Mathematical Modeling of Drug Transport in Brain Tumor

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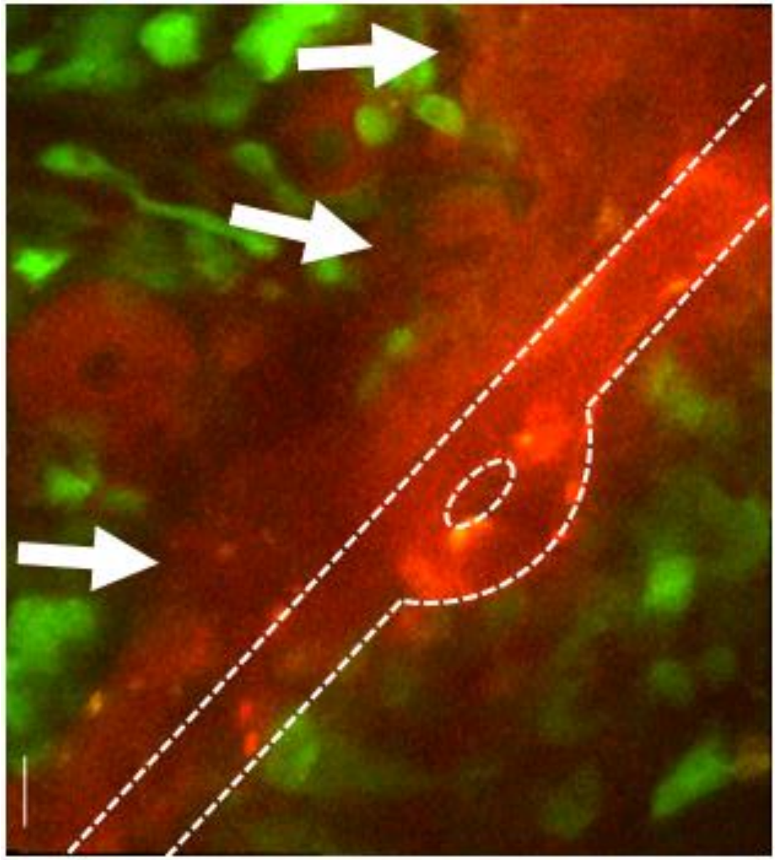
MOTIVATION

- Focused ultrasound (FUS), when combined with circulating microbubbles, provides a noninvasive method to locally and transiently disrupt the Blood Brain Barrier (BBB). [1]
- Preclinical research have shown that FUS-BBB disruption can lead to an seven-fold increase in the delivery of anticancer agents(doxorubicin) in brain tumors.[2]
- However, there is a lack of fundamental understanding of how physicochemical drug properties influence the effects of FUS-mediated BBB disruption on drug transport and cellular uptake in the highly heterogeneous tumor microenvironment.

