A biology-based, mathematical model to predict the response of recurrent glioblastoma to treatment with ^{186}Re-labeled nanoliposomes

Chase Christenson[1], Chengyue Wu[2], David A. Hormuth, II[2], Shiliang Huang[3], Andrew Brenner[3], and Thomas E. Yankeelov[1,2]

Department of Biomedical Engineering[1], Oden Institute for Computational Engineering and Sciences[2]; The University of Texas at Austin
University of Texas Health Science Center[3]

2742

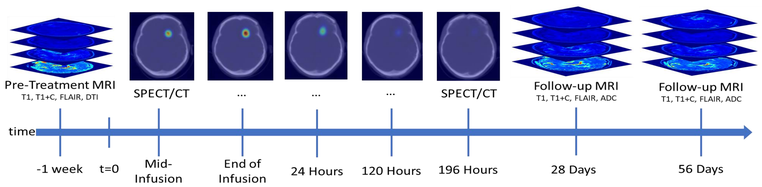
Introduction

- Prognosis for patients with recurrent glioblastoma is extremely poor
- 186Re-labeled nanoliposome (RNL) treatment has the potential to deliver radiation doses greater than 100 Gy
- Predicting early response can aid in determination if concurrent or alternate therapy is required
- In this work we calibrate a mechanistic model to patient specific imaging data to predict response to RNL treatment

Methods

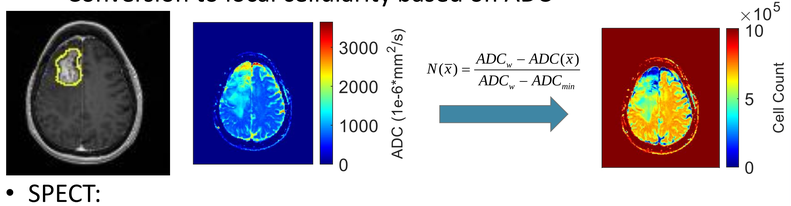
Clinical Data

- Quantitative MRI acquired pre- and post-treatment
  - T1, T1+Contrast, ADC
- Time resolved SPECT acquired during RNL infusion

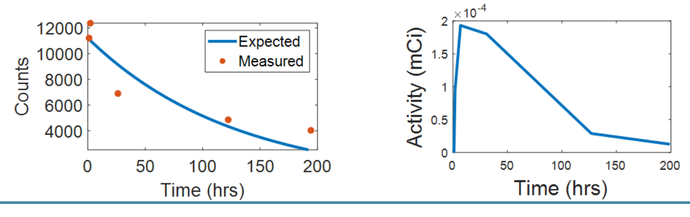


Preprocessing

- All patient images interpolated and aligned to the baseline T1 scan using rigid-registration
- MRI:
  - Tumor burden segmented from enhanced region of T1+C scan for all time points
  - Conversion to local cellularity based on ADC



- SPECT:
  - Decay correction and quantification
    - Using counts and known activity of phantom placed in image
  - Voxel specific time course estimate
    - Linear interpolation between measured time points



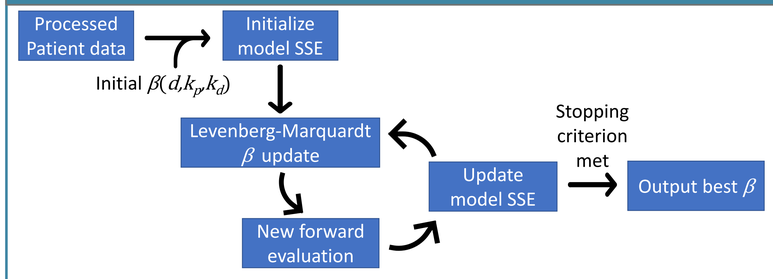
Mathematical Model

Reaction diffusion model with treatment response

$$\frac{\partial N(\bar{x},t)}{\partial t} = \underbrace{\nabla\cdot\left(D\nabla N(\bar{x},t)\right)}_{\text{Invasion}} + \underbrace{k_p(\bar{x})N(\bar{x},t)\left(1-\frac{N(\bar{x},t)}{\theta}\right)}_{\text{Proliferation}} - \underbrace{k_d RNL(\bar{x},t)N(\bar{x},t)}_{\text{Treatment}}$$

