Online Resource 2

Article Title: Glioma Growth Modeling based on the Effect of Vital Nutrients and Metabolic Products

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Online Resource 2 contains additional model results concerning the rest three diffusion-proliferation pairs, namely low-diffusion / low proliferation, high-diffusion / low proliferation and high-diffusion / high proliferation tumors. Moreover, additional real-tumor frames of model simulation results are illustrated, demonstrating the tumor evolution 22.5 months after its detection, in comparison to the respective follow-up MRI slices.

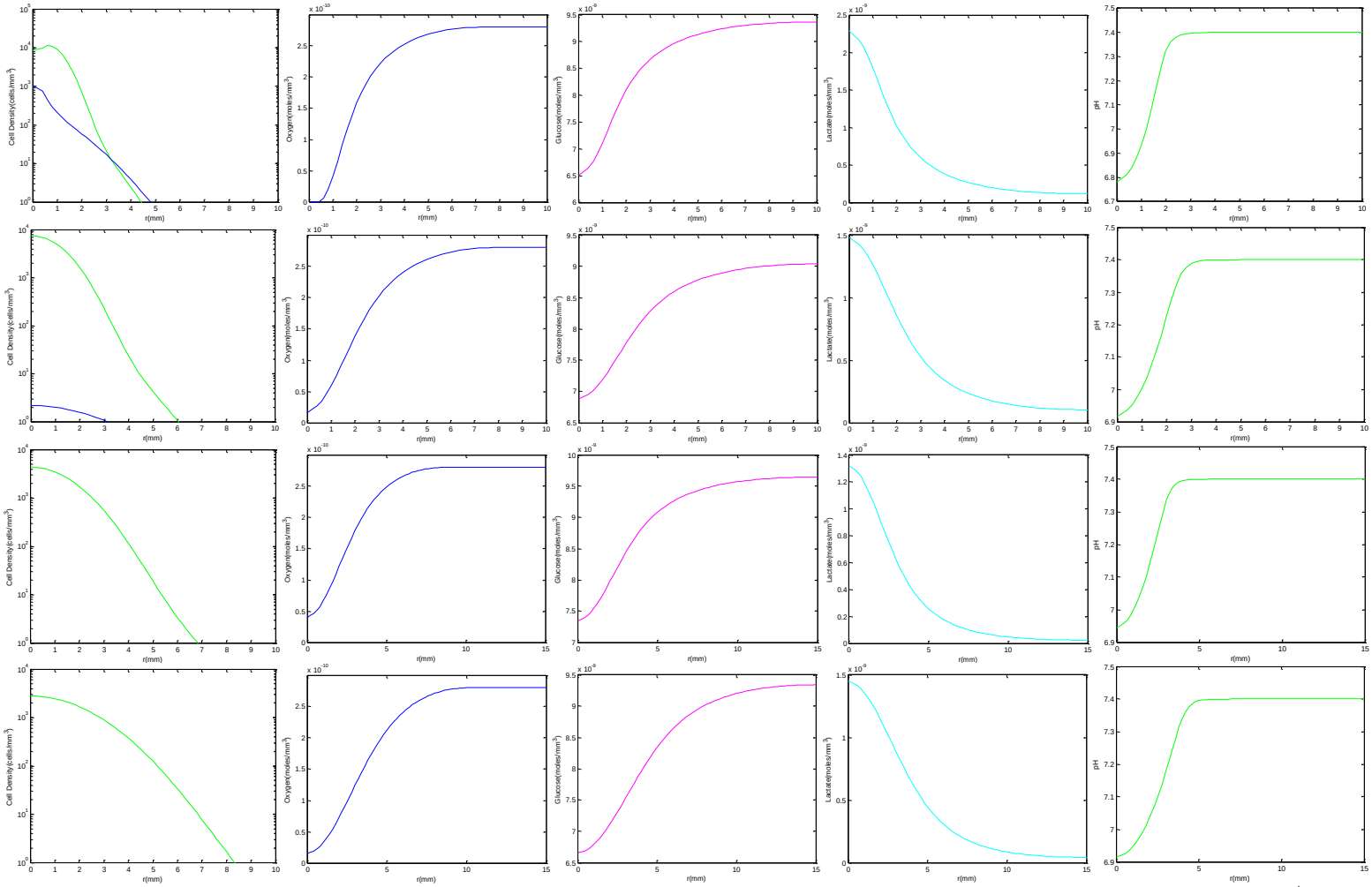

Fig. 1 Simulation of a low-diffusion/low-proliferation tumor. Lines 1-4: Evolution after 1, 3, 6 and 12 months. Columns: 1st: cell densities, 2nd: oxygen, 3rd: glucose, 4th: lactate concentrations and 5th: pH value with respect to the tumor radius

The first graph of Fig. 1 illustrates the evolution of a low-diffusion / low-proliferation tumor 1 month after its assumed detection, where its radius has increased from r = 1mm to r = 4.9 mm. It can be noticed that in this early growth stage a hypoxic cell density has appeared in the central part (blue curve), which is depicted in the second graph of oxygen concentration in respect to the tumor radius. However, as time proceeds the hypoxia is decreased, to finally disappear at 6 months, since the cell density has decreased at the core due to the low proliferation. At this time the tumor radius has reached the r = 6.9mm and the glucose supplies still remain adequate (third column). Additionally, the lactate and H^+ concentrations (fourth and fifth columns) are low throughout the tumor, even after 1 year (r = 8.4mm); hence acidity conditions do not exist and all cells are normoxic, normoglycemic and proliferative.