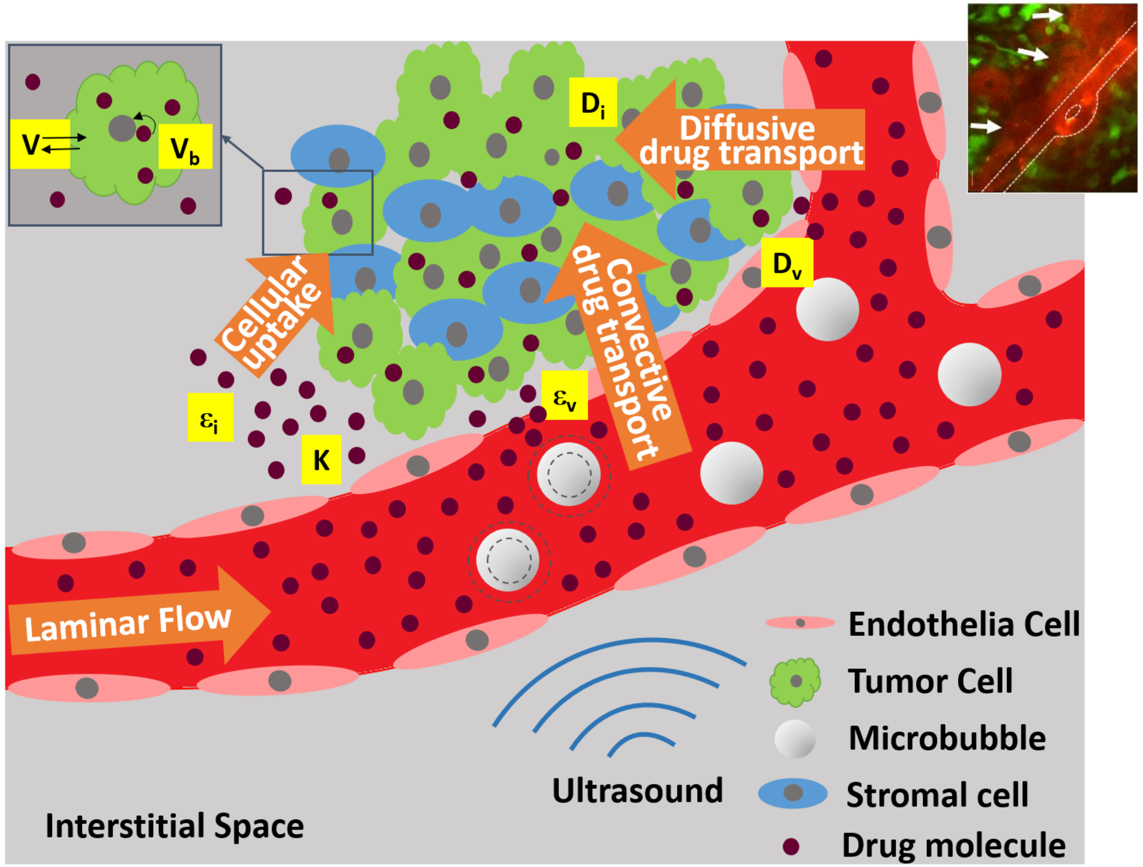


Anticancer agent/cancer cells (GFP)

