Numerical methods and CFD techniques for drug application in tumor treatment

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Introduction

- Motivation
- Schematic view

Mathematical model

- Equations
- Discretization
- Results

Summary

Motivation

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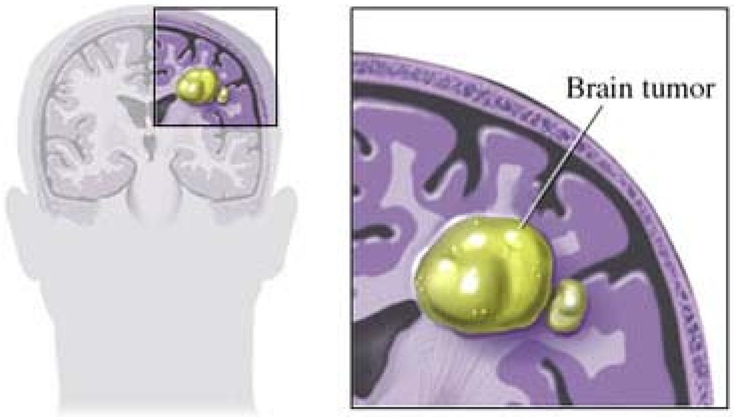
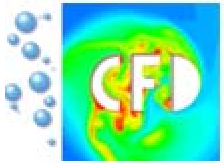
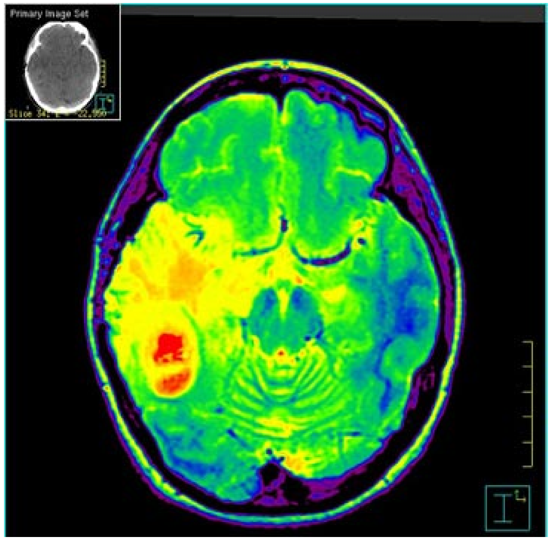
- Each year a lot of people in the world are diagnosed with a primary or metastatic tumor
- There are over 120 different types of brain tumors



- application to drug delivery in brain tumors
- solution of derived partial differential equations (PDE's)
- use modern computational fluid dynamics (CFD) tools (Featflow)



There are two principal physiological barriers:



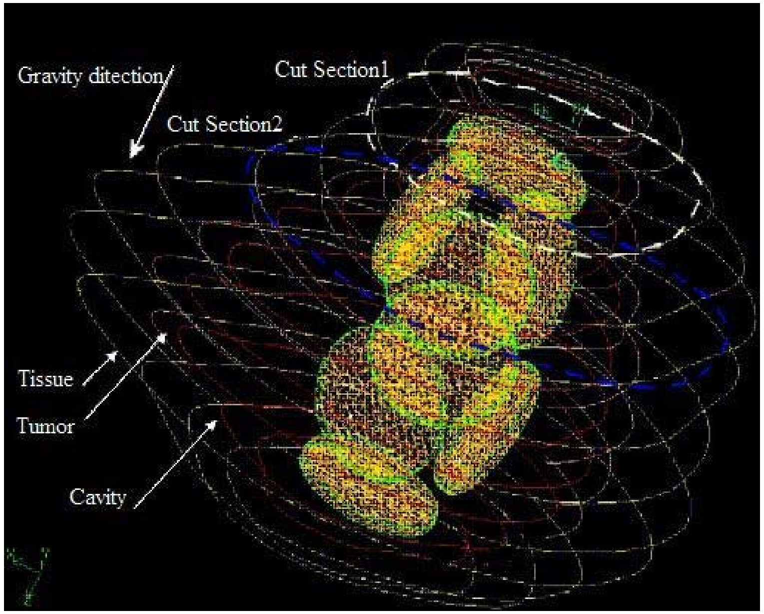
the blood-brain barrier (BBB)

