Modeling Drug Delivery to Gliomas

Clayton Pierce[1,3], Xyden Procaccianti[1,2], Guadalupe Garcia[4], Yeqing Ni[4], Cynthia Hajal[4]

[1]Northeastern University Young Scholars Program, [2]Bishop Feehan High School, [3]Gloucester High School,
[4]Northeastern University Department of Mechanical and Industrial Engineering

Northeastern University College of Engineering

Northeastern University Michael B. Silevitch and Claire J. Duggan Center for STEM Education

Abstract

Gliomas are a type of brain tumor; a subset of gliomas called Glioblastoma (GBM) is a more severe type. The Blood Brain Barrier (BBB) restricts access of foreign species entering the human brain. This poses a challenge when trying to treat gliomas, as the drugs used to treat the tumors have trouble permeating through the BBB. This research aims to understand how that stiffness affects tumor growth and drug response. There are two components to the research, one which involves the physical experimentation, while the latter component consists of simulating the expected results of the experiment via COMSOL. The physical experiments consist of making microfluidic devices and seeding them with tumor cells in hydrogels of varying stiffness. While differences were not statistically significant, we did observe a trend suggesting that cells in softer hydrogels exhibited greater growth as a responsive to chemotherapy compared to those in stiffer environments. Prior to this physical experiment, the microvascular network was simulated in COMSOL using different physics systems incorporated in the software to account for permeability of cell tissue and vascular fluid velocity. In the simulation the velocity of the blood was in the physiological range, that result being 400-1000 μm/s. The concentration of the medicine in the tumor mass was higher approaching the edge of the mass and was lower when approaching the center of the mass.

Background

Glioblastoma (GMB) is the most malignant type of glioma. Patients with GBM are initially treated via resection of the tumor, followed by radiation and chemotherapy. Due to GBMs being present in the brain, delivery of treatment is limited by the blood brain barrier (BBB) due to its tight junctions and active efflux transporters. Restricted transport of therapy can lead to limited therapy efficacy and the development of therapy resistance.

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LAB
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Simulation Problem Definition

Used COMSOL to simulate the fluid dynamics of Gemcitabine (chemotherapy drug) in microvascular vessels and its diffusion into tumor spheroids

- Coupled Creeping Flow (SPF) physics and Transport of Diluted species (TDS) physics to simulate how concentration (TDS) is affected by velocity (SPF)
  - Domain 2 is the domain that the physics are coupled in

