Towards an image-informed mathematical model of response to fractionated radiation therapy

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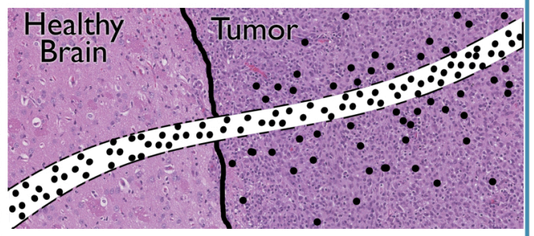
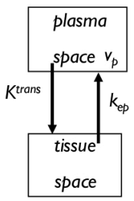
Introduction

- Mathematical modeling of tumor growth and response could be used identify the optimal treatment regimens for individual patients.
- Medical imaging can non-invasively assess variations in anatomy and physiological properties relative to tumor growth and response.
- Image-driven modeling efforts have shown promise in predicting tumor growth, response to radiation therapy, and angiogenesis[1-3]
- The purpose of this project is to develop a spatiotemporal model that can be calibrated with subject-specific imaging measures to predict individual tumor response to fractionated radiation therapy.

Data types

Dynamic contrast-enhanced MRI





v_p , v_e = plasma and extracellular-extravascular volume fractions

DCE-MRI is an imaging technique used to assess perfusion, blood vessel permeability, blood volume, and the extracellular-extravascular volume fraction.

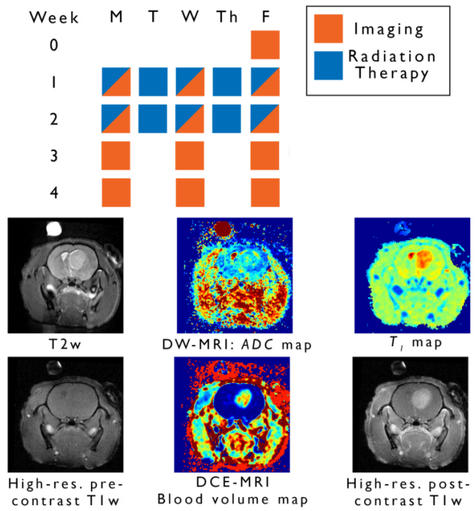
Images are collected before, during, and after the injection of a contrast agent.

Diffusion weighted MRI

DW-MRI is an imaging technique used to assess the diffusion of water molecules within tissue. This diffusion is described by the apparent diffusion coefficient or *ADC*. The *ADC* is effected by cell density, cell size, cell permeability, and tissue tortuosity. Thus, we use it to provide an estimate of cell density[2].

$$\phi_T = \frac{ADC_w - ADC(\bar{x},t)}{ADC_w - ADC_{\min}}$$

Experimental data



Quantitative magnetic resonance imaging (MRI) data was collected in two rats with intracranially injected U87 glioblastomas cells, before, during, and following 10 fractionated doses of 2 Gy.

At each visit, DW-MRI and DCE-MRI were collected to measure tumor and blood volume fractions, respectively.

Tumor regions of interest were segmented from the post-contrast T_1-weighted MRI data, while tissue regions of interest were segmented from the *T_2-weighted* MRI data.

The voxel resolution was 0.25 x 0.25 x 1 mm.

Mathematical model

We have developed a 3D mechanically coupled model of tumor growth and response to chemoradiation.

$$\frac{\partial \phi_T(\bar{x},t)}{\partial t} = \overbrace{\nabla\cdot\left(D_T(\bar{x},t)\cdot\left(\left(1-\frac{\phi_V(\bar{x},t)}{\theta_{T,V}(\bar{x},t)}\right)\nabla\frac{\phi_T(\bar{x},t)}{\theta_{T,V}(\bar{x},t)}+\left(\frac{\phi_T(\bar{x},t)}{\theta_{T,V}(\bar{x},t)}\nabla\frac{\phi_V(\bar{x},t)}{\theta_{T,V}(\bar{x},t)}\right)\right)\right)}^{\text{Diffusion}}$$
$$+\overbrace{k_{p,T}\phi_T(\bar{x},t)\left(1-\phi_T(\bar{x},t)/\theta_T(\bar{x},t)\right)}^{\text{Logistic Growth}}$$

$$\frac{\partial \phi_V(\bar{x},t)}{\partial t} = \overbrace{\nabla\cdot\left(D_V(\bar{x},t)\cdot\left(\left(1-\frac{\phi_T(\bar{x},t)}{\theta_{T,V}(\bar{x},t)}\right)\nabla\frac{\phi_V(\bar{x},t)}{\theta_{T,V}(\bar{x},t)}+\left(\frac{\phi_V(\bar{x},t)}{\theta_{T,V}(\bar{x},t)}\nabla\frac{\phi_T(\bar{x},t)}{\theta_{T,V}(\bar{x},t)}\right)\right)\right)}^{\text{Diffusion}}$$
$$+\overbrace{k_{p,V}\phi_V(\bar{x},t)\left(1-\phi_V(\bar{x},t)/\theta_V\right)d}^{\text{Logistic Growth/ Angiogenesis}}-\overbrace{k_{d,V}\phi_V(\bar{x},t)(1-d)}^{\text{Death}}$$

