Digital Twins for Advancing Nano-Particle Mediated Radiotherapy Against Glioblastoma

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ABSTRACT

Purpose: Nanoparticle-mediated radiation therapy (NPRT) is an emerging clinical research frontier which seeks to improve radiotherapy outcomes through local tumor dose enhancement and radiosensitization. We recently showed improved NPRT outcomes for 2D glioblastoma (GBM) cells treated with graphene quantum dots (GQD) in vitro. To better mimic the in vivo tumor response in 3D microenvironments, we use Digital Twin-driven experimental-computational framework that integrates machine learning with advanced 3D in-vitro tumor models to characterize response to NPRT.

Methods: 3D spheroids of GBM were produced and used to replicate physiologically relevant tumor architecture and microenvironmental conditions. Spheroids were treated with biocompatible GQD to effect both the increased release of electrons that promote reactive oxygen species (ROS) generation and dose enhancement. We implemented time-resolved imaging and biophysical measurements that provide readouts of cell viability, morphology, growth, migration from a tumor and clonogenic cell survival. Unsupervised machine learning (UML) algorithms were developed in-house in MATLAB to extract therapeutic signatures from the 2D and 3D treatment results. Convolutional neural networks (CNNs) were trained based on extracted therapeutic signatures and used for automated image analysis and feature extraction. A digital twin model continuously coupled experimental observations with computational predictions, enabling iterative model updates.

Results: Our UML algorithms have successfully clustered images of cells treated with GQD and temozolomide, without radiation, in a manner distinct from clustering patterns when radiotherapy is introduced. Deep learning models are being optimized to enable comparison with prior 2D NPRT data. Correlations between tumor viability, migration from spheroids/clonogenic survival and UML image clusters are being established and results will be presented.

Conclusion: This combined experimental-computational approach offers a scalable path toward patient-specific modeling and optimization of GBM radiotherapy. This framework will hopefully accelerate clinical trials involving NPRT, especially in cases of highly radioresistant brain cancers such as GBM.

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BACKGROUND

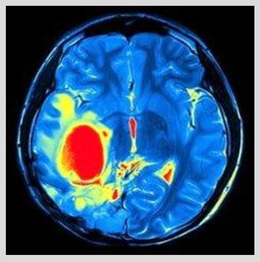

Figure 1. MRI demonstrates a tumor in the posterior left temporal lobe

Glioblastoma (GBM) is the most common malignant primary brain tumor and is characterized by aggressive invasion and poor prognosis. Median survival remains approximately 12–15 months with treatment despite recent advancements. The standard of care, which includes surgery followed by radiotherapy and chemotherapy with temozolomide, is limited by significant radio-resistance and chemoresistance, underscoring the need for more effective, individualized therapeutic strategies.

Figure 2. Standard of care of glioblastoma includes (a) radiotherapy, (b) surgical resection, and (c) chemotherapy in the management of glioblastoma.

EXPERIMENTAL METHODS

3D spheroids were treated with radiotherapy (RT) and sensitized with graphene quantum dots (GQDs). Enhancement is driven by the physical interaction between incident X-rays and the nanoparticle lattice, specifically the increased production of low-energy secondary electrons that amplify localized DNA damage.

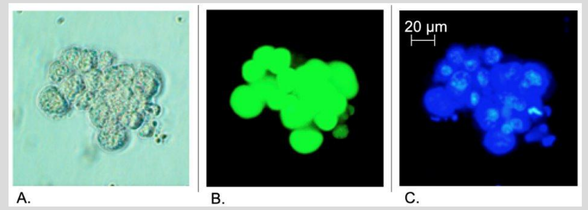

Figure 3. T98G 3D cell spheroids: A) phase contrast, B)Calcein-stained and C) Hoechst-stained images of the same 3D spheroid comprising of around 20 cells

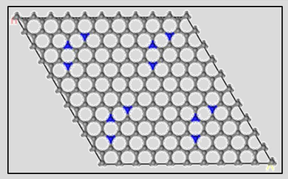

Figure 4. Schematic of a single-layer graphene quantum dot

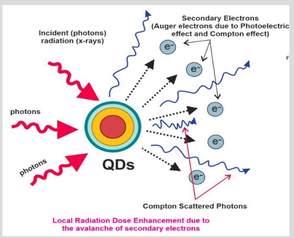

Figure 5. Model of NPRT: Incoming radiation collides with quantum dots in cancerous tissue, acting as a local radiosensitizer

COMPUTATIONAL METHODS

UML clusters subtle morphological changes within images, revealing distinct therapeutic signatures. Once identified, these signatures serve as labeled training inputs for CNNs, allowing for automated classification and high-input screening of treatment responses. Experimental and computational data are fed into a digital twin, continuously updating the model on treatment predictions.

