Physiologically Based Multiscale Pharmacokinetic Model for Determining the Biodistribution of Targeted Nanoparticles

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Purpose

Develop a ***multiscale*** pharmacokinetic model to determine ***nanoparticle biodistribution*** in 7 organ tissues ***over time*** to ultimately….

1. Aid experimentalists
2. Determine critical nanoparticle design aspects

Nanoparticle Targeting

Nanoparticle Composition

1. Drug
2. Shell (Polymeric)
3. Coating (I-CAM Antibody)

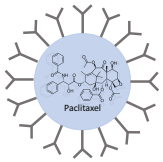


Figure 1. Example Nanoparticle Composition

Determination of Endothelial Cell Binding Constants

Ramakrishnan (2016) developed a static model to predict %idg for I-CAM antibody coated nanoparticles (NPs) after using NP translation and rotation dynamics, membrane receptor flexure, and Monte-Carlo membrane mechanics. From this multi-scale model, we can determine the binding constants of NPs to the endothelial cell surface receptors.

Ramakrishnan 2016 Model

$$\%idg = \left\{\kappa_p K_{EC} C_{out} + \frac{\varphi_{EC} K_{EC} \mathcal{L}}{D_{EC}} C_{out}\right\} \times \frac{L_{cap}}{L_{EC,b}} \quad (1)$$

1) Targeted Uptake
2) Macrophage Uptake

$$+ \frac{\varphi_M K_M \mathcal{L}}{D_{EC}} C_{out} \times \frac{L_{cap}}{L_{M,b}} \quad (2)$$

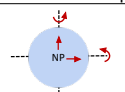


Figure 2. Nanoparticle Rotation/ Translation

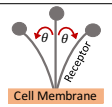


Figure 3. Receptor Flexure

General Model Development

Cardiovascular Scale Model

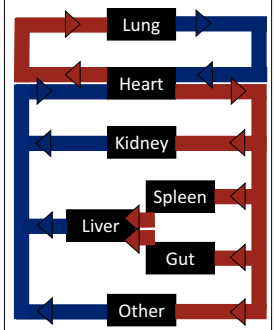


Figure 5. Schematic of Cardiovascular Scale Model

Cellular Scale Model

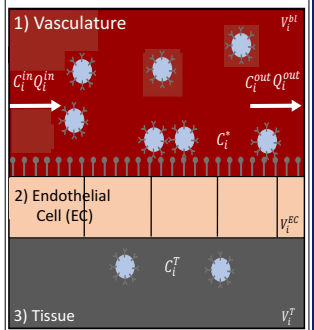


Figure 6. Schematic of Cardiovascular Scale Model

System of Linear ODEs

Cardiovascular Model Equations

$$\underbrace{V_{ven}\frac{dC_{out}}{dt}}_{\Delta\,[NP]\text{ in veins over time}} = \underbrace{\sum_i C_i^{out} Q_i^{out}}_{\text{Total exiting organ compartments}} - \underbrace{C^{out} Q}_{\text{Exiting venous compartment}}$$

$$\underbrace{V_{art}\frac{dC_{in}}{dt}}_{\Delta\,[NP]\text{ in arteries over time}} = \underbrace{QC_{out}}_{\text{Entering arterial compartment}} - \underbrace{\sum_i Q_i C_{in}}_{\text{Total entering organ compartments}}$$

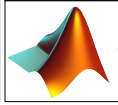
Cellular Model Equations

$$\underbrace{V_i^{bl}\frac{dC_i^{out}}{dt}}_{\Delta\,[NP]\text{ in bloodstream over time}} = \underbrace{Q_i C_i^{in}}_{\text{Total entering}} - \underbrace{Q_i C_i^{out}}_{\text{Total exiting}} - \underbrace{K_i^{on} V_i^{EC} C_i^{out}}_{\text{Bound to EC}} + \underbrace{K_i^{off} V_i^{EC} C_i^*}_{\text{Unbound from EC}} - \underbrace{K_{NS} V_i^{EC} C_i^{out}}_{\text{Non-specific uptake}} - \underbrace{K_i^{deg} V_i^{bl} C_i^{out}}_{\text{Degraded in blood}}$$

