2026 JULY 19–22 VANCOUVER, BC
JOINT AAPM | COMP MEETING

Investigating Intra-tumoral Heterogeneity Driven by Nutrient Dynamics and Radiotherapy Using an In-silico Avascular Tumor Growth Model

R. Tan[1], J. B. Stevens[1], C. Wang[1,2], K. J. Lafata[1,2,3,4,5]

[1]Medical Physics Graduate Program, Duke University, [2]Department of Radiation Oncology, Duke University School of Medicine, [3]Department of Radiology, Duke University School of Medicine, [4]Department of Mathematics, Duke University, [5]Department of Electrical and Computer Engineering, Duke University Pratt School of Engineering.

ABSTRACT

Purpose: To develop an in-silico tumor model that incorporates nutrient-driven growth and radiotherapy response to generate spatio-temporal proliferating (P), quiescent (Q), and necrotic (N) cell maps for radiomics-based heterogeneity analysis.

Method: We implemented a framework of early avascular solid tumor growth under dynamic nutrient conditions based on the Chaplain–Sherratt partial-differential-equation (PDE) model for P/Q/N evolution. Radiotherapy was modeled using linear–quadratic (LQ) survival model applied to proliferating cells, with a delayed kill effect representing post-radiation mitotic death/repair kinetics. A probabilistic dose threshold was used to trigger local extinction of proliferating cells at high dose. Immune-mediated debris removal via necrotic clearance was modeled as a radial-dependent washout of necrotic cells. We calculated statistical energy of P-cell density curves at different radiation doses as an aggregate feature. To generate spatial heterogeneity, a Monte-Carlo scheme was used to sample radial shells and assign cell types based on solutions to the PDE model. Cell coordinates were pixelized into density maps weighted by their entropy to characterize total-cell heterogeneity. As an experiment, we ran the model for different nutrient uptake factors α and radiation doses. Radiomic texture features were extracted from the time-dependent cells maps to quantify biological-driven heterogeneity.

Results: Increasing α lowered nutrient level, narrowed the proliferative rim faster, and expanded Q/N compartments earlier, leading to lower texture heterogeneity and earlier necrotic saturation. Simulated heterogeneity peaked during tumor expansion followed by stabilization. Across modeled radiation doses, the simulation captured P-cell spatial distribution changes in energy over time. The post-irradiation energy decreased, followed by a recovery towards reconcentration of the proliferating cell maps. At later times, this effect decayed as necrotic cells became more dominant.

Conclusion: Our model mechanistically links nutrient dynamics and radiation-induced cell death to intra-tumoral heterogeneity via radiomic features. It provides an in-silico framework for computational radiation-biology experiments.

CONTACT

Runhe Tan
Lafata Lab, Duke University
runhe.tan@duke.edu

INTRODUCTION

- Early avascular tumor growth is governed by **diffusion-limited nutrient supply**, producing layered **proliferating (P), quiescent (Q), and necrotic (N)** structure.
- Tumor response to radiotherapy depends on this **microenvironmental heterogeneity**.
- **Radiomics** studies have shown that image texture features can be correlated with **tumor biology**, but feature values often vary with imaging parameters and segmentation choices, which limits reproducibility and biological interpretability.
- **Goal:** To develop an in-silico tumor model that incorporates **nutrient-driven growth and radiotherapy response** to generate spatiotemporal proliferating (P), quiescent (Q), and necrotic (N) cell maps for **radiomics-based heterogeneity** analysis.

METHODS AND MATERIALS

The simulation begins with a **1D PDE model** for proliferating (P), quiescent (Q), necrotic (N), and nutrient distributions. Radiation response is incorporated through **Linear Quadratic (LQ)-based** survival, **delayed kill,** and a **probabilistic high-dose extinction gate**. The 1D solution is converted into **2D Monte Carlo cell maps**, then pixelized into density, entropy-weighted, and segmented maps for **heterogeneity and radiomics-style** feature analysis.