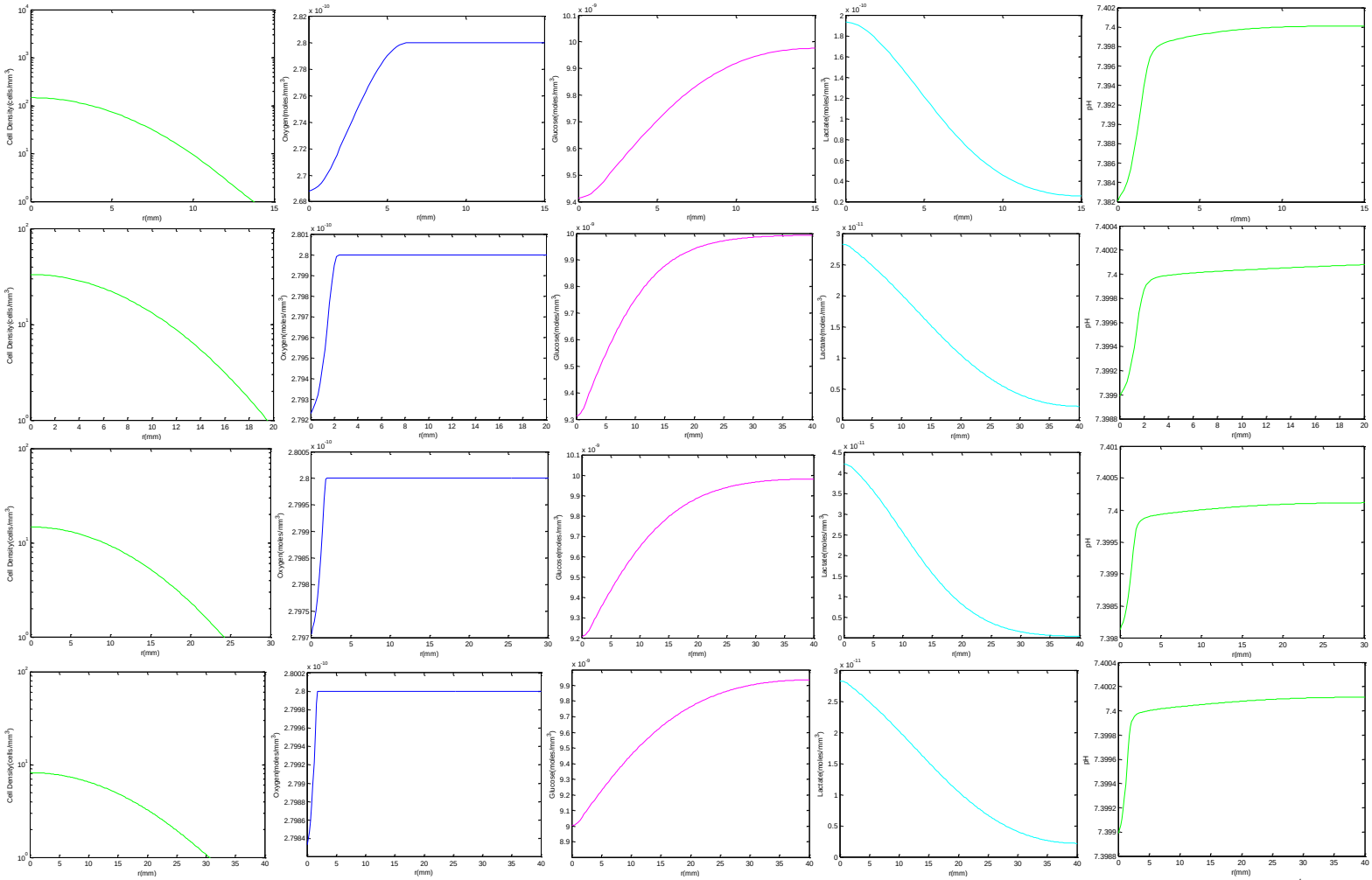

Fig. 2 Simulation of a high-diffusion/low-proliferation tumor. Lines 1-4: Evolution after 1, 3, 6 and 12 months. Columns: 1st: cell densities, 2nd: oxygen, 3rd: glucose, 4th: lactate concentrations and 5th: pH value with respect to the tumor radius

In the case of high-diffusion / low-proliferation the tumor expands until it exceeds the radius of r = 3cm after 1 year. However, since the density throughout the tumor body is low enough, cancer cells do not encounter any hypoxic, hypoglycemic, or acidic adverse conditions; hence no necrosis exist and all cells remain proliferative. The growth rate is initially higher but it is reduced over time and the tumor volume increases.