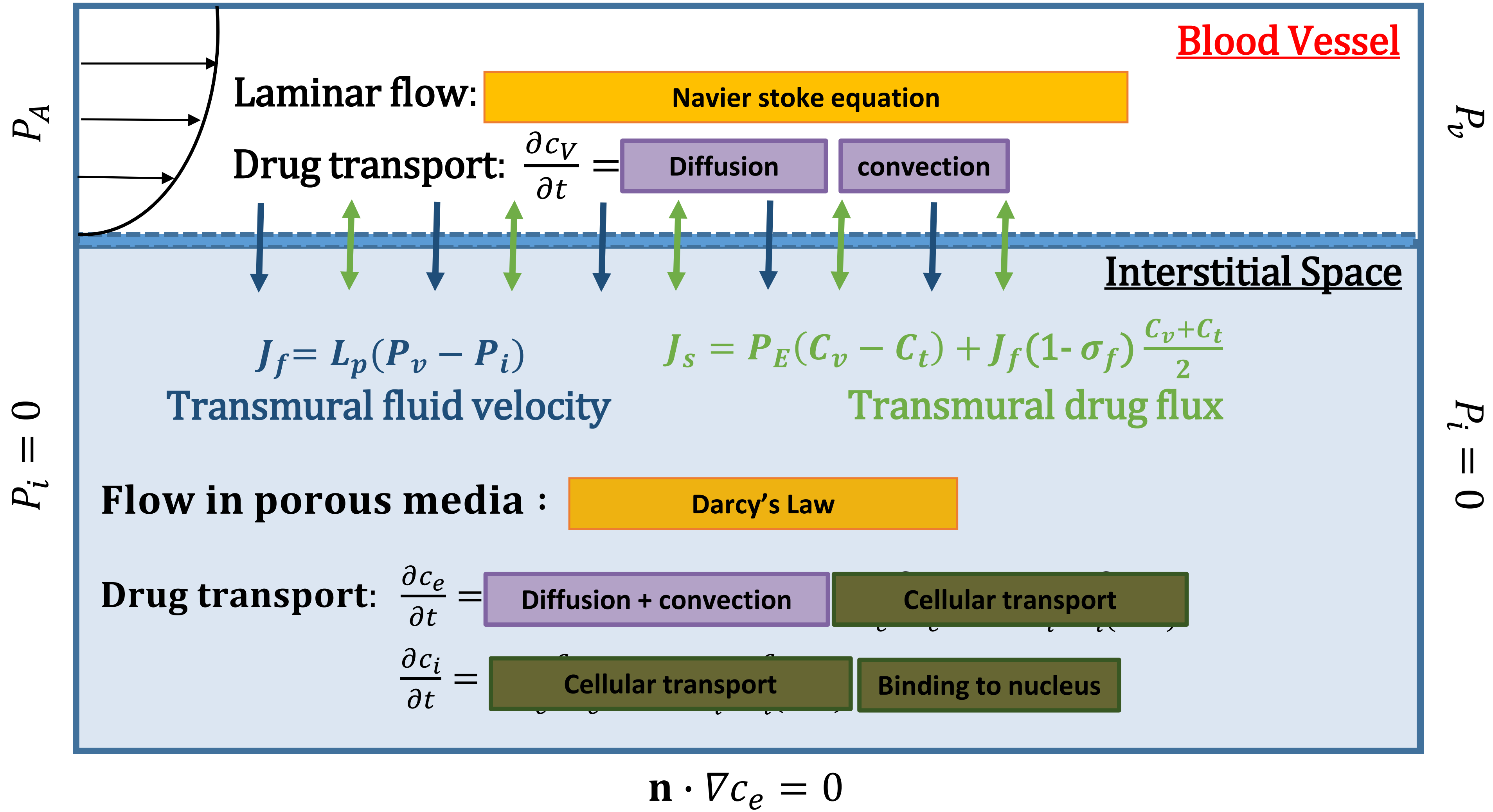
[1] Aryal M et al Advanced Drug Delivery Reviews | 2014 | Vol 72 | pp94-109
[2] Arvanitis, Costas D., et al. *Proceedings of the National Academy of Sciences* (2018): 201807105.

MATHEMATICAL MODEL

- We developed a mathematical model using COMSOL Multiphysics to simulate:
  - ➢ Blood and interstitial fluid flow
  - ➢ Transport of anticancer agents through the bloodstream and across the endothelium into the interstitial space of a tumor
  - ➢ Drug uptake by tumor cells and drug binding to cell nucleus.



MATHEMATICAL MODEL

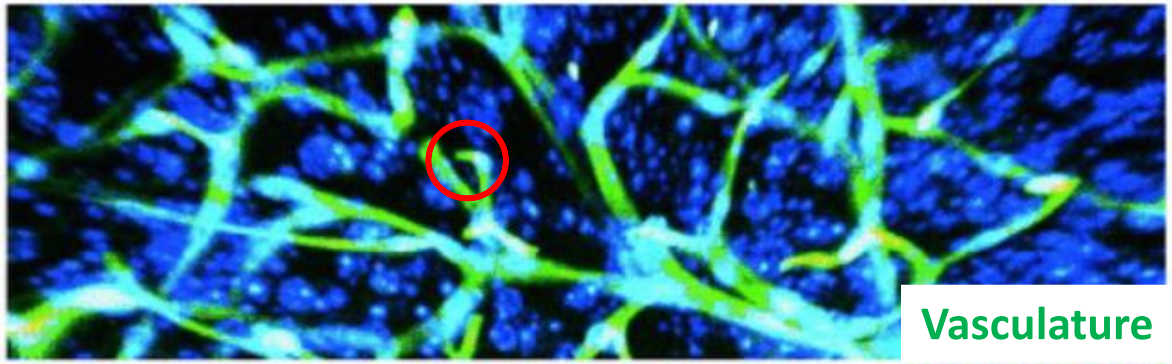


GEOMETRY

Properties of brain tumor vasculature:

