Physics-Informed Neural Network for Estimating Cellular Microenvironment Parameters in Radiotherapy Treatment Response Assessment

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INNOVATIONS

Clinical innovation: Quantifying tumor cell microenvironment characteristics plays a critical role in the early assessment of anti-cancer treatment response. Biopsy is the golden standard, but it is invasive, time-consuming, and limited to local sampling, making it unsuitable for repeated and comprehensive monitoring purposes. Diffusion-weighted MRI (dMRI) provides a promising noninvasive alternative. This study contributes to quantitatively estimate valuable tumor microenvironment parameters from dMRI.

Technology innovation: Estimating microstructural parameters from low-signal-to-noise ratio dMRI data, particularly at 1.5 T, remains a major technical challenge. Conventional deep learning approaches that directly map signals to parameters offer limited robustness under noisy conditions and lack interpretability. This study introduces a physics-informed neural network (PINN) that explicitly embeds the dMRI signal model into the learning process via a novel framework. By combining data-driven learning with established diffusion physics, the proposed approach enhances accuracy at clinically relevant field strengths and potentially provides a transparent, reliable framework for quantitative tumor microenvironment assessment in radiotherapy.

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INTRODUCTION

Background: Diffusion-weighted MRI (dMRI) is promising for estimating tumor microenvironment characteristics from measured signals that encode the microscopic diffusion of water molecules constrained by cellular architecture. Estimation accuracy is compromised by low signal-to-noise ratios. While deep learning-based end-to-end mapping can improve performance, they suffer from limited interpretability.
Purpose: This study proposes a physics-informed neural network (PINN) framework to enhance cell parameter estimation accuracy while preserving explainability.

METHODS AND MATERIALS

Data: IMPULSED-model [1] simulations covered clinically relevant acquisition protocols and parameter ranges; training and validation samples were generated on the fly, with 30000 fixed test cases.
Para2Sig model: A parameter-to-signal (Para2Sig) model was first trained to represent the biophysical relationship from cell parameters to dMRI signals using data generated by theoretical dMRI model [1].
Sig2Para PINN: The PINN framework minimized losses in both dMRI signal domain and cell-parameter domain to establish a signal-to-parameter (Sig2Para) prediction model. The pre-trained Para2Sig was integrated to the PINN framework as a constraint of the dMRI physical model, and in lieu of the theoretical dMRI model to enable error backpropagation using auto-differentiation approach. The entire framework was trained in a self-supervised scheme using on the fly generated data.
Evaluation: We evaluated the effectiveness of the proposed framework in simulated data and experimental data with Jurkat cell line. A simulated brain tumor dataset was further employed to qualitatively assess the performance in a realistic clinical scenario.

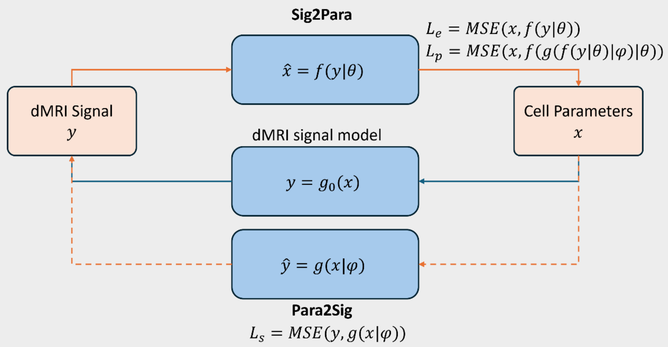

Figure 1. Workflow of the PINN framework. L_e, L_p, L_s represent the estimation loss, physics-consistency loss, and the loss of the offline Para2Sig model.

RESULTS

Physics surrogate: The offline pre-trained Para2Sig model reproduced ground-truth dMRI signals with 99.92% accuracy.
Simulation: Incorporating Para2Sig as a physical constraint, the PINN reduced prediction errors to 3.5%, 5.3%, and 8.4% for cell diameter (d), intracellular volume fraction (V_{in}), and extracellular diffusion coefficient (D_{ex}), respectively, outperforming the baseline model trained without physics constraint (5.1%, 8.0%, 10.6%).
Jurkat cells: On experimental data, PINN yielded a d estimation of 9.19 µm (ground truth: 10 µm), compared with 14.23 µm from the baseline.
Brain case: On the brain tumor dataset, PINN achieved PSNR/SSIM values of 35.51/0.975, 30.91/0.978, and 23.60/0.782 for d, V_{in}, and D_{ex}, respectively.

Table 1. Cell microenvironment parameters estimation performance comparison between the baseline Sig2Para_nonPINN model and PINN on simulation data.

	Sig2Para_nonPINN	PINN
d	5.1%	3.5%
V_{in}	8.0%	5.3%
D_{ex}	10.6%	8.4%

Table 2. Cell microenvironment parameters estimation performance comparison between the baseline Sig2Para_nonPINN model and PINN on experimental data.

	Ground Truth	Sig2Para_nonPINN	PINN
d	10 µm	14.23 µm	9.19 µm

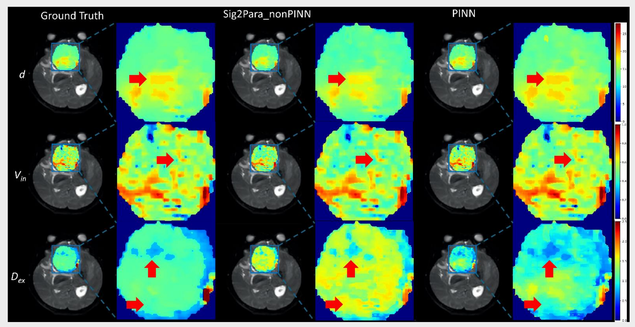

Figure 2. Tumor microenvironment parameter estimation results. From top to bottom, the three rows show the ground-truth parameter maps, the estimation results from the reference Sig2Para model, and the results from the proposed PINN framework for d, V_{in}, and D_{ex}, respectively.

DISCUSSION AND CONCLUSIONS

In this study, we developed a PINN framework for estimating cellular microenvironment parameters from dMRI signals. Compared with the baseline model trained without the physics-informed constraint, the proposed PINN consistently improved the estimation accuracy of d, V_{in}, and D_{ex}. The improved performance may be attributed to the additional physics-consistency constraint imposed during training. Specifically, the estimated parameters are passed through the Para2Sig model and constrained to reproduce signals consistent with the underlying diffusion physics. Our results demonstrate that the proposed PINN improves performance not only on simulated data but also on experimental Jurkat cell data and a simulated brain-tumor imaging case, suggesting the potential of the proposed PINN for noninvasive tumor microenvironment quantification and radiotherapy treatment-response assessment. Future studies should validate the framework using ex vivo, and in vivo datasets and evaluate its reproducibility across acquisition protocols and MRI systems.

REFERENCES

[1] Jiang X, Li H, Xie J, Zhao P, Gore JC, Xu J. Quantification of cell size using temporal diffusion spectroscopy. Magnetic resonance in medicine. 2016 Mar;75(3):1076-85.