Biophysics and Cancer ~ Improving Detection and Treatment

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Breast Cancer is the Most Commonly Diagnosed Cancer in Women

- More than 200,000 new cases per year\(^1\)
- 1 in 8 chance of developing breast cancer\(^2\)
- 40,500 women die each year\(^1\)
- 1 in 33 chance of dying from breast cancer\(^3\)
- Nearly 1 in 3 cancers diagnosed\(^1\)
- 2% per year decrease in the mortality rate since 1990\(^4\)

Brain Tumors are Particularly Difficult to Treat

- American Cancer Society estimates that 20,500 new cases of brain and nervous system tumors will be diagnosed this year
- 359,000 Americans have already been diagnosed with brain and nervous system tumors
- Five year survival rates are very low for glioblastomas and astrocytomas:
  - Glioblastoma – 2%
  - Astrocytoma – 30%
  - Meningioma – 70%
Brain Tumor Types - Meningioma

- Arise from cells of the Meninges
- Meninges: the system of membranes that envelope the central nervous system
- Appear on MRI as a discrete homogenous mass
- Easier to treat due to location and demarcation from other brain tissue
Brain Tumor Types - Glioma

- Arise from Glial Cells
- Glial Cells: non-neuronal cells that provide support and nutrition, maintain homeostasis and participate in signal transmission
- Appear on MRI as a heterogeneous mass
Cancer Induces Changes in the Physiology of the Tissue

- Abnormal vasculature
  - Increased vessel density
  - Abnormal branching
  - Defective architecture
  - Hyperpermeability
    - Increased fluid and solute transport
    - High extravascular pressure
- Increased stiffness
- Increased metabolic generation

Figure of capillary mesh adapted from:
Current Treatment Options are Effective for Many Types of Cancers

• Surgery

• Chemotherapy
  – Systemic therapy
  – Damages healthy tissue
  – Significant side effects: fatigue, hair loss, mouth sores, nausea, anemia, low platelet and white blood cell counts, infertility, osteoporosis

• Radiation
  – Side effects: swelling, radiation burn, fatigue

• Hyperthermia

• Hormone therapy
  – Limited application
  – Side effects: blood clots, osteoporosis, fatigue, muscle and joint pain, mood swings

Novel Treatment Options - Application of Nanoparticles to Therapy

- **Nanoparticles**
  - Bind chemotherapeutic agents, radioisotopes, or radiosensitizing agents
  - Used in hyperthermia therapy
  - Targeting
    - Passive targeting: changes in the vasculature of cancerous tissue results in increased accumulation
    - Active targeting: bind targeting agents to the nanoparticle
    - Provide opportunity for prophylactic cancer treatments

Nanoparticles Utilize Passive and Active Targeting to Detect Tumors

- Nanoparticles as contrast agents
  - Particles with one or more dimensions of the order 100 nm or less
  - Bind contrast agents to nanoparticles
  - Design with desired imaging properties: Magnetic for MRI, photoemitters for fluorescence microscopy

Figure adapted from:
Solute Size is Important to Cancer Detection and Treatment

- Important factors
  - Passive targeting
  - Active targeting
- Other applications
  - Drug delivery
  - Nutrient delivery

Common drugs ≤ normal capillary pores

Normal capillary pores < nanoparticles

Nanoparticles ≤ tumor capillary pores

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Human Injury Research & Regenerative Technologies
Porous Media Models Link Numerical Modeling to Physiological Processes
Implementing the Model Requires an Idealization of the Capillary Bed
Unit Cell Division of Tissue into 3 Regions

- Extravascular Space
- Intravascular Space
- Vessel Wall
- Extravascular Flux
- Plasma Skimming Layer
- Red Blood Cell
- Cell
- Interstitial Space

Tissue
Fluid Mechanics Model

Solid mechanics → Fluid Mechanics

Solute transport → Heat transfer

Magnetic field → Nanoparticle distribution → Drug delivery → Nutrient delivery

Particle aggregation → Nanoparticle drug carriers

Binding/Uptake → Hyperthermia therapy

Metabolic generation
Fluid Mechanics Model: Intravascular Flow Characteristics of Blood

- Blood
  - inhomogeneous
    - Plasma + solutes
  - Plasma
    - Virtually Newtonian fluid
  - Red blood cells
    - Hematocrit 40 – 45%
    - Comparable in size to microvessels
    - Tend to flow single file
Intravascular Flow – Governing Equations

- Blood
  - inhomogeneous
    - Plasma + solutes
  - Plasma
    - Virtually Newtonian fluid
- Continuity
  \[
  \frac{\partial \rho^\alpha}{\partial t} + \nabla \cdot (\rho^\alpha \mathbf{u}^\alpha) = \dot{q}^\alpha
  \]
- Balance of Linear Momentum
  \[
  \rho^\alpha \frac{d\mathbf{u}^\alpha}{dt} = \nabla \cdot \mathbf{T}^\alpha + \rho^\alpha \mathbf{b}^\alpha + \Pi^\alpha
  \]