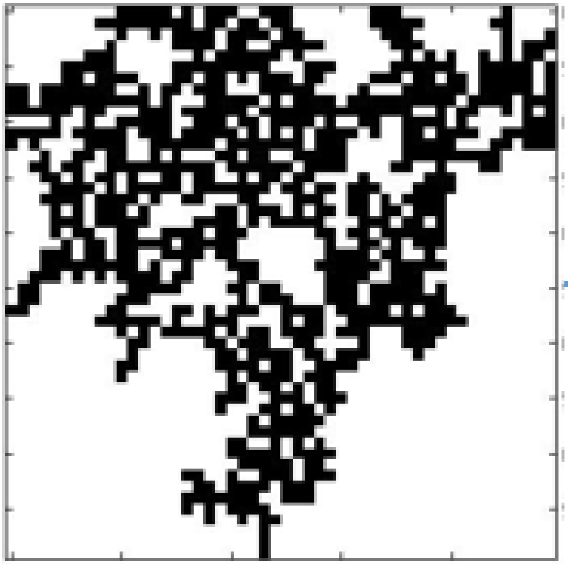
- Disorganized
- Unevenly distributed.

Intravital confocal imaging of microvasculature in glioblastoma

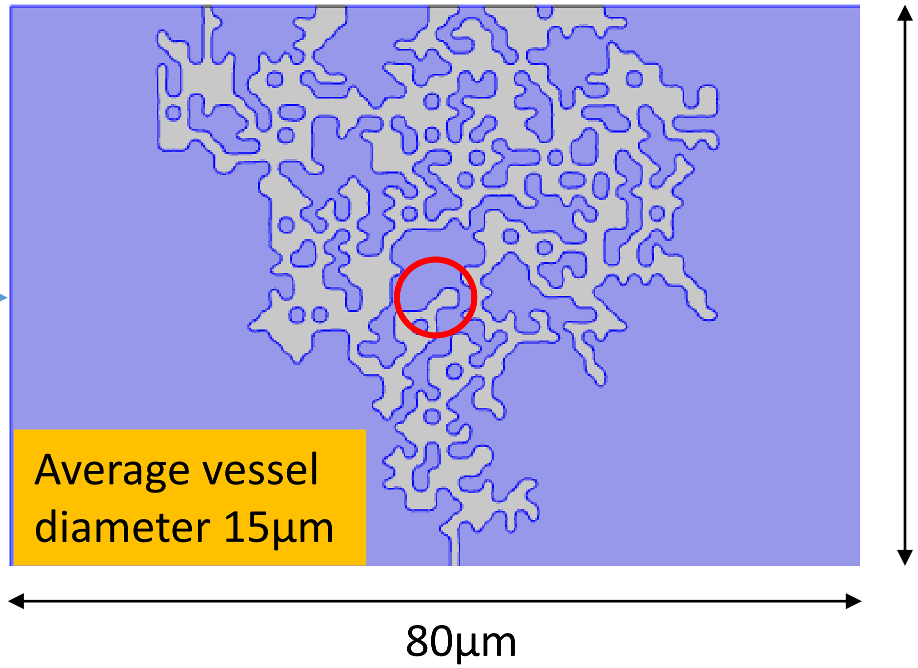


Lagerweij, Tonny, et al. *Angiogenesis* 20.4 (2017): 533-546.

