[1] Process Systems and Operations Research Laboratory

[1] UCONN UNIVERSITY OF CONNECTICUT

[2] 東京大学 THE UNIVERSITY OF TOKYO

Rigorous Parameter Estimation for Model Validation in Oncological Systems

Chenyu Wang[1], John D. Martin[2], Horacio Cabral[2], Matthew D. Stuber[1]

Objectives

1 Establish physical transport model in tumor to characterize nanomedicine delivery
- Study the mass transfer in tumor and establish a 1-dimensional spherical transport model
- Apply the pore theory to characterize nanomedicine transport
- Employ numerical methods to discretize the system and solve PDEs
- Analyze the transient convective and diffusive transport over the tumor space domain

2 Implement optimization to estimate critical parameters in tumor model
- Use multistart local optimization to obtain preliminary results for parameter values
- Analyze transport in tumor before and after treatment to validate vascular normalization
- Establish and implement global optimization for the parameter estimation problem
- Manuscript under review[5]

3 Use differential inequalities to provide rigorous enclosure for global solve
- Establish discrete-time differential inequalities algorithms in Julia language
- Apply differential inequalities to the tumor model (PDEs) for rigorous global bounds

[5] J. D. Martin, M. Panagi, C. Wang, T. T. Khan, M. R. Martin, C. Voutouri, K. Toh, P. Papageorgis, F. Mpekris, C. Polydorou, G. Ishii, S. Takahashi, N. Gotohda, T. Suzuki, M. Willhelm, V. A. Melo, S. Quaser, J. Normanton, R. M. Lanning, M. Kojima, M. D. Stuber, T. Stylianopoulos, H. Cabral, and K. Katsuda, "A low-dose of chemotherapy adjunct increases nanocarrier delivery and efficacy against metastatic breast cancer by normalizing the tumor microenvironment," *ACS Nano*

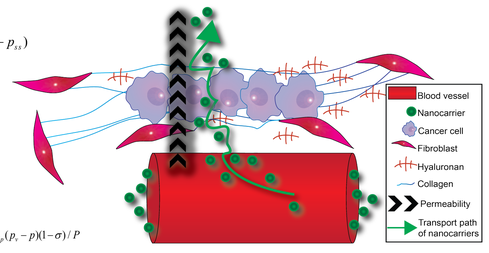
1. Tumor Transport Model[5]

- Fluid Transport Model

  Darcy's law $u = -K\nabla p$

  Continuity equation $\nabla \cdot u = \phi_v(r)$ → $\nabla^2 p = \frac{\alpha^2}{R^2}(p - p_{vs})$

  $\phi_v(r) = \frac{L_p S}{V}(p_v - p)$



- Solute Transport Model

  Transient diffusion-convection equation

  $\frac{\partial C}{\partial t} + \frac{1}{r^2}\frac{\partial (r^2 uC)}{\partial r} = D\frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial C}{\partial r}) + \phi_s(r)$

  Convection Diffusion

  Source term

  $\phi_s = L_p\frac{S}{V}(p_v - p)(1-\sigma)C_v + P\frac{S}{V}(C_v - C)\frac{Pe}{e^{Pe}-1}$ → $Pe = L_p(p_v - p)(1-\sigma)/P$

  Convection Diffusion

- Pore Theory

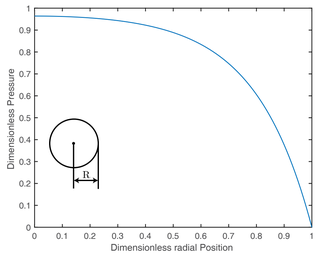
  Cylindrical pores

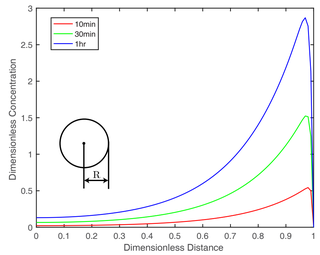
  $L_p = \frac{\gamma r_o^2}{8\mu L}$ $P = \frac{\gamma H D_s}{L}$ $\sigma = 1 - W$

- Numerical Methods

  Model discretization: fluid transport: finite difference method; solute transport: upwind scheme.

