing any dependence on the underlying fiber architecture. Two simulations were performed to simulate the anisotropic spread of tumor cells: one without and the other with the outward gradient of cell migration and both with spread in the migration direction ($\Delta\Theta\&\Delta\Phi$) of 35/20/10^o corresponding to a FA of 0-0.3, 0.3-0.6 and 0.6-1 respectively. In the run without an outward gradient the cells have a 50% chance of moving toward or away from the primary tumor at each step. The effect of lowering the affinity of tumor cells for fibers on the pattern of tumor spread was modeled by doubling the spread of direction of migration from 35/20/10^o to 70/40/20^o respectively. To verify the hypothesis that cells travel with higher velocity along the fibers, simulations were performed with step-size varying with FA values: 0.15, 0.25 and 0.4 mm corresponding to a FA of 0-0.3, 0.3-0.6 and 0.6-1, respectively, versus a constant step-size. To quantify the similarity of the model predictions with constant and variable step-size, the Jaccard Index and Dice Coefficient were calculated on the resulting cell count matrix, thresholded at 20%.

Results and Conclusions: The results of the simulations to determine the effect of fiber affinity on predicted cell migration are shown in Figure 1. Cancer cells travel farther away from the primary tumor when fiber affinity is increased (Comparing rows 3 and 4). The presence of an outward motion constraint on cell migration results in a dramatic increase in migratory distance (Comparing rows 2 and 3). The Jaccard Index and Dice Coefficient between the model predictions with variable versus constant step-size (images not shown) were 0.8470 and 0.9712, respectively, showing that the model predictions were similar in both the cases and suggesting that a variable step-size is not effective in modeling higher velocity of cells migrating along fibers and that the higher velocity is due instead to the higher affinity to fibers and persistence of travel along fibers.

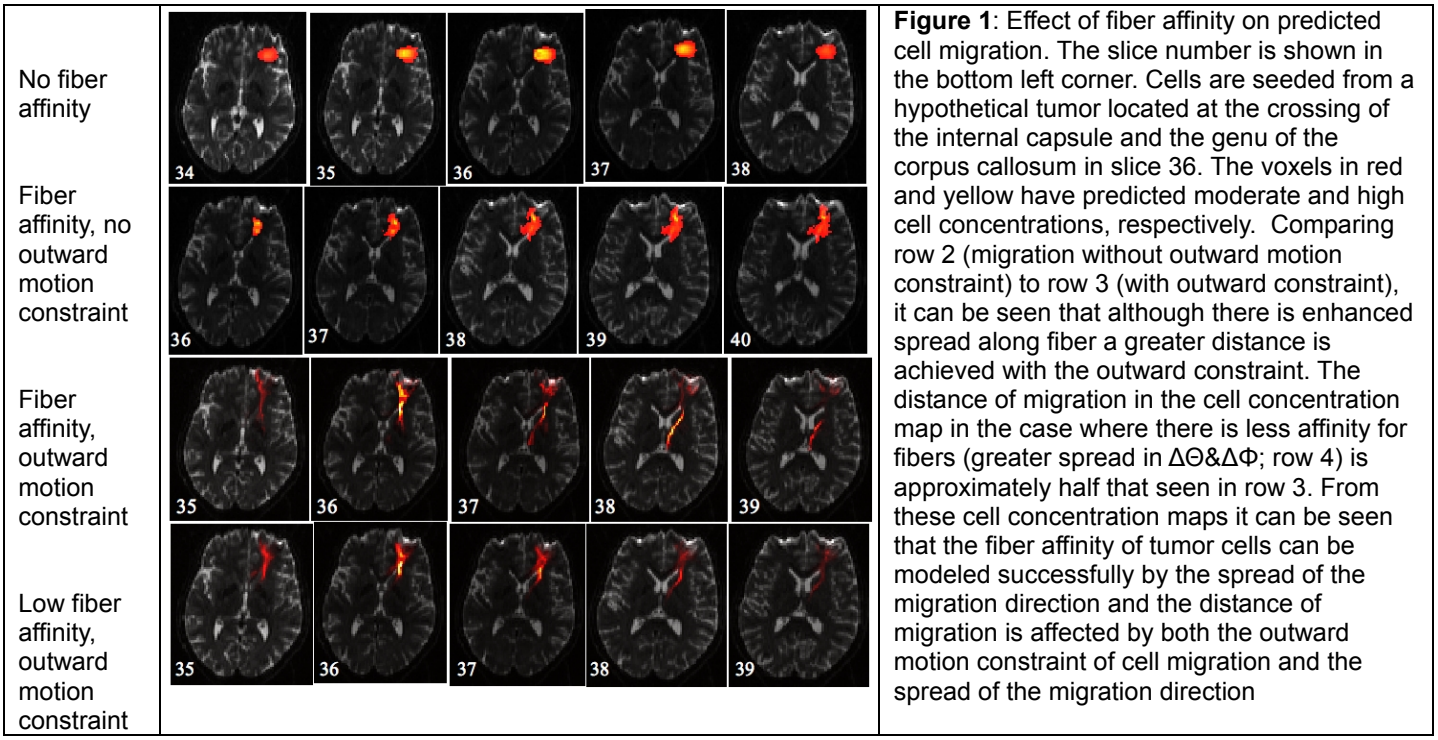

Figure 1: Effect of fiber affinity on predicted cell migration. The slice number is shown in the bottom left corner. Cells are seeded from a hypothetical tumor located at the crossing of the internal capsule and the genu of the corpus callosum in slice 36. The voxels in red and yellow have predicted moderate and high cell concentrations, respectively. Comparing row 2 (migration without outward motion constraint) to row 3 (with outward constraint), it can be seen that although there is enhanced spread along fiber a greater distance is achieved with the outward constraint. The distance of migration in the cell concentration map in the case where there is less affinity for fibers (greater spread in $\Delta\Theta\&\Delta\Phi$; row 4) is approximately half that seen in row 3. From these cell concentration maps it can be seen that the fiber affinity of tumor cells can be modeled successfully by the spread of the migration direction and the distance of migration is affected by both the outward motion constraint of cell migration and the spread of the migration direction