Matlab (percolation model)



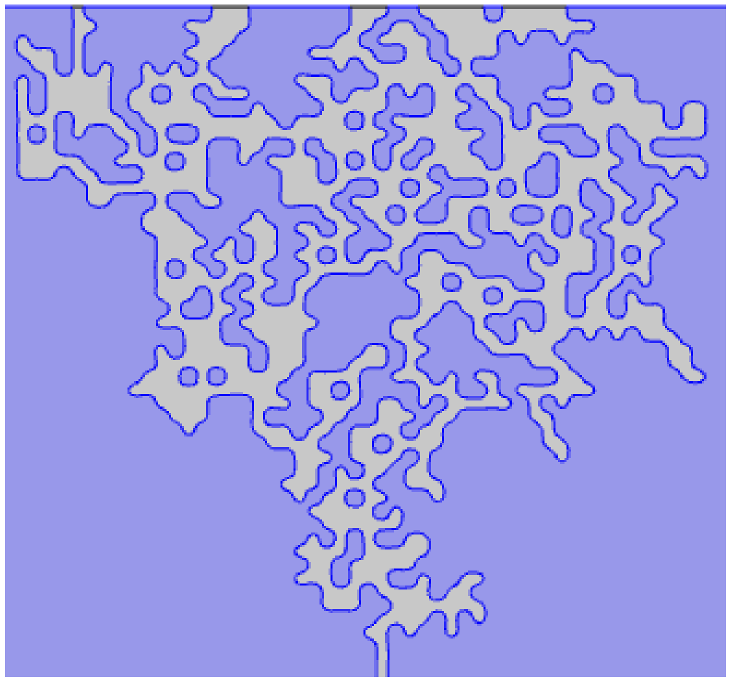
Comsol



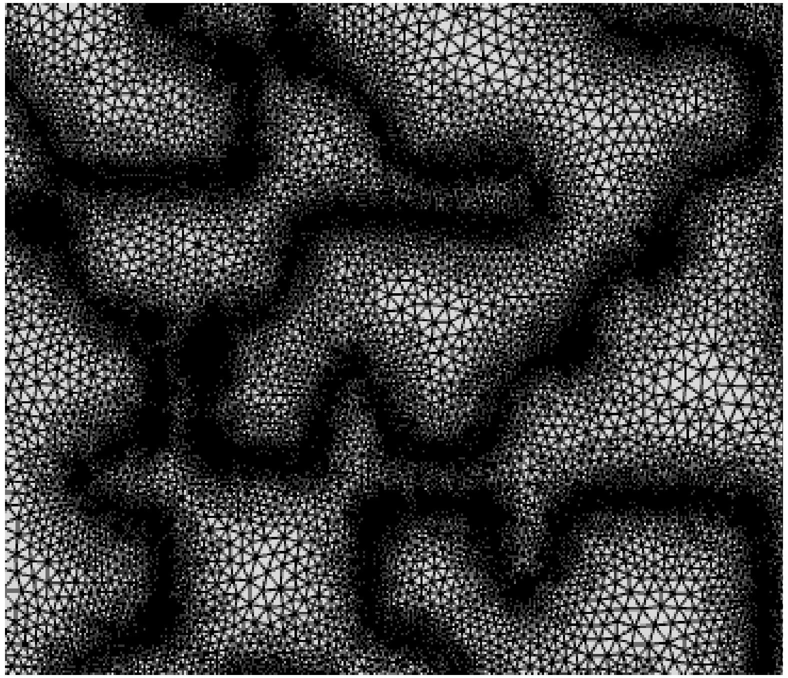
MESH

- Computational domain is discretized using triangular elements
- Average mesh edge length: 3μm
- Mesh is refined around the vascular wall (average mesh edge length 0.8μm along the vascular wall)