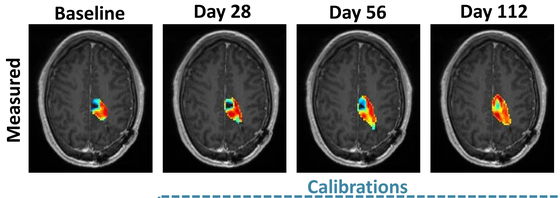
Parameter	Description	Value set by	Unit
$N(x,t)$	Cell count	ADC images, simulation	[Cells]
$RNL(x,t)$	RNL time course	SPECT images	[mCi]
θ	Carrying capacity	Image resolution	[Cells]
D	Diffusivity	Calibration	[mm^2/day]
$k_p(x)$	Proliferation rate	Calibration	[1/day]
k_d	Death rate	Calibration	[1/mCi*day]

Calibration



- Two fitting scenarios:
  1. Calibrate to all visits (*T*)
  2. Calibrate to *T-1* visits, predict for final follow-up scan

Individual Patient Results

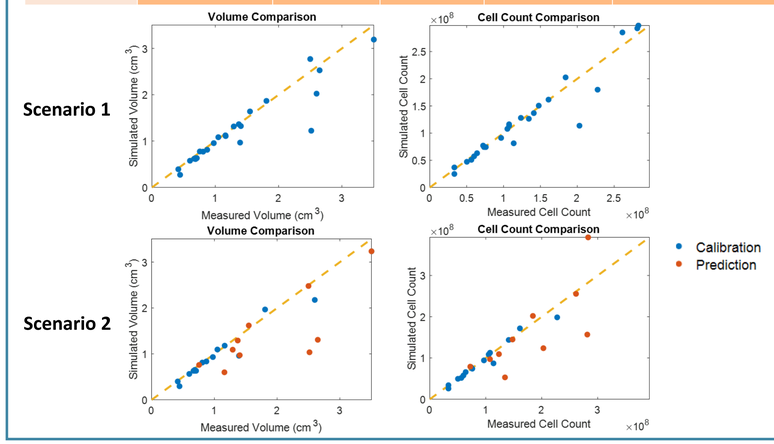


Scenario 1	Day 28	Day 56	Day 112
CCC	0.81	0.86	0.82
DICE	0.84	0.87	0.95

Scenario 2	Day 28	Day 56	Day 112
CCC	0.86	0.90	0.40
DICE	0.85	0.94	0.84

Cohort Results

N=10		CCC	DICE	Cell % Error	Volume % Error
Scenario 1		0.69	0.92	9.5%	10.2%
Scenario 2	Calibrations	0.79	0.93	7.8%	7.9%
	Prediction	0.21	0.78	21.5%	23.4%



Discussion & Conclusion

- Reaction-diffusion model calibrates with high CCC and DICE to patient specific MRI
- High DICE for predicted time points but poor local cell estimates
- Volume and cell count changes are unable to predict overall survival
- Parameters are less dependent on dosage than initially expected

Future Work

- Improving local prediction accuracy
  - Tissue specific diffusivities
  - Coupling of mechanical forces developed in microenvironment
- Improving connection to dosage overlap and intensity
  - Treatment induced diffusivity and proliferation alterations
  - Identifying sensitive and in-sensitive regions
- Predicting for overall survival of patients based on calibrations

References

[1] J. Liu *et al.*, "A time resolved experimental-mathematical model for predicting the response of glioma cells to single-dose radiation therapy." Submitted manuscript in revision.
[2] D. A. Hormuth, S. L. Eldridge, J. A. Weis, M. I. Miga, and T. E. Yankeelov, "Mechanically Coupled Reaction-Diffusion Model to Predict Glioma Growth: Methodological Details," *Methods Mol Biol*, vol. 1711, pp. 225–241, 2018, doi: 10.1007/978-1-4939-7493-1_11.
[3] A. J. Brenner *et al.*, "Safety and feasibility of rhenium-186 nanoliposome (186RNL) in recurrent glioma: The ReSPECT phase 1 trial.," *JCO*, vol. 39, no. 15_suppl, pp. 2061–2061, May 2021, doi: 10.1200/JCO.2021.39.15_suppl.2061.

Acknowledgements

R01 CA235800/CA/NCI NIH HHS/United States; T32 EB007507/EB/NIBIB NIH HHS/United States; R01 CA186193/CA/NCI NIH HHS/United States; U01 CA253540/CA/NCI NIH HHS/United States; U01 CA174706/CA/NCI NIH HHS/United States