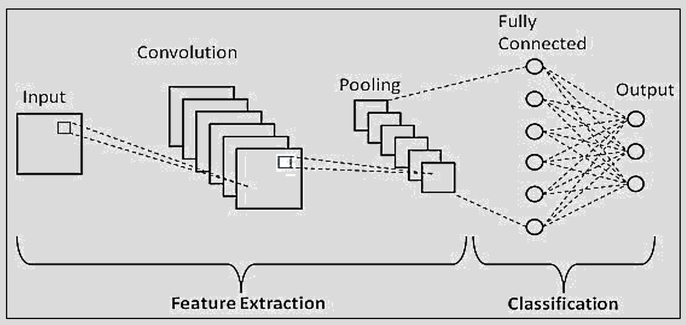

Figure 6. Convolutional Neural Network

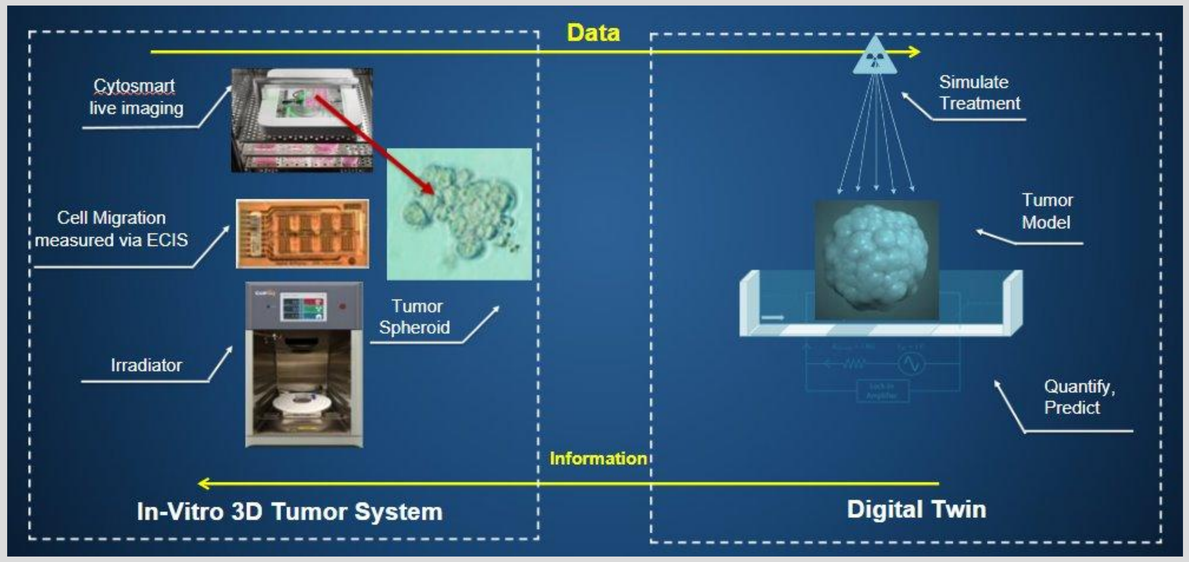

Figure 7. Visual Concept of a Digital Twin in TBP. 3D spheroid computationally replicated in MATLAB continuously receives real time feedback, allowing for increased model accuracy for future predictions.

RESULTS

Condition	Dose (Gy)	Cells Plated	Day 14 Plating Efficiency	Day 14 Colony Count	Day 14 Surival Fraction
1. T98G only	0	50	0.24	12	1
2. T98G + 2Gy	2	100	0.24	9	0.375
3. T98G + 5Gy	5	500	0.24	27	0.225
4. T98G + 10Gy	10	1000	0.24	11	0.045833333
5. T98G + 20Gy	20	2000	0.24	0	0
6. T98G + 50Gy	50	5000	0.24	0	0
7. T98G + GQD	0	50	0.24	24	2
8. T98G + GQD + 2Gy	2	100	0.24	26	1.083333333
9. T98G + GQD+ 5Gy	5	500	0.24	58	0.483333333
10. T98G + GQD + 10Gy	10	1000	0.24	31	0.129166667
11. T98G + GQD + 20Gy	20	2000	0.24	2	0.004166667
12. T98G + GQD + 50Gy	50	5000	0.24	0	0

Figure 9. ECIS Migration of T98G glioblastoma cells treated with RT and GDQs

*Current clonogenic data is preliminary. Given a 21-day incubation period required per assay, two additional replicated experiments are underway to confirm findings.

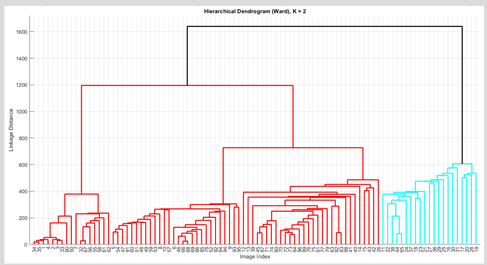

Figure 8. Dendrogram of clusters generated from UML for T98G cells treated with RT and GQDs 24 hours following treatment, highlighting the hierarchical distribution of identified morphological signatures.

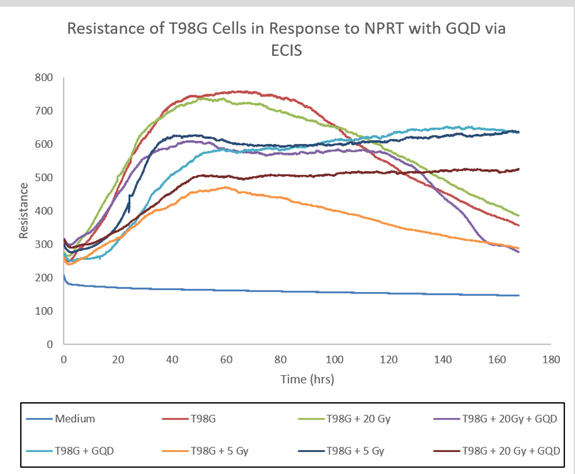

Figure 9. ECIS Migration of T98G glioblastoma cells treated with RT and GDQs

*Divergence was observed between identical treatment conditions (T98G + 20 Gy + GQD). This variation is attributed to localized evaporation within the sensing well, resulting in resistance values that deviate from an expected trend.

FUTURE WORK

In progress CNN will be trained to identify features based on UML clusters and will transmit data to a DT model that will then predict treatment outcomes by comparing simulations against experimental data for accuracy. The model is refined through an iterative optimization process using supplemental therapeutic signature data.

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