Geometry



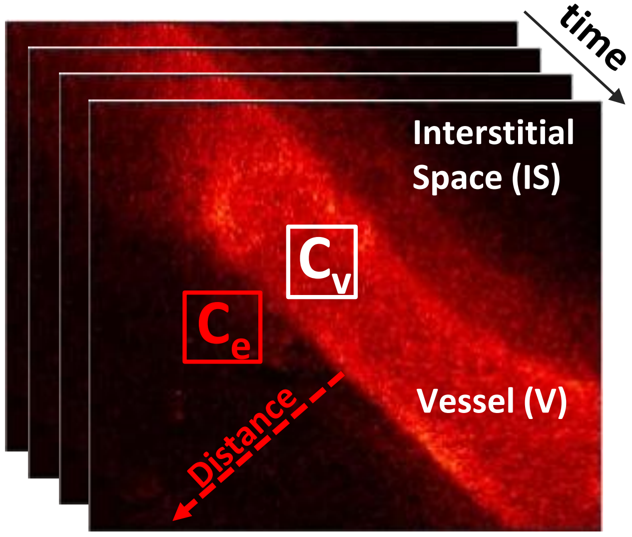
Mesh

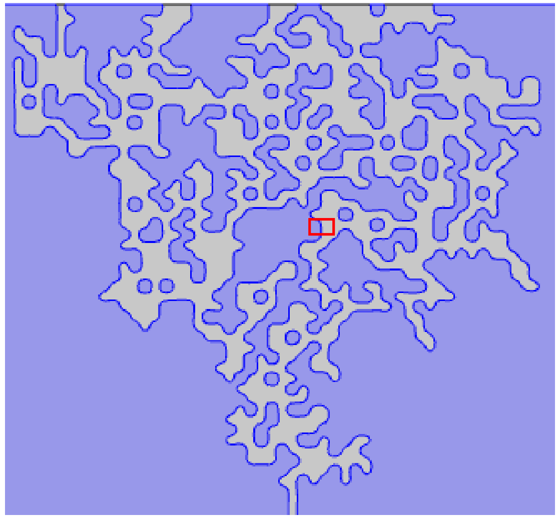


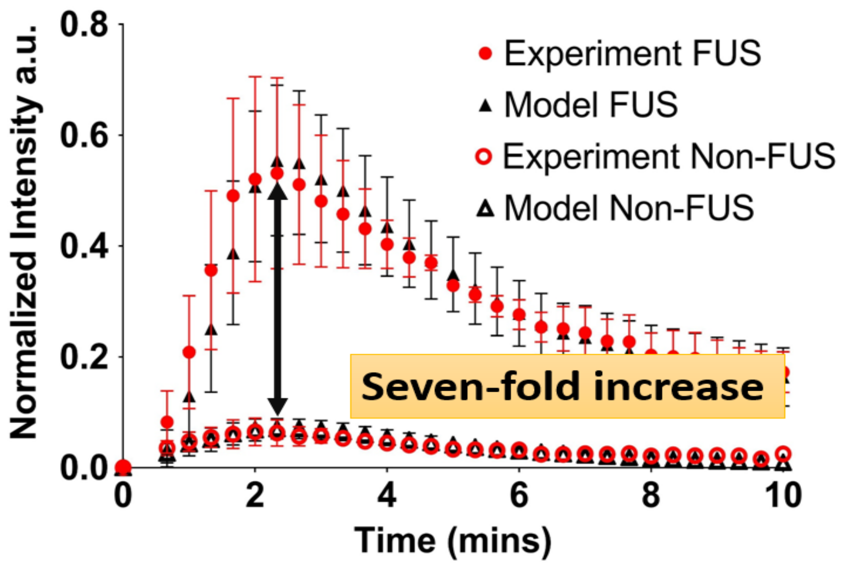
PARAMETER FIT

To obtain the drug transport parameters: Single vessel geometry is used to fit model prediction to the experimentally determined interstitial drug pharmacokinetics using a numerical optimization procedure

