Carboplatin Pharmacokinetic and Pharmacodynamic Mathematical Model for FUS-BBB Disruption in the Brain Tumour Microenvironment

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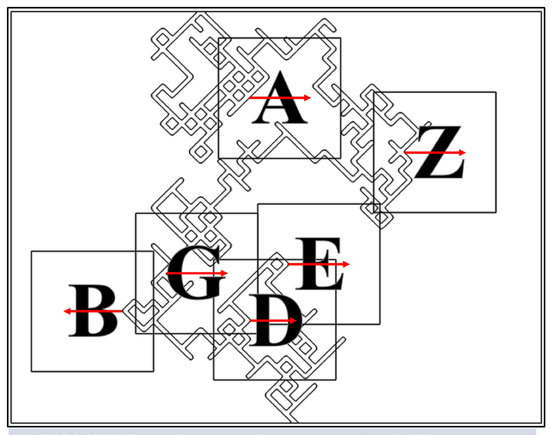
INTRODUCTION

- Glioblastoma Multiforme (GBM) is a highly invasive form of glioma with extremely poor prognosis and a median survival time of 14.6 months.
- The Blood-Brain Barrier (BBB) is a major obstacle to large chemotherapeutics extravasating into the brain tumour microenvironment (TME).
- Focussed Ultrasound (FUS) offers a non-invasive and transient mechanism to disrupt the BBB, increasing drug delivery to the TME.
- Previous studies [1] using Doxorubicin (543.52 g/mol) and T-DM1 (148.5 kg/mol) have shown the efficacy of this method [1]. Phase III Clinical Trials for FUS-BBB Disruption using **Carboplatin** (371.249 g/mol) are in preparation.
- Pharmacokinetic (PK) modelling was needed **to develop a mechanistic understanding of drug transport** and **evaluate therapeutic efficacy.**

COMPUTATION

- COMSOL v5.3a used as computational engine & MATLAB 2018a used for data analyses.
- Boundary conditions introduced based on experimentally-verified previous work by *Arvanitis et al* [1].



[ABOVE] Random-walk–generated 2D vasculature geometry. ABGDEZ data set cut-lines (red arrows) are shown within 100μm x 100μm square subdomains centred on the midpoints.

FLUID MECHANICAL & DRUG TRANSPORT PHYSICS

- Coupled physical equations through the vasculature (pipe model) and interstitium (porous media flow).
- Carboplatin transport parameters used to set boundary conditions within model.

Blood Vessel

Laminar flow: $\nabla p = \nabla[\mu(\nabla \boldsymbol{u} + (\nabla \boldsymbol{u})^T)]$, $\nabla \cdot \boldsymbol{u} = 0$

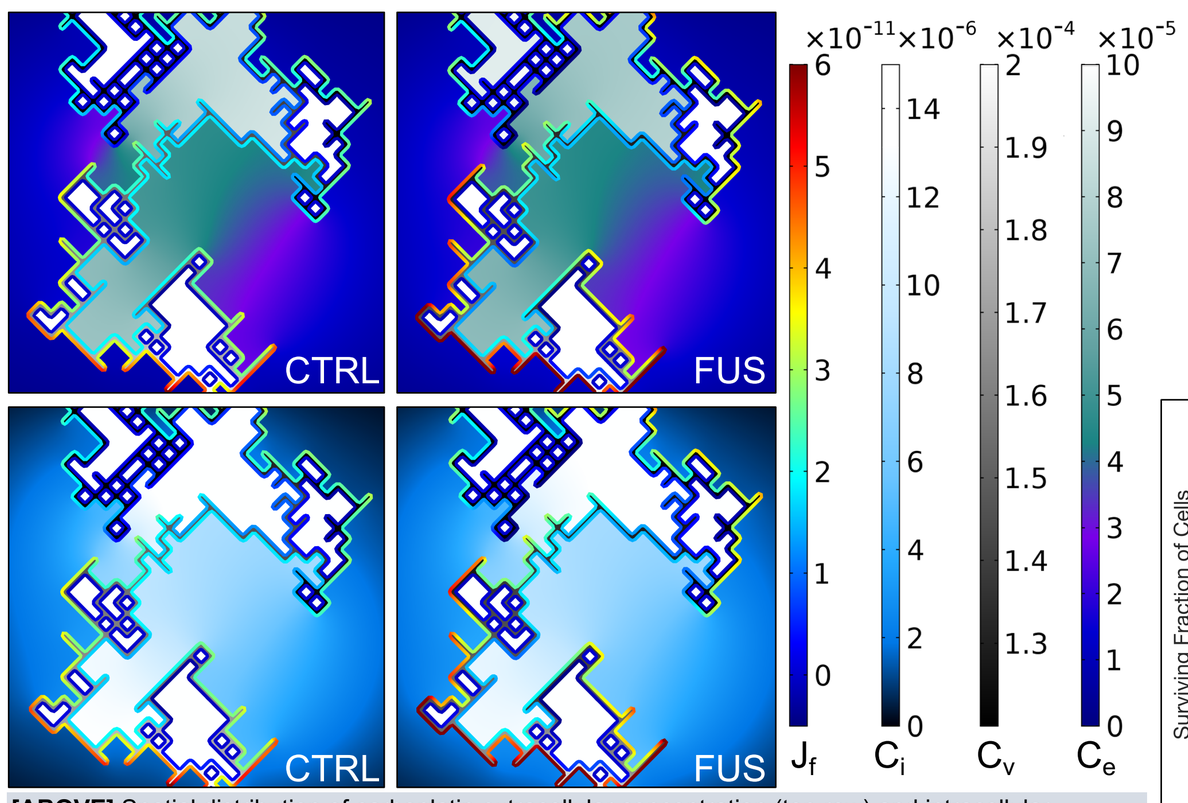
Drug transport: $\frac{\partial c_V}{\partial t} = D_b \nabla^2 c_V - \boldsymbol{u} \cdot \nabla c_V$