Measured or calculated parameters

ϕ_T: Tumor volume fraction (estimated from DW-MRI)
ϕ_V: Blood volume fraction (estimated from DCE-MRI)
$\theta_{T,V}$: Combined carrying capacity
θ_T, θ_V: Carrying capacities
d: Normalized distance from the periphery of the tumor
C: Spatial coupling parameter

Calibrated from ϕ_T time courses

D_T, D_V: Mechanically-coupled diffusion coefficient
$k_{p,T}$, $k_{p,V}$: Proliferation rates
$k_{d,V}$: death rate
$P(survival)$: Probability of survival
$k_{d,\bar{T}}$: death rate due to radiation therapy

Model 1: Delayed death
Assume tumor cells die slowly following radiation therapy

$$k_{d,T,postRT}(\bar{x},t) = (1-P(survival)^n)\cdot C\cdot k_{d,T,postRT}(\bar{x},t)\phi_T(\bar{x},t)$$
$$k_{p,T,postRT}(\bar{x},t) = (P(survival)^n)\cdot C\cdot k_{p,T,postRT}(\bar{x},t)$$

Model 2: Immediate death
Assume tumor cells die immediately after treatment (Linear quadratic model)

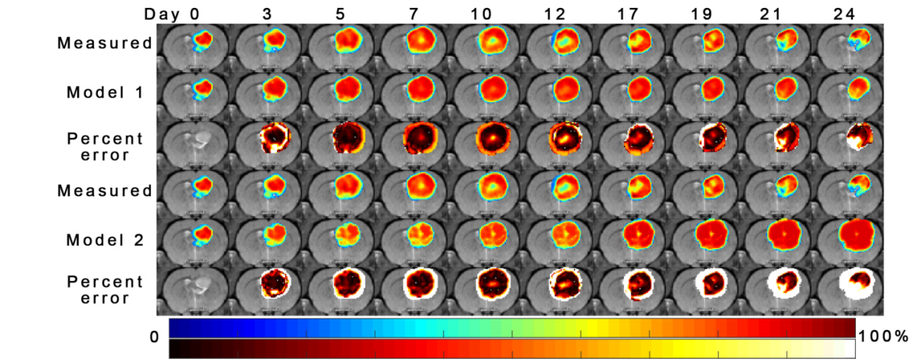
$$\phi_{T,postRT}(\bar{x},t) = \phi_{T,preRT}(\bar{x},t) - (1-P(survival))\cdot C\cdot\phi_{T,preRT}(\bar{x},t)$$

Model calibration and analysis

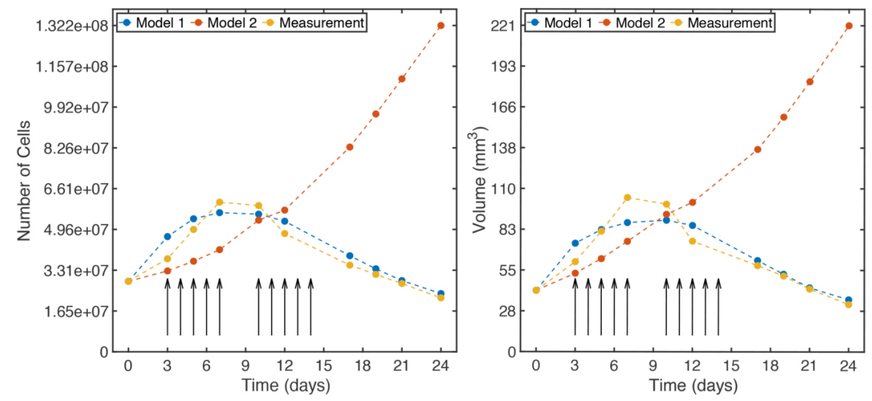
Model parameters were calibrated using the pre- and early treatment data and then used to predict future tumor growth at the remaining imaging visits.

Error between the model and the measured tumor growth was assessed by calculating the percent error in tumor volume and cell number at the local and global levels.

Results



Above: The first and fourth rows, show the central slice of tumor volume fraction (estimated from diffusion-weighted MRI) is depicted at days 0 to 24. The second and fifth rows, show the simulated tumor distribution for model 1 and model 2, respectively. The percent error between the model and the measurement is shown in the third and sixth rows. Data from day 0 to 12 was used to calibrate model parameters which was then used to predict tumor growth at days 17, 19, 21, and 24. Model 2 (in comparison to model 1) overestimates the final tumor size following radiation therapy.



Above: The left plot shows the total number of tumor cells during radiation therapy (black dots) for model 1 (blue dots), model 2 (red dots), and the measurement (yellow dots). Similarly, the right plots show the total tumor volume for model 1, model 2, and the measurement. Model 1 more closely fits the data, whereas model 2 underestimates the total number of tumor cells and volume at the post-treatment time points.

Conclusions

Quantitative imaging data can be used to calibrate a predictive mathematical model of response to fractionated therapy and, importantly, a linear-quadratic characterization of radiation induced cell death may not be optimal.

Acknowledgements

1. Hormuth II D, Jarrett A, et al 2019; *J Clin Oncol Clin Cancer Informatics*. **3** 1–10.
2. Hormuth DA, Jarrett AM, Yankeelov TE. 2020; *Radiat Oncol* **15** 1 4.
3. Hormuth DA, Jarrett AM, Feng X, Yankeelov TE. 2019; *Ann Biomed Eng.* **47** 7 1539–51.
4. Hormuth II DA et al 2017; *J R Soc Interface*. **14** 128 .

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