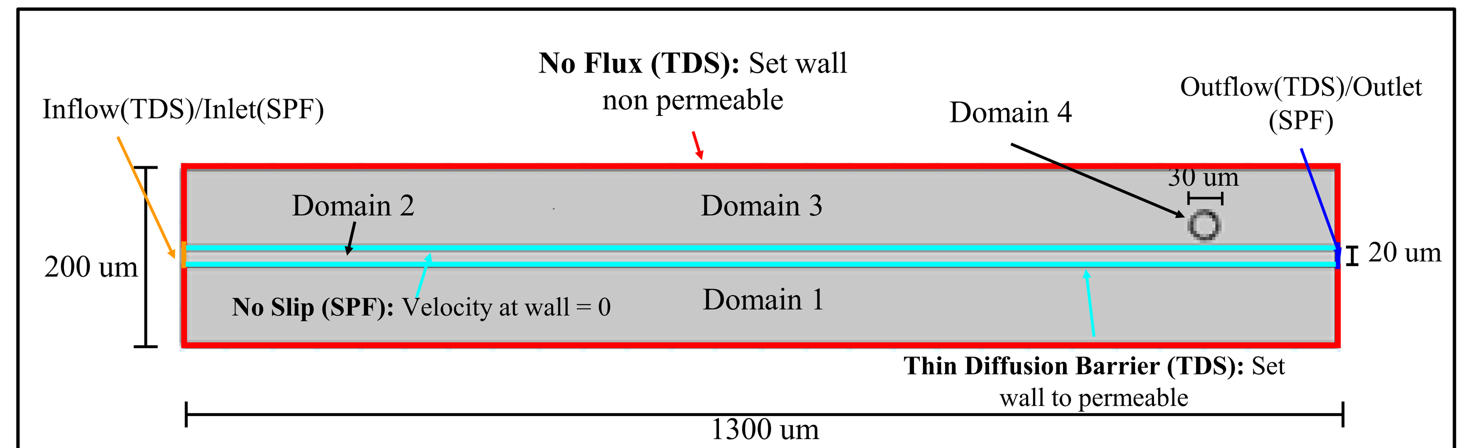

Figure 1: Schematic of domains and boundary conditions on the model geometry

TDS Domain / Boundary Conditions:

- **Fluid 1:** Sets domains 1 / 3 to have diffusion coefficient of 1.63*10^-10 [m²/s]
- **Initial value:** Set concentration (C) = 0
- **Fluid 2:** Sets diffusion coefficient in domain 4 to written if statement: if(R_tumor > r_transition, k_outer, k_inner)
- **Reaction:** Sets reaction rate = to $1*10^{-4}$ * C [mol/m³*s]

SPF Domain / Boundary Conditions (Refer to figure for those not listed)

- **Fluid properties:** Fluid density and viscosity 1000[kg/m³] and $1*10^{-3}$[Pa*s] respectively
- **Initial Value:** sets pressure in Domain 2 equal to zero

Lab Experimental Methods

❖ Microfluidic devices made using standard protocols.1

I. Tumor cells are derived from patients
II. Tumor spheroids made by plating 2000 cells/well of a 96-well plate (by mentor) and grown for 4-7 days.
III. Spheroids seeded in devices with different hydrogel stiffnesses (by mentor)
IV. Devices treated with TMZ or DMSO on Day 1; drug replenished daily
V. Imaged over 8 days using brightfield microscopy (by mentor)

❖ Spheroid Quantification: Analyzed using ImageJ for area, optical density, and diameter (by mentor)