- The BBB hinders the delivery of many potentially important diagnostic and therapeutic agents to the brain

the interstitial fluid pressure

- The interstitial fluid pressure is present within the tumor and reduces the driving force for fluid and solute to be extravasated into the brain tissues

Schematic view



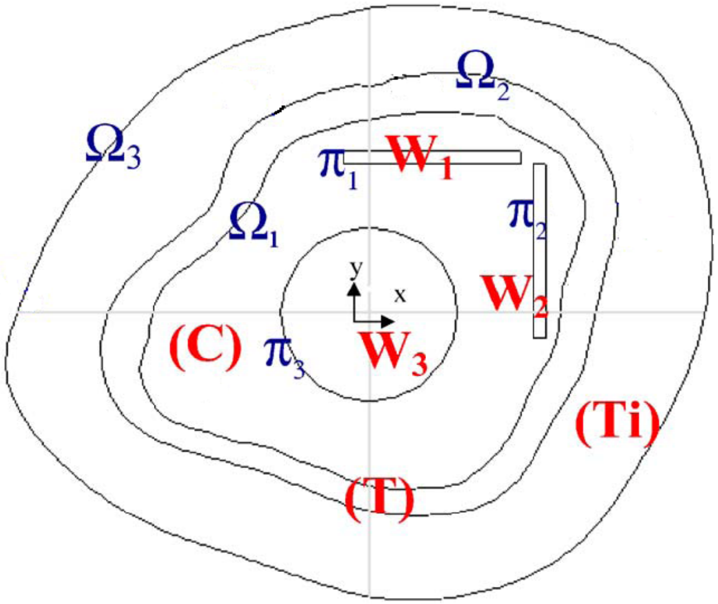


Fig.1: $W_{1,2,3}$ - wafers 1-3, (C) - the resection cavity after the surgery, (T) - the remnant tumor that are not removed in the surgery,(Ti) - the normal tissues surrounding the tumor, Ω_1 - boundary between cavity and tumor, Ω_2 - boundary between tumor and tissues, Ω_3 - external boundary, $\pi_{1,2,3}$ - boundaries cavity and wafers

Governing equations

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The mass conservation equation

$$\nabla\cdot\vec{V} = \begin{cases} F_v - F_l + q & \text{in tumor (T) and normal tissues (Ti)} \\ 0 & \text{in cavity (C) and wafers } (W_{1,2,3}) \end{cases}$$

The momentum equation

$$\frac{\partial\rho\vec{V}}{\partial t} + \nabla\cdot(\rho\vec{V}\vec{V}) = \rho\vec{g} - \nabla P_i + [\nabla\cdot\mathbf{\Gamma}] + \mathbf{\Theta}\mu\vec{V} + \frac{\rho}{2}\mathbf{\Psi}|\vec{V}|\vec{V}$$

The drug concentration

$$\frac{\partial C}{\partial t} + \vec{V}\cdot\nabla C = D\triangle C - R + F_s - F_{ls}$$

(T.Lee, W. Tan, C.-H. Wang, 2004)

Formulas

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$$F_v = \frac{K_v S}{V}(P_v - P_i - \sigma_T(\pi_v - \pi_i))$$ Starlings law

$$F_s = \begin{cases} S_0 e^{-t/\tau} & \text{in wafers } (W_{1,2,3}) \\ F_v(1-\sigma)C_v + \frac{\pm S}{V}(C_v - C)\cdot\frac{Pe_v}{e^{Pe_v}-1} & \text{in tumor (T) and tissues (Ti)} \\ 0 & \text{in cavity (C)} \end{cases}$$

$$R = \begin{cases} k_c C & \text{in cavity (C)} \\ \frac{V_{max} C}{K_m + C} + k_e C & \text{in tumor (T) and normal tissues (Ti)} \\ 0 & \text{elsewhere} \end{cases}$$

$$Pe_v = \frac{F_v(1-\sigma)}{\pm S/V}$$ Peclet number

$$\pi_{i,v} = R \cdot T \cdot C_{i,v}$$ Van Hoff 's law

Abstract view of the dimensionless equations

$$
\begin{cases}
\nabla\cdot\vec{V} - \tilde{k}\cdot P = 0 \\
\frac{\partial\vec{V}}{\partial t} + \nabla\cdot(\vec{V}\vec{V}) = \vec{g} - \nabla P_i + [\nabla\cdot\mathbf{\Gamma}] + \mathbf{\Theta}\nu\vec{V} + \frac{1}{2}\mathbf{\Psi}|\vec{V}|\vec{V} \\
\tilde{q}\cdot\dfrac{\partial C}{\partial T} + \tilde{d}\vec{V}\cdot\nabla C = \triangle C - \tilde{f}\cdot C
\end{cases}
\quad \Rightarrow
$$