Interstitial Space

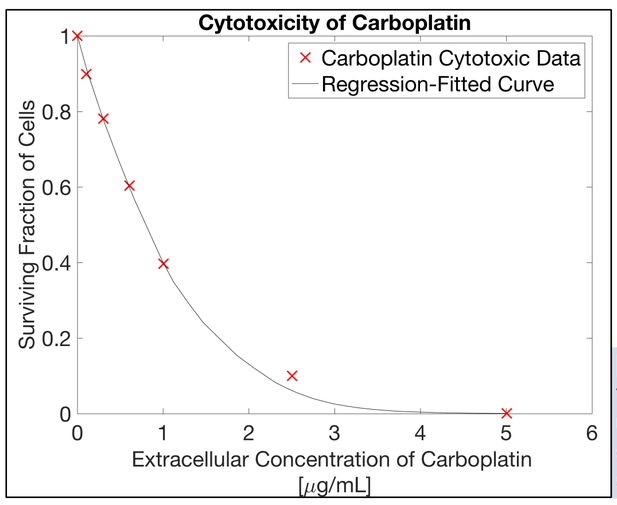
Flow in porous media: $\frac{\mu}{k}\boldsymbol{u} + \nabla \mathrm{p} - \frac{\mu}{\varepsilon_i}\nabla^2 \boldsymbol{u} = 0$

Drug transport: $\frac{\partial c_e}{\partial t} = D_i \nabla^2 c_e - \boldsymbol{u} \cdot \nabla c_e + R$

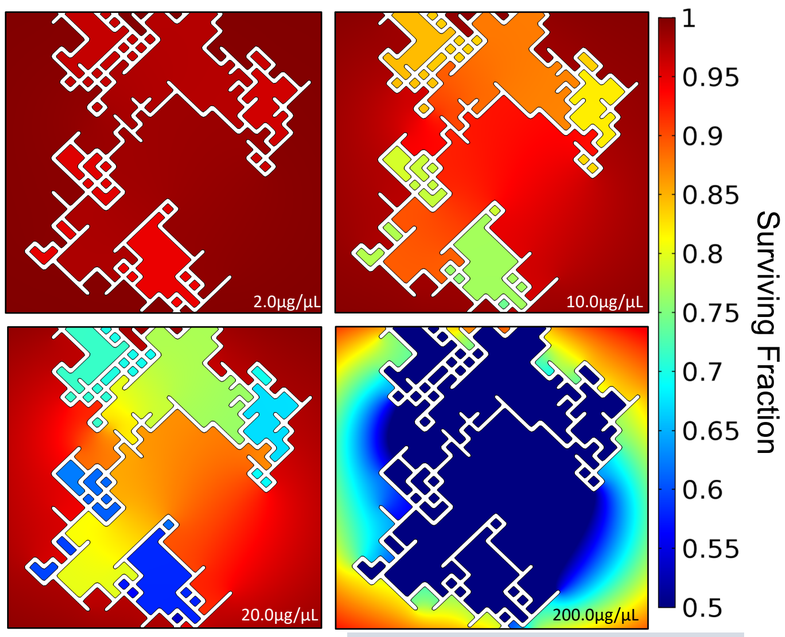
[ABOVE] Fluid-mechanical and drug transport model equations.



