A Laplace-Domain Transport Dominance Spectrum for Characterizing Acute Radiation-Induced Vascular Response in DCE-MRI

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ABSTRACT

Purpose: To characterize acute radiation-induced vascular responses using a Laplace-domain analysis of DCE-MRI.

Methods: Twenty rats with intracranial U251N tumors underwent 7T DCE-MRI before and 1–5 hours after 20 Gy whole-brain radiotherapy. A voxel-wise Transport-Dominance Spectrum (TDS) was derived from probabilistically combined nested pharmacokinetic models in the Laplace domain to quantify flow- and leakage-driven transport across temporal scales.

Results: Radiotherapy induced distinct frequency-dependent changes in transport dominance. Normal brain regions exhibited increased high-frequency leakage, tumor rim regions showed enhanced long-time-scale flow with faster leakage, and highly permeable tumor regions demonstrated reduced sustained leakage dominance.

Conclusions: Acute radiation reweights flow- and leakage-mediated transport in a tissue- and time-scale–dependent manner. Laplace-domain TDS analysis provides a sensitive and mechanistically interpretable framework for early assessment of radiation-induced vascular response.

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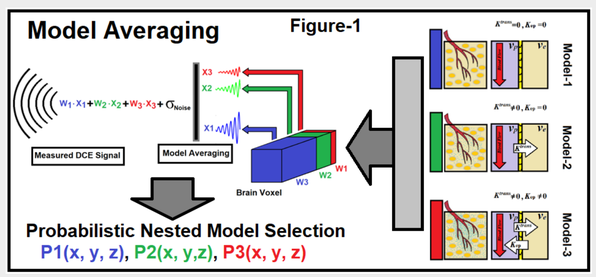
INTRODUCTION

- Dynamic contrast-enhanced (DCE)-MRI is widely used to evaluate vascular perfusion and permeability, but conventional time-domain pharmacokinetic models often fail to distinguish flow- and leakage-mediated transport.
- In this study, we introduce a Laplace-domain framework that provides a frequency-resolved characterization of vascular transport using a Transport Dominance Spectrum (TDS) derived from probabilistic nested model selection technique[1,2,3].
- Applied to a preclinical brain tumor model, this approach reveals that acute radiotherapy induces tissue- and time-scale–dependent reweighting of vascular transport rather than uniform permeability changes, offering a mechanistically interpretable and sensitive biomarker for early assessment of radiation response.

METHODS AND MATERIALS

- Twenty rats with intracranial U251N tumors underwent 7Tesla DCE-MRI before and 1-5 hours after a single 20 Gy whole-brain radiotherapy dose.
- Voxel-wise vascular transport was characterized using probabilistic nested model selection (PNMS)[1,2,3], combining three physiologically ordered models (Figure-1): Model-1 (no leakage), Model-2 (vascular outflow without backflux), and Model-3 (bidirectional exchange).
- Longitudinal relaxivity changes (ΔR_1) were transformed into the Laplace domain to derive probabilistic blood-to-tissue transfer functions based on the Extended Tofts model (Eqs.1-5).
- Voxel-wise probabilistic weights (Eq. 6) enabled model averaging and propagation of uncertainty, allowing multiple transport mechanisms to coexist within heterogeneous tumor tissue [1,2,3].
- Real and imaginary components of the combined transfer function (Eqs. 7-8) were used to compute frequency-dependent amplitude and phase (Eqs. 9-10) information, from which the bounded Transport Dominance Spectrum, TDS(ω), was derived (Eq. 11) to quantify flow- and leakage-driven transport across temporal scales.
- TDS(ω), was computed to quantify the relative dominance of leakage versus flow across temporal scales and assess RT-induced changes.