Discretized equations

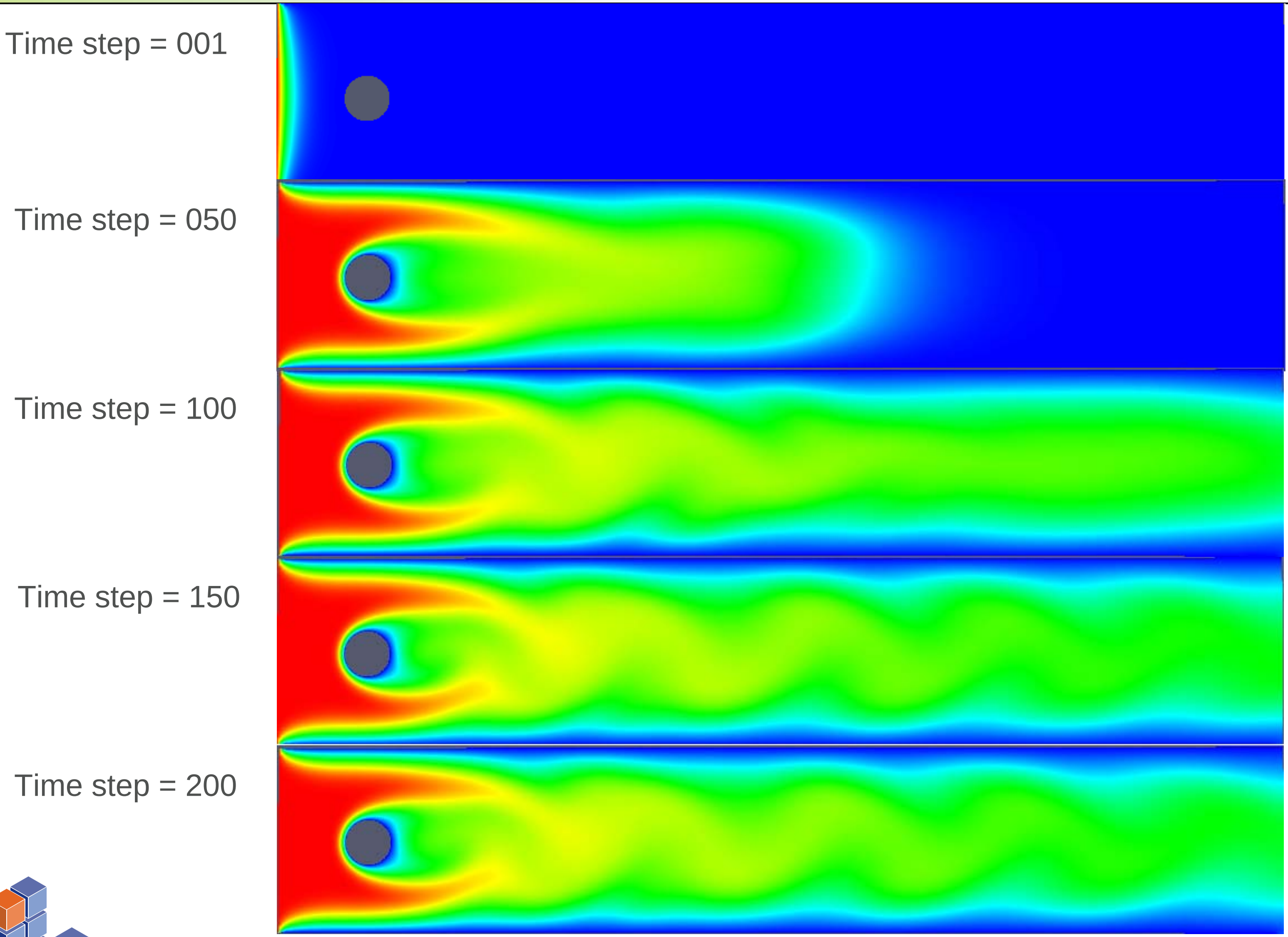
$$
\Rightarrow \begin{bmatrix} A & B \\ B^T & -k\cdot I \end{bmatrix} \begin{bmatrix} \tilde{V} \\ P \end{bmatrix} = \begin{bmatrix} f \\ g \end{bmatrix}
$$