[ABOVE] Spatial distribution of carboplatin extracellular concentration (top row) and intracellular concentration (bottom row) within the tumour interstitium; blood concentration within the BBB; and molar flux across the vessel walls, under control conditions and after FUS-BBB disruption at t = 1800s.



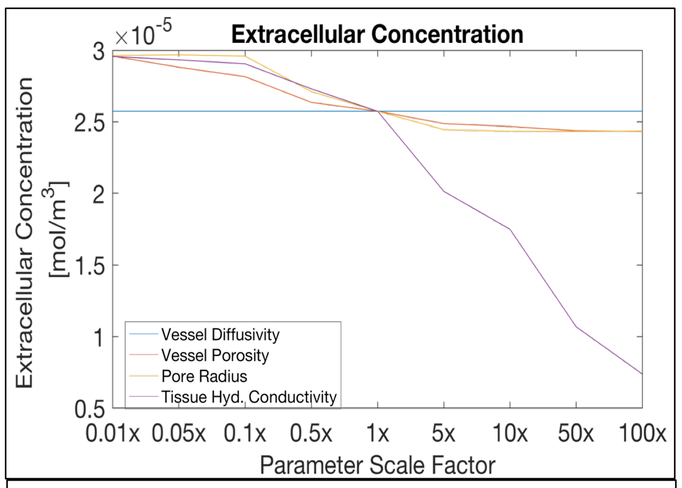
[LEFT] Cytotoxicity function; the surviving cell fraction under various extracellular carboplatin concentrations is shown [2].



[ABOVE] Spatial distribution of carboplatin cytotoxicity within the tumour interstitium in response to various IV doses.

EXPERIMENTAL PROCEDURE

- Two phase computational study: 1) Stationary initialisation of TME physics with velocity and pressure fields. 2) Time-dependent study for drug transport, PK (cellular uptake/release) and cytotoxicity concurrent with carboplatin IV up to t = 1800s.
- Carboplatin CTRL parameters obtained from experimental data (literature). Data for FUS-BBB disruption conditions obtained via ratios for Doxorubicin parameters [1].
- Continuous IV infusion of carboplatin at 2.0 μg/μL at 0.33 μL/min for 30 minutes in accordance with F98 cell line dosages [2]. Molar inlet (d =7.34 μm) flux of 2.20 mol/m²s.



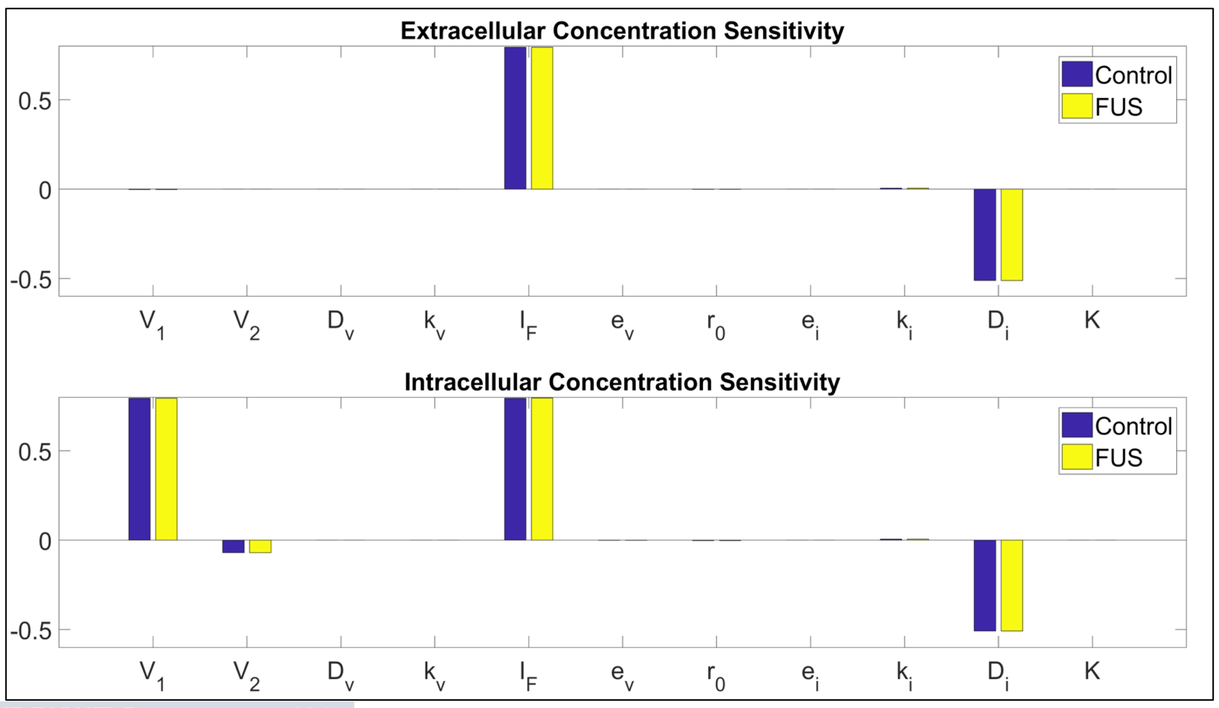
[ABOVE] Order of magnitude study for parameters sensitive to FUS-BBB disruption. Data taken from ABGDEZ medians at t = 1800s.