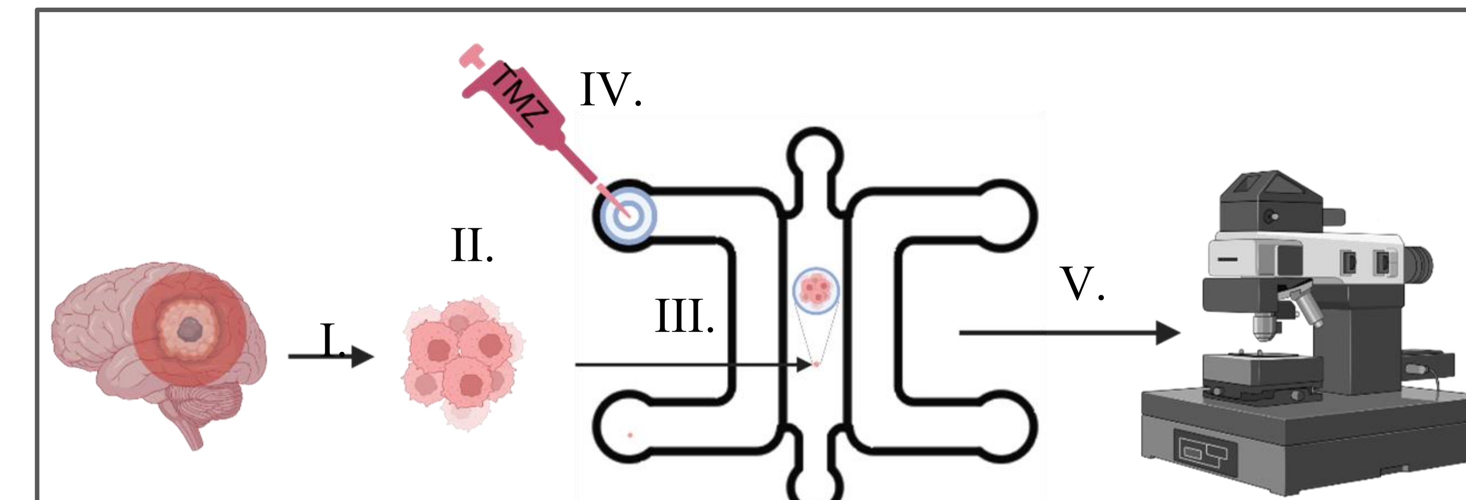

Figure 2: Schematic of lab experimental procedure

COMSOL Results

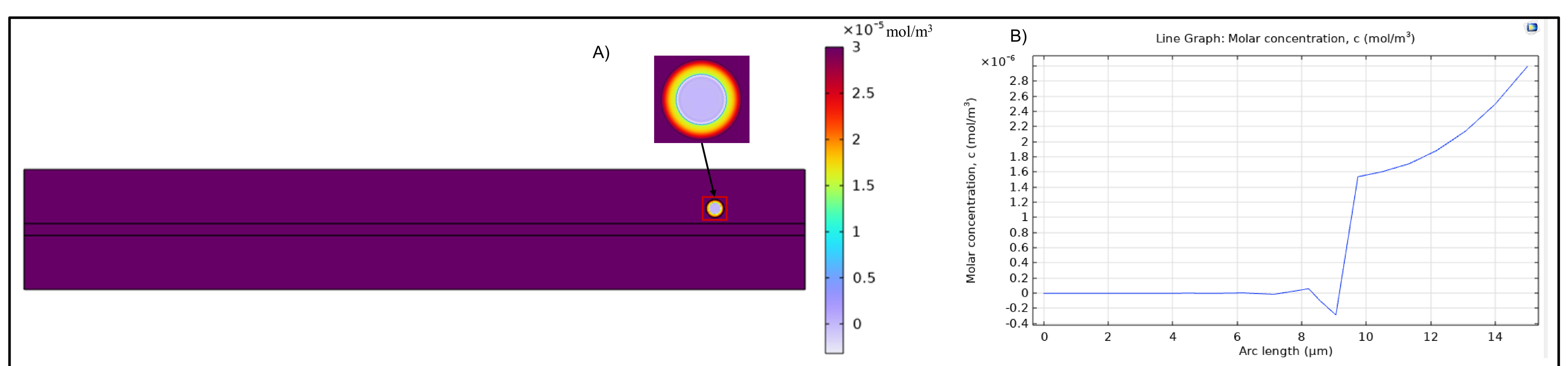

Figure 3: COMSOL time dependant study of drug concentration (A) Concentration field of spheroid (B) Graph of concentration for unit arclength

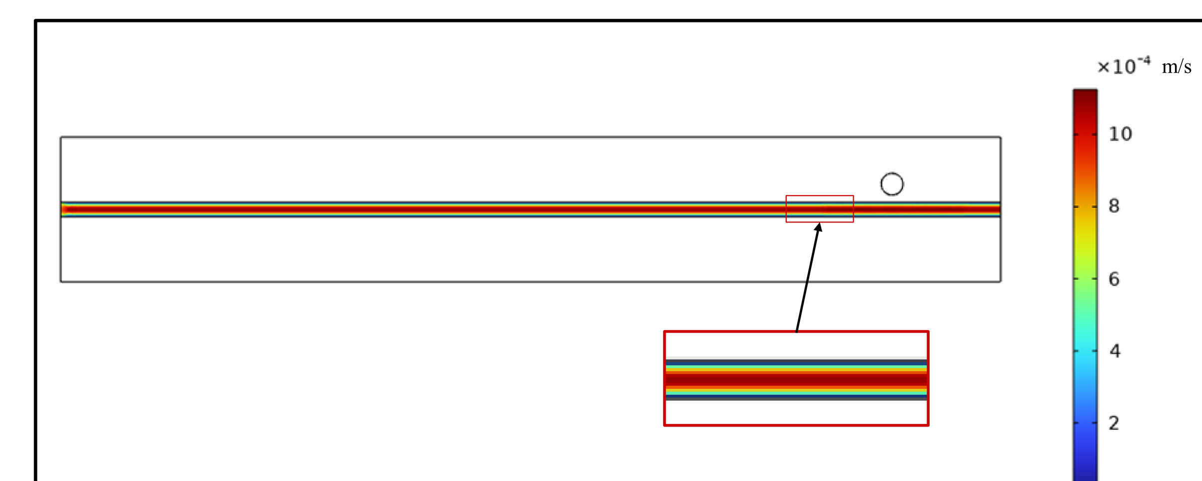
Figure 4: Schematic of velocity field inside the vessel