, where $\tilde{V} = (V, C)$

Discretization

	Velocity/Pressure	Concentration
element	$\tilde{Q}_1/Q_0$	Q_1
solver	Multigrid	Umfpack
grid	unstuctured	unstuctured

Results


Time step = 001
Time step = 050
Time step = 100
Time step = 150
Time step = 200

Improved model

Non-dimensionalized equation for tumor and normal tissues

$$
\begin{cases}
\frac{\partial V_x^\star}{\partial x^\star} + \frac{\partial V_y^\star}{\partial y^\star} = a \cdot P^\star + b \cdot C^\star + \frac{q \cdot L_0}{V_0} \\
\frac{L_0}{t_0 V_0} \frac{\partial V_x^\star}{\partial t^\star} + \frac{\partial}{\partial x^\star}\left(V_x^\star V_x^\star\right) + \frac{\partial}{\partial y^\star}\left(V_x^\star V_y^\star\right) = -\frac{P_\infty - P_e}{\rho V_0^2}\frac{\partial P^\star}{\partial x^\star} + \frac{\mu}{\rho}\frac{L_0}{V_0 k} V_x^\star + \frac{0.55}{k^{0.5}}\frac{V_x^\star}{V_0 k}\left|\vec{V}^\star\right| \\
\frac{L_0}{t_0 V_0} \frac{\partial V_y^\star}{\partial t^\star} + \frac{\partial}{\partial x^\star}\left(V_y^\star V_x^\star\right) + \frac{\partial}{\partial y^\star}\left(V_y^\star V_y^\star\right) = -\frac{P_\infty - P_e}{\rho V_0^2}\frac{\partial P^\star}{\partial y^\star} + \frac{\mu}{\rho}\frac{L_0}{V_0 k} V_y^\star + \frac{0.55}{k^{0.5}}\frac{V_y^\star}{V_0 k}\left|\vec{V}^\star\right| \\
\frac{L_0^2}{D t_0}\frac{\partial C^\star}{\partial t^\star} + Pe\left(V_x^\star \frac{\partial C^\star}{\partial x^\star} + V_y^\star \frac{\partial C^\star}{\partial y^\star}\right) = \left(\frac{\partial^2 C^\star}{\partial x^2} + \frac{\partial^2 C^\star}{\partial y^2}\right) - \frac{L_0^2 k_c}{D} C^\star
\end{cases}
\Rightarrow
$$

Discretization by FEM

$$
\Rightarrow
\begin{bmatrix} A & B & 0 \\ B^T & -k \cdot I & -\mu \cdot I \\ 0 & 0 & A \end{bmatrix}
\begin{bmatrix} V \\ P \\ C \end{bmatrix}
=
\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}
$$

Discretization

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	Velocity/Pressure/Concentration
element	$\tilde{Q}_1/Q_0/Q_1$
solver	Multigrid
grid	unstuctured

Summary

- closed system of PDE's for the velocity, pressure and drug concentration
- saddle-point problem requires techniques for incompressible flow problems
- the fully coupled problem
- numerics for CFD

The end

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Thank you for your attention!!!

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Basic notation

μ- interstitial fluid viscosity	R- reaction in the cavity
ρ- interstitial fluid density	Pe_v- transcapillar Peclet number
θ- matrix for viscous term	F_s- drug gain from the blood capillaries
Γ- stress tensor	$F_l s$- drug loss to the lymphatic vessels
Ψ- matrix for inertial term	C- drug concentration
F_l- net gain fluid	$N_{1,2,3}$- outward normal vectors of $\Omega_{1,2,3}$
F_v- net fluid loss	K_v- hydraulic conductivity
P_v- interstitial pressure	S/V- exchange area of blood vessels per
$\vec{V}$-vector of velocity	unit volume of tissues
P_i- vascular pressure	σ- osmotic reflection coefficient
π_v- osmotic pressure of plasma	π_i- osmotic pressure of interstitial pressure