$$\underbrace{V_i^{EC}\frac{dC_i^*}{dt}}_{\Delta\,[NP]\text{ bound to EC over time}} = \underbrace{K_i^{on} V_i^{EC} C_i^{out}}_{\text{Bound to EC}} - \underbrace{K_i^{up} V_i^{EC} C_i^*}_{\text{Endocytosed}} - \underbrace{K_i^{off} V_i^{EC} C_i^*}_{\text{Unbound from EC}} - \underbrace{K_i^{deg} V_i^{EC} C_i^*}_{\text{Degraded in EC}}$$

$$\underbrace{V_i^T\frac{dC_i^T}{dt}}_{\Delta\,[NP]\text{ in organ tissue over time}} = \underbrace{K_i^{up} V_i^{EC} C_i^*}_{\text{Endocytosed}} + \underbrace{K_{NS} V_i^{EC} C_i^{out}}_{\text{Non-specific uptake}} - \underbrace{K_i^{deg} V_i^T C_i^T}_{\text{Degraded in tissue}}$$

Solving System



MATLAB ode23tb ODE Solver

Model Parameterization

Physiological Parameters	*Binding Constants*	*Variable Parameters*
Blood Flow Organ Volume **Previous Studies**	Binding Rate Unbinding Rate **Ramak. 2016**	Degradation Rate Uptake Rate **Sensitivity Analysis**

Incorporating Arterial Branching

Rationale

Branching elements were incorporated into arteries and veins to create a ***more physiologically relevant*** model

Model Alteration

- Q_i determined for each branching generation
- Total surface area of branches at each generation determined
- Resulting in altered V_i^{EC} and Q_i

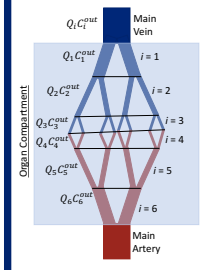


Figure 5. Single Branching Architecture

Model Output

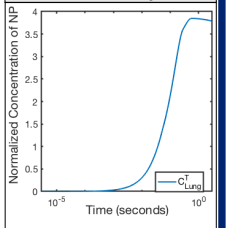


Figure 5. Single Branching Element Output

Applications to ARDS and COVID-19

Rationale

ARDS is major cause of respiratory failure in ***COVID-19 patients***. Experimentalists are exploring the use of ***targeted NP therapies*** to inflamed lung regions.

Model Alteration

- Development of four lobed lung model
- Validated with data and parameters from Brenner et. al., 2017

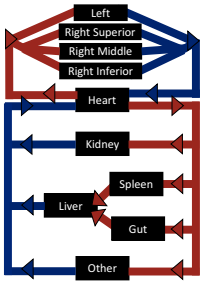


Figure 5. Schematic of ARDS Model

Model Output

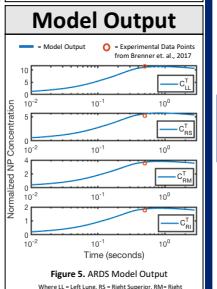


Figure 5. ARDS Model Output

Where LL = Left Lung, RS = Right Superior, RM= Right Middle, RI = Right Inferior

General Model Validation

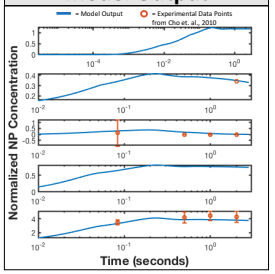
Sensitivity Analysis

Local Sensitivity Analysis was used to determine values of K_i^{up}, K_{NS}, K_i^{up}, that result in model output that most ***closely match experimental data***.

Validation with Experimental Data

- Cho et. al., 2010
- 100 nm PEG coated gold nanoparticles in murine model
- Four data points from 0 - 200 hours used to compare with model

Model Output



Conclusions

General Model

A seven organ compartment model successfully created

- Model output is consistent with experimental data provided by Cho et. al., 2010

Arterial Branching

A single element branching model was successfully created

- Mass was conserved in the single element model

ARDS and COVID-19

A four-lobed lung model was successfully created

- Model output and sensitivity analysis parameters consistent with data in Brenner 2017

Future Directions

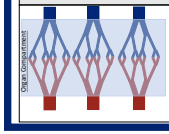
Prediction of Experimental Data

Use dynamic model to predict experimental data with nanoparticles of different compositions, different experimental models, or different organ targets.

Rapid Equilibrium Assumptions

Reduces the number of linear ODEs in the system by assuming some reaction is infinitely fast

Branching in General Model



Incorporate ***multiple branching elements*** into each organ compartment to create a complete, ***more physiologically relevant model***

Utilize HPC

Run more variations of the model in parallel

BRIDGES

Acknowledgements

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