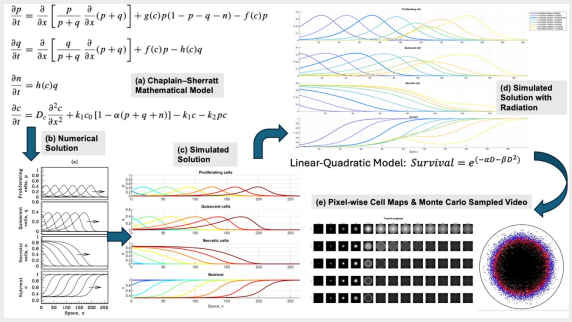

Figure 1: In-silico avascular tumor growth and radiation response model. (a) PDE describing internal transitions between cell states. **(b)** Analytical cell density and nutrient distribution curves from the PDE. **(c)** Computational solution curves of P/Q/N and nutrient channel distribution from the implemented PDE. **(d)** Computational solution curves of P/Q/N and nutrient channel distribution with single radiation dose at t=15 from the implemented PDE. **(e)** Monte Carlo sampling of the 1D solution curves generates 2D cloud point cell maps, which are converted into pixelized maps and segmented masks, ready for radiomics feature extraction.

RESULTS

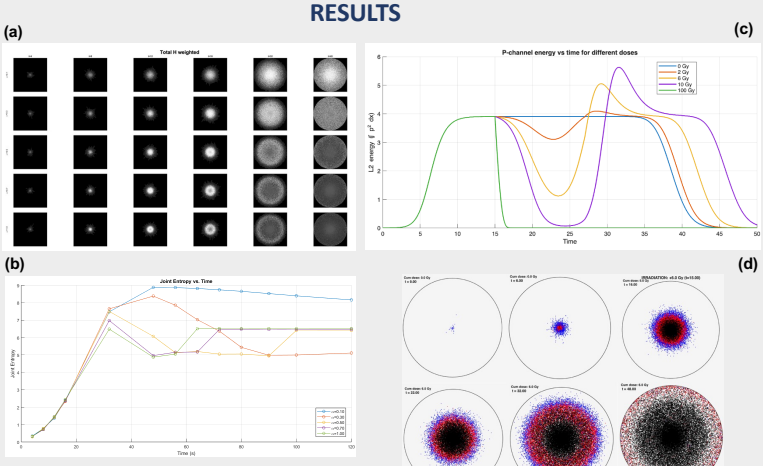

Figure 2: Parameterization of nutrient uptake factor α. (a) *Time-resolved Shannon Entropy weighted total cell grey scale pixel map across α=0.1:0.3:1 with black backgrounds. Rows show increasing nutrient uptake factor α and columns show time. Brighter regions indicate stronger local mixing of simulated P/Q/N cell states, while darker regions indicate either lower density or dominance of a single cell state. Higher α produced earlier P/Q/N transition and earlier necrotic-core dominance.* ***(b)*** *A representative radiomic texture feature (joint entropy) used to quantify image heterogeneity shown across time for different values of the nutrient uptake factor α. From top to bottom, the α value increases, meaning faster nutrient uptake during the tumor growth, which leads to a narrower proliferating rim and faster saturation of necrotic cells.*

Figure 3: Radiation response experiment. (c) *Statistical energy of proliferating cell density with various radiation doses at t = 15. With increasing doses, all curves drop in a sigmoidal way transiently, then turning up again, except for the bottom 100 Gy curve that had extinction of the viable cell population triggered by the high dose threshold. This shows simulated radiotherapy can slow the in-silico tumor cell culture with appropriate parameterization.* ***(d)*** *Snapshots from the Monte-Carlo sampling algorithm for 2D tumor growth. Subject to initial cell densities and nutrient access, the simulation can model resulting heterogeneity in cell distributions. Clear layers of P/Q/N cells appear at later times with the formation of a necrotic core near the end of the simulation. Radiation induces a perturbation that selectively reduces the density of proliferating cells, which has downstream effects on cell heterogeneity.*

DISCUSSION

- The model reproduces expected qualitative behavior of nutrient-limited avascular growth, including a proliferating rim, quiescent transition region, and necrotic core.
- Nutrient uptake factor **α** had a strong effect on the timing of P/Q/N transition and radiomic-based heterogeneity.
- Radiation dose altered the proliferating-cell profile in a time-dependent manner, with delayed decrease and recovery patterns that depend on the LQ, delay, and extinction parameters.
- Necrotic clearance changed late-time map appearance and may affect texture features, especially when necrotic regions dominate.

CONCLUSIONS

- We implemented an in-silico tumor cell culture model combining nutrient-limited P/Q/N growth, simplified radiotherapy response, and necrotic clearance.
- This framework provides a practical computational platform for controlled radiation-biology and radiomics-methodology experiments.

MEDICAL PHYSICS GRADUATE PROGRAM

Lafata Laboratory