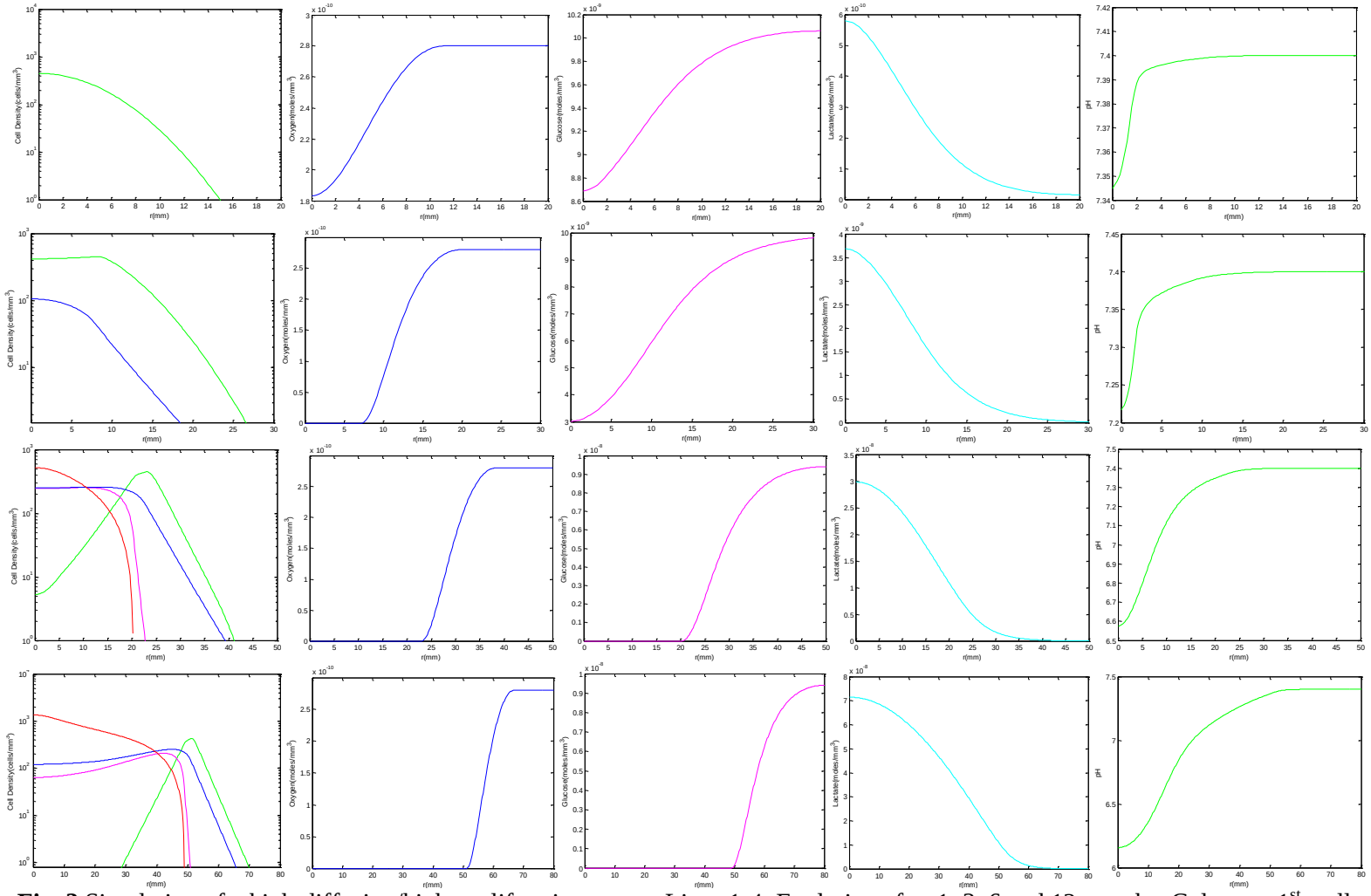

Fig. 3 Simulation of a high-diffusion/high-proliferation tumor. Lines 1-4: Evolution after 1, 3, 6 and 12 months. Columns: 1st: cell densities, 2nd: oxygen, 3rd: glucose, 4th: lactate concentrations and 5th: pH value with respect to the tumor radius

The high-diffusion / high-proliferation tumor rapidly grows above the radius of r=2cm within the first 3 months. However, the hypoxic state occurs very soon (second line) and once the hypoglycemic population appears the necrotic core is almost instantly formed before the sixth month (third line), at the expense of proliferating cells. As far as acidity is concerned it can be clearly noticed that no acidic cell density exists during the entire year, although as it is depicted in the pH graph (fifth column) of the fourth line in respect to the tumor radius, pH value has fallen below the acidic threshold (pH<6.4) in the central part, which justifies the existence of acidic tumor cells. This contradiction can be explained by the fact that since the acidic cells can also be hypoxic and/or hypoglycemic, the severe hypoxic/hypoglycemic condition leads to the inclusion of the acidic cells to the hypoxic and/or hypoglycemic population. After 6 months the tumor consists of discrete regions, namely the necrotic core, surrounded by the hypoxic along with hypoglycemic zone and the outward proliferating ring and has already exceeded the fatal radius of r = 4cm. The same pattern is observed after 1 year when the tumor includes an extensive necrotic core and has reached the radius of r=7cm; it has actually invaded the entire brain. Moreover, the tumor expansion is initially very fast, while it slows down later, as opposed to the necrosis growth rate, which gradually increases until the necrotic region finally occupies the widest part of the tumor body.