• Axial velocity
  
  **Poiseuille**
  
  \[ u_z = \frac{R_o^2}{4\mu} \left( -\frac{dP_c}{dz} \right) \left( 1 - \frac{r^2}{R_o^2} \right) \]

  **Axial Train**
  
  \[ u_z = \begin{cases} 
  \frac{R_o^2}{4\mu} \left( -\frac{dP_c}{dz} \right) \left( 1 - \frac{R_i^2}{R_o^2} \right), & r < R_i \\
  \frac{R_o^2}{4\mu} \left( -\frac{dP_c}{dz} \right) \left( 1 - \frac{r^2}{R_o^2} \right), & r \geq R_i 
  \end{cases} \]

• Flow rate
  
  **Poiseuille**
  
  \[ Q_z = \frac{\pi R_o^4}{8\mu} \left( -\frac{dP_c}{dz} \right) \]

  **Axial Train**
  
  \[ Q_z = \frac{\pi R_o^4}{8\mu} \left( -\frac{dP_c}{dz} \right) \left( 1 - \frac{R_i^4}{R_o^4} \right) \]
Fluid Mechanics Model: Extravascular Flux Application of Starling’s Law

- Capillary wall treated as semi-permeable membrane
- Starling’s law

\[ q_e = L_p \left( P_c - P_i \bigg|_{r=R_o} - \sigma \left( \pi_c - \pi_i \right) \right) \]

- Equal to change in intravascular flow rate

\[ \frac{dQ_z}{dz} + 2\pi R_o q_e = 0 \]
Fluid Mechanics Model: Interstitial Flow
Application of Darcy’s Law

- Extravascular space treated as isotropic porous media
- Darcy’s law
  \[ \mathbf{U}_i = -\kappa \nabla P_i \]
- Combine Darcy’s law with the conservation of mass
  \[ \nabla \cdot \mathbf{U}_i = -\kappa \nabla^2 P_i = 0 \]
Fluid Mechanics Model: Poiseuille vs. Axial Train Axial Velocity Profile
Fluid Mechanics Model:
Increased Extravascular Flux for Cancer
Solute Transport Model

- Solid mechanics
- Fluid Mechanics
- Solute transport
- Heat transfer
  - Magnetic field
  - Particle aggregation
  - Binding/Uptake
  - Nanoparticle distribution
  - Drug delivery
  - Nutrient delivery
  - Nanoparticle drug carriers
  - Hyperthermia therapy
  - Metabolic generation
Solute Transport Model: Intravascular (PSL) Summary of Equations

- Fluid

\[ \nabla \cdot \mathbf{u}^f = 0 \]

\[ 0 = -\nabla P^f + \mu^f \nabla^2 \mathbf{u}^f + \sum_{\alpha \neq f} \rho_T^{\alpha} \phi^{\alpha} \mathbf{b}^{\alpha} \]

- Solute

\[ \frac{\partial \mathbf{c}^{\alpha}}{\partial t} + \mathbf{u}^f \cdot \nabla \mathbf{c}^{\alpha} + \nabla \cdot \left( -D_{\alpha/f} \nabla \mathbf{c}^{\alpha} \right) + \nabla \cdot \left( \frac{\rho_T^{\alpha}}{A_{\alpha/f}} \mathbf{c}^{\alpha} \mathbf{b}^{\alpha} \right) = \hat{R}^{\alpha} \]
Vessel Wall – Governing Equations for Solute Phase

- Balance of linear momentum

\[ \phi^\alpha (u^\alpha - u^m) = -D_{\alpha/cw} \nabla \left( \frac{\phi^\alpha}{\phi^f} \right) + (1 - \sigma^\alpha) \phi^\alpha (u^f - u^m) + \frac{\rho^\alpha \phi^\alpha}{A_{\alpha/f} + A_{\alpha/m}} b^\alpha \]

- Assume thin wall

\[ \nabla x \cdot n \approx -\frac{\Delta x}{\delta} \]

- Extravascular solute flux given by

\[ J_{\alpha} = \phi^f c^\alpha (u^\alpha - u^m) \cdot n \]

\[ = P_d^{\alpha} \Delta c^\alpha + (1 - \sigma^\alpha) \bar{c}^\alpha q_e + \frac{\rho_T \phi^f}{A_{\alpha/f} + A_{\alpha/m}} \bar{c}^\alpha b^\alpha \]
Extravascular Space – Governing Equations