METHODS AND MATERIALS

$$C_t(t) = v_p C_p(t) + K^{trans} \int_0^t C_p(\tau) e^{-k_{ep}(t-\tau)}\, d\tau \quad \text{Extended Toft's Model} \quad (1)$$

$$\Delta R_{1,t}(t) = \mu\left[v_p \Delta R_{1,b}(t) + K^{trans} \int_0^t \Delta R_{1,b}(\tau) e^{-k_{ep}(t-\tau)}\, d\tau\right],\ \mu = \frac{r_{1,t}}{r_{1,b}(1-H_{ct})} \quad (2)$$

$$H_1(s,\mu,v_{p1}) = \mu[v_{p1}] \quad \text{Laplace Transfer Function for Model 1} \quad (3)$$

$$H_2(s,\mu,v_{p2},K_2^{trans}) = \mu\left[v_{p2} + \frac{K_2^{trans}}{s}\right] \quad \text{Laplace Transfer Function for Model 2} \quad (4)$$

$$H_3(s,\mu,v_{p3},K_3^{trans},k_{ep}) = \mu\left[v_{p3} + \frac{K_3^{trans}}{s+k_{ep}}\right] \quad \text{Laplace Transfer Function for Model 3} \quad (5)$$

Let $P_1(x,y,z)$, $P_2(x,y,z)$, and $P_3(x,y,z)$ be the voxel-wise probabilities for nested Models 1, 2, and 3, respectively with $P_1(x,y,z) + P_2(x,y,z) + P_3(x,y,z) = 1$ (6)

$$\Omega(\omega,x,y,z,\boldsymbol{P},\boldsymbol{\theta}) = \boldsymbol{P_2}(\boldsymbol{x},\boldsymbol{y},\boldsymbol{z})\frac{K_2^{trans}(x,y,z)}{\omega} + \boldsymbol{P_3}(\boldsymbol{x},\boldsymbol{y},\boldsymbol{z})K_3^{trans}(x,y,z)\frac{\omega}{k_{ep}^2(x,y,z)+\omega^2} \quad (7)$$

$$\Psi(\omega,x,y,z,\boldsymbol{P},\boldsymbol{\theta}) = \boldsymbol{P_1}(\boldsymbol{x},\boldsymbol{y},\boldsymbol{z})v_{p1}(x,y,z) + \boldsymbol{P_2}(\boldsymbol{x},\boldsymbol{y},\boldsymbol{z})v_{p2}(x,y,z) + \quad (8)$$

Probabilistic Transfer Function $\boldsymbol{P_3}(\boldsymbol{x},\boldsymbol{y},\boldsymbol{z})\left[v_{p3}(x,y,z) + \frac{K_3^{trans}(x,y,z)k_{ep}(x,y,z)}{k_{ep}^2(x,y,z)+\omega^2}\right]$

$$|H_{Pnms}(\omega,\mu,\boldsymbol{P},\boldsymbol{\theta})| = |\mu|\sqrt{\Psi(\omega,x,y,z,\boldsymbol{P},\boldsymbol{\theta})^2 + \Omega(\omega,x,y,z,\boldsymbol{P},\boldsymbol{\theta})^2} \quad \text{Amp. Information} \quad (9)$$

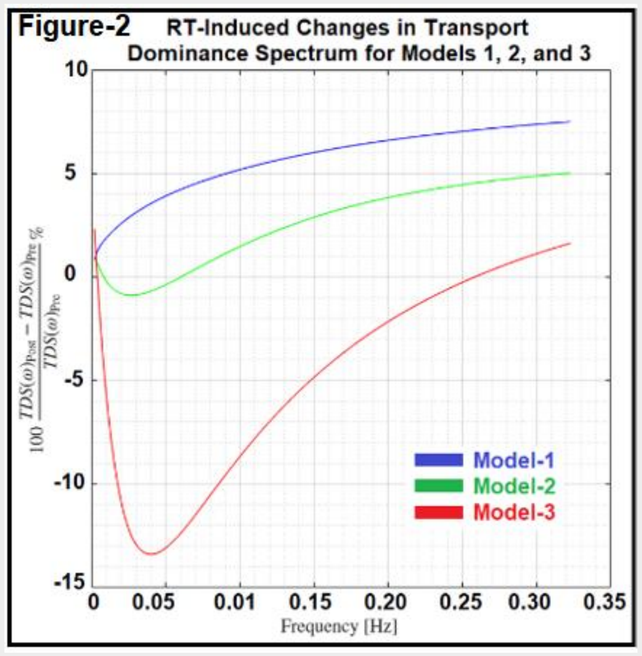
$$\overrightarrow{H_{Pnms}(\omega,\mu,\boldsymbol{P},\boldsymbol{\theta})} = -\frac{180}{\pi} Arctan\left[\frac{\Omega(\omega,x,y,z,\boldsymbol{P},\boldsymbol{\theta})}{\Psi(\omega,x,y,z,\boldsymbol{P},\boldsymbol{\theta})}\right] \quad \text{Phase Information} \quad (10)$$

$$TDS(\omega) = \frac{|\Omega(\omega,x,y,z,\boldsymbol{P},\boldsymbol{\theta})|}{|\Psi(\omega,x,y,z,\boldsymbol{P})| + |\Omega(\omega,x,y,z,\boldsymbol{P},\boldsymbol{\theta})|} \in [0,1] \quad (11)$$