  PDEs: 4th-order Runge-Kutta method

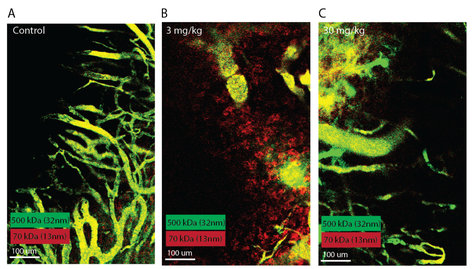




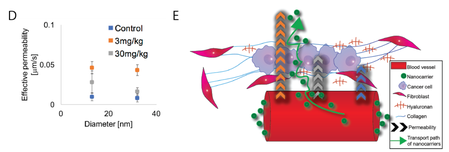
[2] L. T. Baxter and R. K. Jain, "Transport of fluid and macromolecules in tumors. i. role of interstitial pressure and convection," *Microvascular research*, vol. 37, no. 1
[3] W. Deen, "Hindered transport of large molecules in liquid-filled pores," *AIChE Journal*, vol. 33, no. 9
[4] P. M. Bungay and H. Brenner, "The motion of a closely-fitting sphere in a fluid-filled tube," *International Journal of Multiphase Flow*, vol. 1, no. 1

2. Chemotherapy Adjunct Increases Nanocarrier Delivery[5]

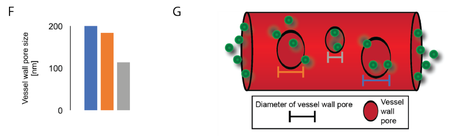
- Confocal intravital microscopy images of 4T1 tumors treated with control (A), low-dose(B), or high-dose (C) chemotherapy adjunct one hour after co-injection of 70 kDa (13 nm,red) and 500 kDa (32 nm, green) fluorescent dextrans.



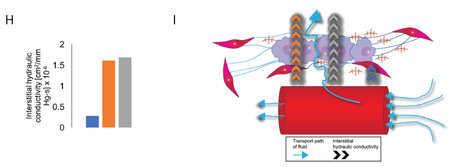
- (D) Low-dose (orange squares) highly increase the effective permeability of the tumor vessels;
- (E) Schematic of effective permeability: a measure of the rate that nanocarriers extravasate blood vessels.



- (F) Prediction of vessel wall pore size from the tumor model;
- (G) The small pore size after high-dose treatment sterically hinders extravasation.



- (H) Prediction of interstitial hydraulic conductivity from the tumor model;
- (I) Schematic of interstitial hydraulic conductivity: a measure of the rate that fluids traverse the extravascular space.



- Parameter Estimation Optimization

  Minimize the SSE between the average concentration of the model and data over the whole time horizon;

  Characterize the vascular normalization process after pretreatment chemotherapy adjunct;

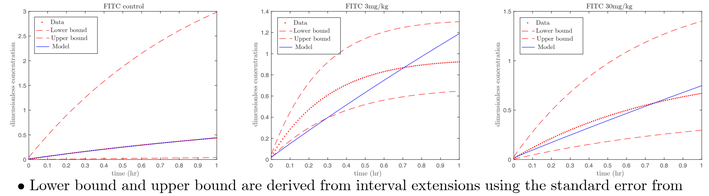
  Local solve ⟶ global solve

$$\min_{\boldsymbol{\pi}\in\Pi} \sum_{i=1}^{n} (C_{avg,mod}(t,\boldsymbol{\pi}) - C_{avg,data}(t))^2$$

- Uncertain parameters - $\boldsymbol{\pi} \in \Pi$

  Permeability of tumor vessels L_p: pore size ↓

  Interstitial hydraulic conductivity K : extracellular matrix (ECM) normalization



- Lower bound and upper bound are derived from interval extensions using the standard error from experiments;
- The effective permeability, determined by the experiments and used for obtaining the average interstitial concentration, significantly overestimates the diffusive contribution.

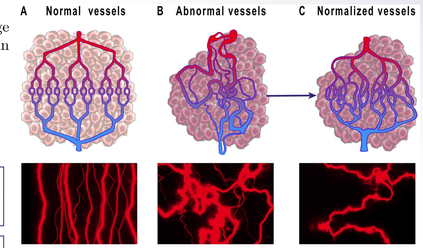
Background & Motivation

- Quantitative and formal methods provide huge opportunities for novel and high-impact discovery in many science fields.
- Cancer research

  Uncertainty in detailed transport mechanism;
  Lacking applicable physiological model;
  Hard to offer systemetical instructions.