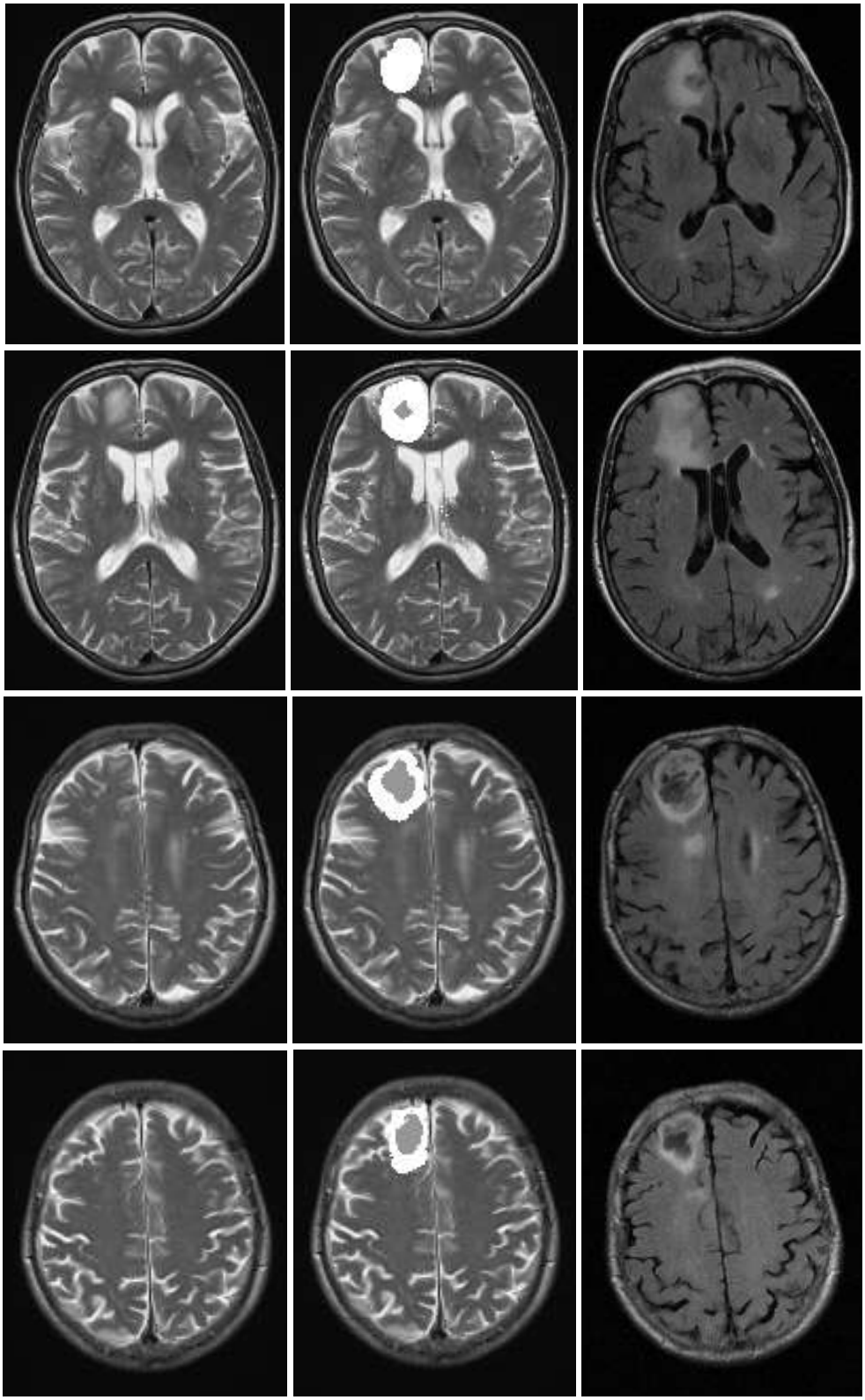

Fig. 4 Model simulation results on a real glioma tumor after 22.5 months. Lines: Four different MRI slices. Columns: 1st: Initial tumor (T2 MRI), 2nd: Model results projected on the initial MRI and 3rd: Real growth after 22.5 months (FLAIR MRI)

The first and the last brain slices indicate the 3D capability of the proposed model, since, while the tumor was not visible in the initial MRI frame (first column) it made its appearance after the time of 22.5 months (second column), in agreement with the real tumor growth depicted in the third column.