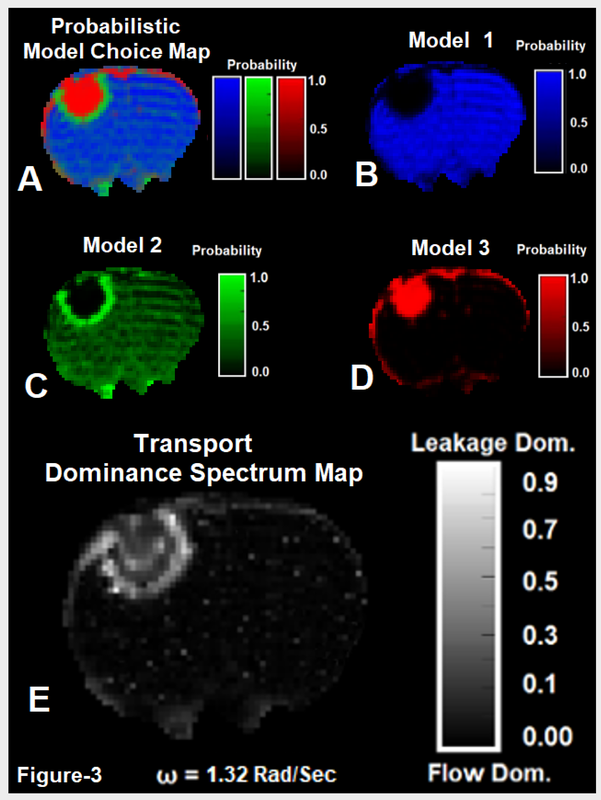
$TDS(\omega) \approx 0 \rightarrow$ Leakage Dominated $\qquad TDS(\omega) \approx 1 \rightarrow$ Flow Dominated

RESULTS

- Figure 2 shows that acute RT induced reproducible, model- and frequency-dependent TDS(ω) changes, indicating tissue- and time-scale dependent redistribution of flow- and leakage-mediated transports.
- Model-1 (normal brain) exhibited a +3.2 to19% increase in TDS(ω); Model-2 (tumor rim) showed reduced low-frequency (−0.6 to −0.8%) and elevated high-frequency (up to +6.2%) TDS(ω); Model-3 (highly permeable tumor) demonstrated marked low-to-mid-frequency suppression (−14 to −16%) with partial high-frequency recovery (Figure 2).
- Subfigures 3A-D show the PNMS and model probability maps for a representative rat brain.
- Subfigure 3E shows the pre-RT TDS(ω) map at 0.21 Hz (ω = 1.32 rad/s), revealing a flow-dominated tumor inner rim and leakage-dominated tumor rim and core, patterns visible only with the frequency-resolved TDS(ω) framework.



RESULTS



DISCUSSION

Laplace-domain analysis revealed that acute RT does not uniformly increase or decrease permeability, but instead, induces tissue- and time-scale dependent reweighting of flow- and leakage-mediated transport mechanisms. These dynamic vascular changes are not fully captured by conventional PNMS maps or time-domain DCE-MRI metrics. By resolving transport behavior across frequencies, the TDS (ω) framework provides mechanistic insight into radiation-induced vascular alterations and enables characterization of distinct responses across tissue compartments. Furthermore, the framework offers a quantitatively sensitive and mechanistically interpretable alternative to conventional time-domain DCE-MRI analysis.

CONCLUSIONS

The TDS (ω) provides a mechanistically interpretable and sensitive biomarker of acute radiation-induced vascular response by revealing tissue- and frequency-dependent reweighting of flow- and leakage-mediated transport, offering advantages over conventional time-domain DCE-MRI analysis.

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