Model-based systems engineering approach
- Well-founded physical transport framework in tumors
- Formal methods for model validation

- Improvements of current therapies;
- Development of novel therapies;
- Optimization of therapy for individual patient.



[1] E. Maj, D. Papiernik, and J. Wietrzyk, "Antiangiogenic cancer treatment: The great discovery and greater complexity," *International journal of oncology*, vol. 49, no. 5

3. Differential Inequalities for Discrete-Time Systems

- Global optimization requires efficient tight interval enclosures of time-dependent nonlinear systems
- Differential inequalities (DI) can be applied to discrete-time nonlinear systems to provide valid reachable set enclosures by forward Euler methods
- Discrete-time DI shows significant advantages compared with traditional interval extension methods
- Implementing Discrete-time DI in Julia programming language

- Nonlinear continuous-time systems

$$\dot{\mathbf{x}}(t) = \mathbf{f}(\mathbf{x}(t), \boldsymbol{\pi}(t)), \quad \mathbf{x}(t_0) = \mathbf{c}_0, \quad \text{a.e. } t \in [t_0, t_f]$$

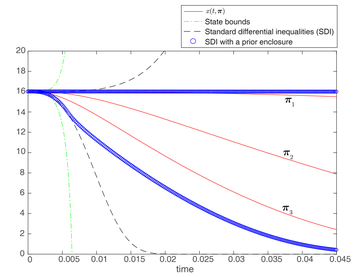
- Explicit Euler discretization

$$\mathbf{x}_{k+1} = \mathbf{x}_k + h\mathbf{f}(\mathbf{x}_k, \boldsymbol{\pi}_k), \quad \mathbf{x}_0 = \mathbf{c}_0, \quad \forall k \in \{0,\dots,K\}$$

- State bounding approach

  Directly apply interval arithmetic using Explicit Euler

$$x_{k+1,i}^L = x_{k,i}^L + hf_i^L([\mathbf{x}_k^L, \mathbf{x}_k^U], \Pi), \quad x_{0,i}^L = c_{0,i}^L$$
$$x_{k+1,i}^U = x_{k,i}^U + hf_i^U([\mathbf{x}_k^L, \mathbf{x}_k^U], \Pi), \quad x_{0,i}^U = c_{0,i}^U$$



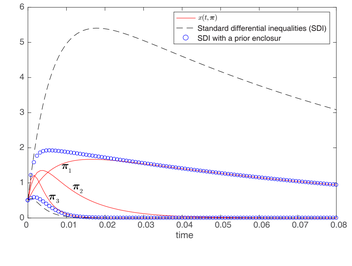
- standard DI method (SDI)

$$\beta_i^L([\mathbf{x}^L, \mathbf{x}^U]) = \{\mathbf{z} \in [\mathbf{x}^L, \mathbf{x}^U] : z_i = x_i^L\}$$
$$\beta_i^U([\mathbf{x}^L, \mathbf{x}^U]) = \{\mathbf{z} \in [\mathbf{x}^L, \mathbf{x}^U] : z_i = x_i^U\}$$

$$x_{k+1,i}^L = x_{k,i}^L + hf_i^L(\beta_i^L([\mathbf{x}_k^L, \mathbf{x}_k^U]), \Pi), \quad x_{0,i}^L = c_{0,i}^L$$
$$x_{k+1,i}^U = x_{k,i}^U + hf_i^U(\beta_i^U([\mathbf{x}_k^L, \mathbf{x}_k^U]), \Pi), \quad x_{0,i}^U = c_{0,i}^U$$

- SDI method with *a prior* enclosure

$$x_{k+1,i}^L = x_{k,i}^L + hf_i^L(\mathcal{I}_G(\beta_i^L([\mathbf{x}_k^L, \mathbf{x}_k^U])), \Pi), \quad x_{0,i}^L = c_{0,i}^L$$
$$x_{k+1,i}^U = x_{k,i}^U + hf_i^U(\mathcal{I}_G(\beta_i^U([\mathbf{x}_k^L, \mathbf{x}_k^U])), \Pi), \quad x_{0,i}^U = c_{0,i}^U$$



[6] X. Yang and J. K. Scott, "Efficient reachability bounds for discrete-time nonlinear systems by extending the continuous-time theory of differential inequalities," *2018 Annual American Control Conference*