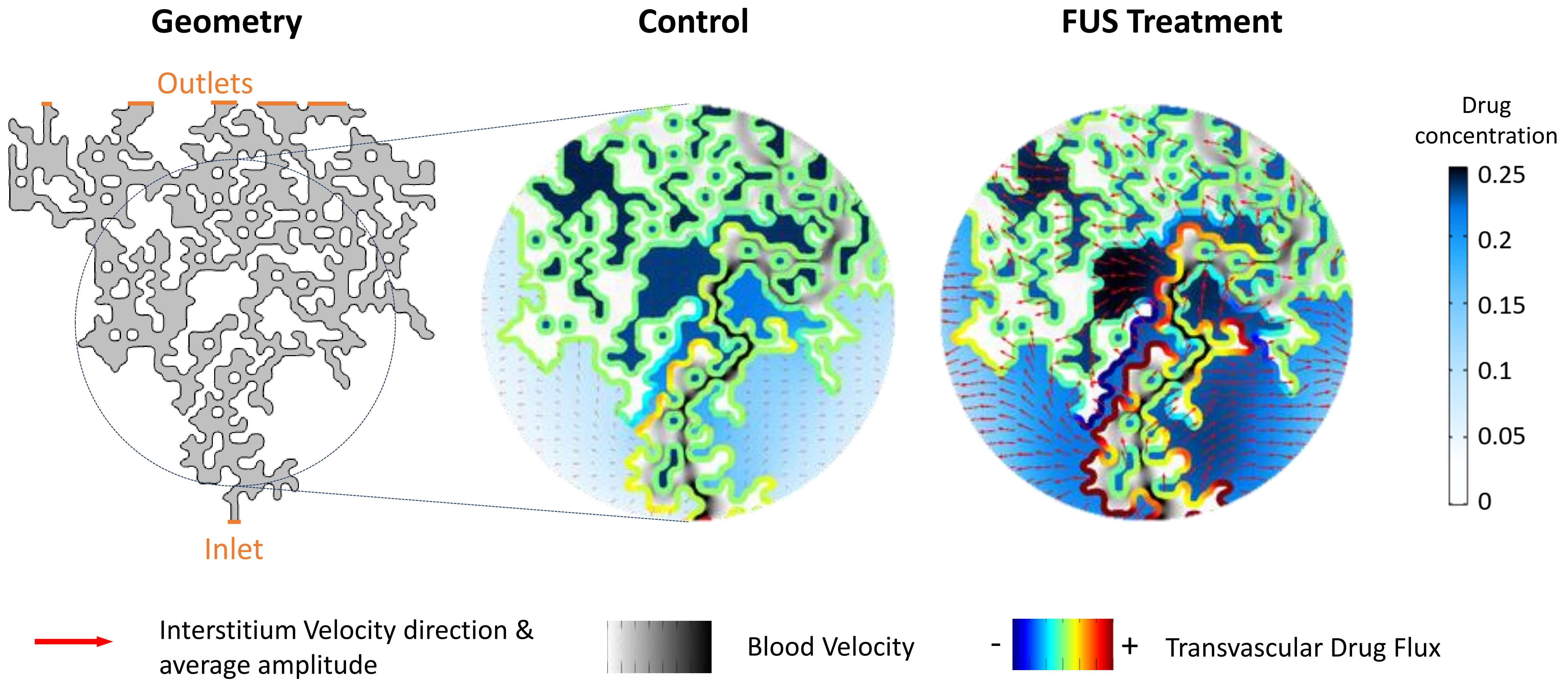
D_v	Dox Diffusion Coefficient in vessel
D_i	Dox Diffusion Coefficient in tumor interstitial space
K	Tissue Hydraulic Conductivity
ε_v	Vessel wall porosity
ε_i	Interstitial porosity
V	Rate of transmembrane transport
V_b	Rate of drug binds to cellular DNA