RESULTS

- Parametric sensitivity analyses suggest that FUS-BBB disruption will **not critically** improve carboplatin extravasation, cellular uptake or cytotoxicity within the brain TME.
- Carboplatin IV dosage is the most critical parameter for increasing cytoxtocity. Invariance to vascular diffusivity, permeability, and porosity is clearly visible.
- Order of Magnitude analyses demonstrate decreasing trend for cellular uptake and cytotoxicity with increased FUS-BBB disruption.

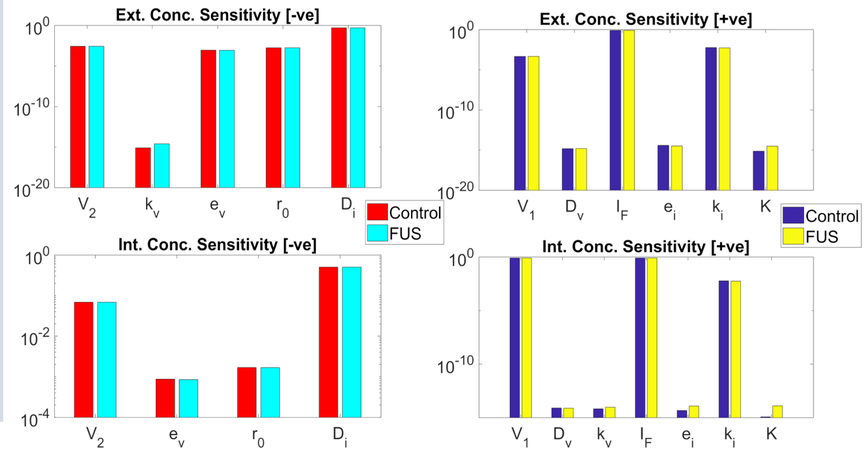
DISCUSSION

- Carboplatin's MW is below the 400 Da (g/mol) threshold [3] for successful BBB extravasation, limiting the impact of FUS-BBB disruption on extravasation.
- Results suggest that **larger chemotherapeutics** molecules such as Doxorubicin and T-DM1 would **more successfully demonstrate the clinical efficacy of FUS-BBB disruption.**
- Laboratory experimentation using murine models to test validity of computational results to follow.
- It is suggested that vascular normalisation using VEGF-2 may prove an effective method for improving carboplatin uptake in the brain TME.



[ABOVE RIGHT] Parameter sensitivity (± 25%) analysis conducted for ABGDEZ data. Sensitivity data normalised by the maximum c_i, c_e value in each ABGDEZ data set and the standard (± 0%) parameter value. Median values taken for each parameter at t = 1800s.

[RIGHT] Logarithmic plots for parameter sensitivity magnitude (normalised) grouped by positive and negative results for carboplatin extracellular and intracellular concentration within the interstitium.



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[1] Arvanitis, Costas D., et al. "Mechanisms of enhanced drug delivery in brain metastases with focused ultrasound-induced blood–tumor barrier disruption." Proceedings of the National Academy of Sciences 115.37 (2018): E8717-E8726.

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[3] Pardridge, William M. "Drug transport across the blood–brain barrier." Journal of cerebral blood flow & metabolism 32.11 (2012): 1959-1972.

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