- **Stress Tensor**
  \[ T^\alpha = -\varphi^\alpha P I + \varphi^\alpha \hat{T}^\alpha \]

- **Fluid**
  \[ \Pi^f = \sum_{\beta \neq f} \left( A_\beta \nabla \left( \frac{\varphi^\beta}{\varphi_{\text{pore}}} \right) + A_{\beta/f} F(\varphi^\beta) (u^\beta - u^f) \right) \]

- **Solutes**
  \[ \Pi^\beta = -A_\beta \nabla \left( \frac{\varphi^\beta}{\varphi_{\text{pore}}} \right) - \sum_{\alpha \neq \beta} A_{\beta/\alpha} F(\varphi^\beta) (u^\beta - u^\alpha) \]

- **Solid**
  \[ \sum_{\alpha} \Pi^\alpha = 0 \]
Model Parameters - Increased Capillary Permeability in Tumors

• Permeability of the capillary wall
  – Hydraulic permeability coefficient ($L_p$)
    • Relate fluid flow to pressure difference across wall
      – Normal: $2 \times 10^{-9}$ – $1 \times 10^{-12}$ m/Pa•s
      – Cancer: 5 – 500 times that of normal tissue
  – Reflection coefficient ($\sigma$)
    • Relate penetration of solute compared to that of the solvent ($\sigma = 1$ impermeable, $\sigma = 0$ freely permeable)
      – Normal: 0.76-0.92 for plasma proteins
      – Cancer: lower than that in normal tissue

• Hydraulic conductivity of the tissue ($\kappa$)
  – Relate fluid flow in porous media to pressure gradients
    • Normal: 0.11 – 1800 m²/Pa•s
    • Cancer: 2.9 – 10200 m²/Pa•s
Mean Red Blood Cell Velocity
Depends on $dP$, viscosity, $R_0$, and $t_{pl}$

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Extravascular Flux Sensitivity Depends on the Tissue Type

Normal

Cancer
Experimental Results from Dreher et al. – Model Calibration and Validation
Models Predict Transport of Nanoparticles and Bioactive Molecules

Capillary axis

Extravascular Tissue
Comparison Between Model and Experimental Results
Comparison Between Model and Experimental Results
Combine Numerical Modeling and Contrast Imaging to Model Transport

Sagittal Plane

Axial Plane
Analysis of MRI Images can be Related to Concentration of the Contrast Agent
The Time Between Scans can be Used to Obtain Concentration vs. Time

Axial Plane:
Time = $T_1 + 3$ mins

Sagittal Plane:
Time = $T_1 + 6$ mins

Coronal Plane:
Time = $T_1 + 9$ mins
3D Reconstruction was Used to Track Concentration at the Intersections
Variation of Hydraulic Permeability and $R_0$ Provides Match to Experimental Data
Future Directions

- Model active targeting
- Determine optimal magnetic particle characteristics and magnetic field stimulus for chemotherapy-based anti-cancer therapies
- Determine optimal magnetic particle characteristics and magnetic field stimulus for hyperthermia-based anti-cancer therapies
- Develop the first prophylactic treatment for high-risk patients.
Experimental Data → Model

- Volume fraction of initial image of gel (stretch = 1)
  - Images were filtered to remove uneven lighting
  - Volume fraction = ratio of Volume of fibril to Volume of ECM
  - Fibril volume = white pixels
ECM Cellular Solid Model

- Unit cell
  - Idealized structure
  - 4 geometric variables
  - Fills space with cubes and 14-sided polyhedrons

(Roeder et al., 2002)
Unit cell model of ECM under uniaxial tension
**ECM Stress**

\[
\sigma_E = \frac{4F}{(2l_c + 2l_d \cos \phi \sin \theta)(2l_c + 2l_d \sin \phi)}
\]

**Fiber Stress**

\[
\sigma_f = \frac{F}{\frac{\pi}{4} d^2}
\]
Biophysical Assessment of Cancer Cell Metabolism via NADPH Autofluorescence

Tumor cell autofluorescence depends on:

1.) Temperature
2.) ECM
3.) O₂ levels
4.) Glucose availability
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Notes

- **Carcinoma:** Malignant tumors derived from epithelial cells. This group represents the most common cancers, including the common forms of breast, prostate, lung and colon cancer.

- **Sarcoma:** Malignant tumors derived from connective tissue, or mesenchymal cells.

- **Lymphoma and leukemia:** Malignancies derived from hematopoietic (blood-forming) cells. Germ cell tumor: Tumors derived from totipotent cells. In adults most often found in the testicle and ovary; in fetuses, babies, and young children most often found on the body midline, particularly at the tip of the tailbone.

- **Blastic tumor or blastoma:** A tumor (usually malignant) which resembles an immature or embryonic tissue. Many of these tumors are most common in children.