- Concentration of Gemcitabine inside spheroid decreases when approaching the center of the mass
- Blood velocity is in the physiological range, the result being $10*10^{-4}$ m/s

Experimental Results

- Tumors in stiffer conditions generally less responsive; those that were treated were less influenced by the drug than those in soft tissue, whereas those who were not treated grew less than those in the soft tissue

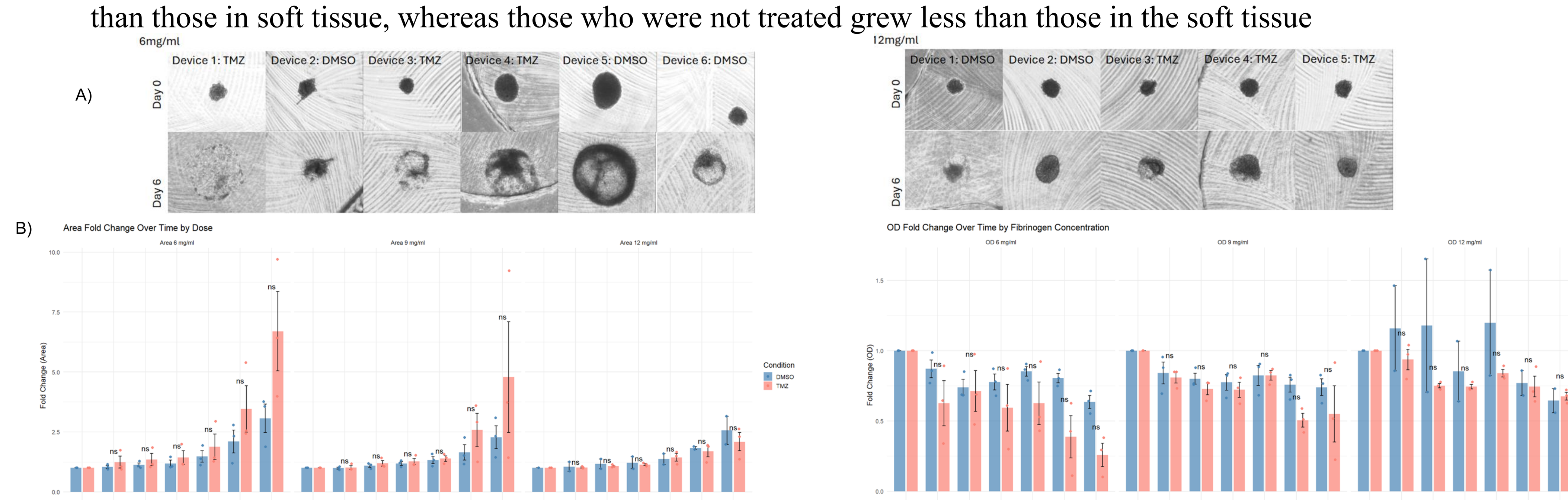

Figure 5: Tumor response to treatment or lack thereof based on hydrogel stiffness; (A): Imaging of tumors over time; (B): Measured changes based hydrogel stiffness & TMZ dosage,

Conclusion and Future Steps

- As expected COMSOL results are physiologically relevant meaning model behaves as it should in vitro
- TMZ has an effect on cell growth when comparing different hydrogel stiffness levels
  - As expected the tumor spheroid behave differently in different stiffness conditions and in stiff conditions tumors respond less
- In the future we would like to make the lab and COMSOL portions more related by growing vasculure in devices and incorporating more complex vasculature as well as tumor shrinking through solid mechanics to the COMSOL simulation

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