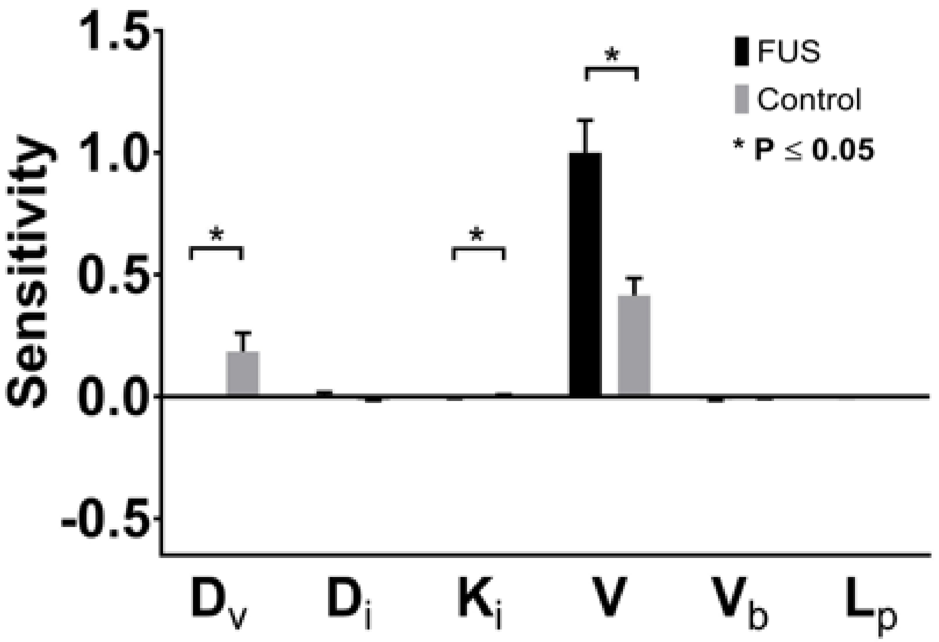
DRUG DISTRIBUTION

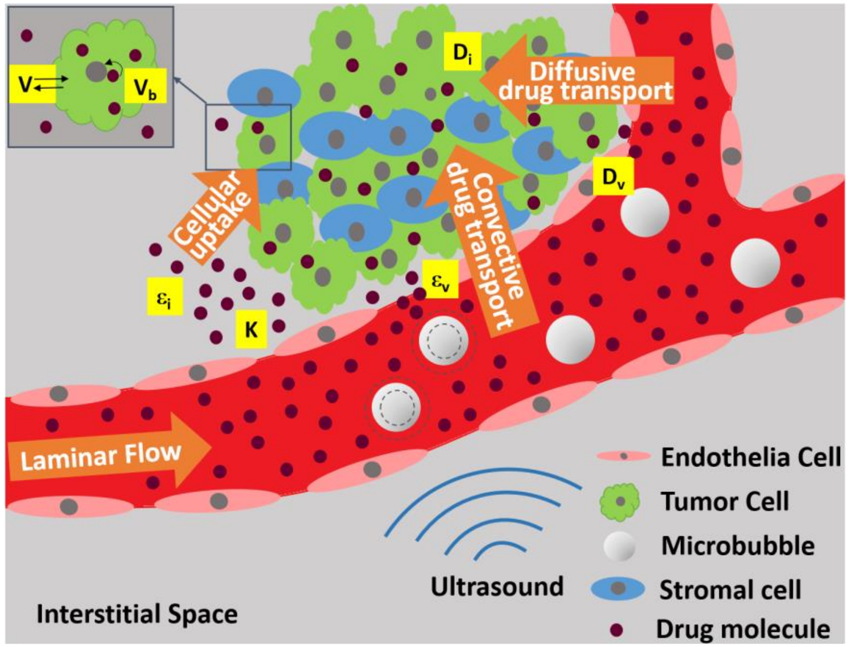


SENSITIVITY ANALYSIS

To study the relative importance of the different transport parameters, we conduct sensitivity analysis using parametric sweep.

- Vary parameter value (P_i) by ±25%
- Sensitivity = $\frac{\Delta c}{\Delta P_i}$, $c =$ drug concentration





CONCLUSION

- FUS increases BBB permeability and induces convective transport, leading to significant increase in drug penetration.
- Sensitivity analysis shows that FUS is able to overcome one of the major obstacles to the transport of relatively small therapeutics in brain tumors.
- Mathematical modeling allow us to further refine therapeutic interventions and identify FUS-nanomedicine combinations for optimal intratumoral penetration and uptake.
- This work forms the basis for the rational design of the anticipated clinical trials (Phase III) of FUS-mediated BBB disruption technology in primary brain tumors

Thank you!