

Nanoparticle-Cell Interaction: Liver Transportation Model

Notes

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[Poster Link](#)

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1 Introduction

This document is a supplementary material for project "Nanoparticle-Cell Interactions: Liver Transportation Model".

Mathematical models of nanoparticle-cell interactions Nanoparticles are a promising tool for the targeted delivery of medicine. However, the complex biological and physical processes that influence nanoparticle-cell interactions are not well understood. This project will develop mathematical models of nanoparticle transport (differential equations) and cell behaviour (differential equations or agent-based models). These models will help us understand which biological and physical processes dictate whether the targeted delivery of medicine via nanoparticles will be successful.

The document contains full model used in the project and scenario analysis after coded the model.



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Nanoparticle-Cell Interactions: Liver Transportation Model

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Introduction

The unique capabilities of nanoparticles can greatly aid medical applications, for example, in vitro/vivo detection and diagnosis, multimodal imaging, chemotherapy and phototherapy. However, to safely and effectively make use of the nanoparticle technology, we have to fully understand its interaction with in-vivo cells (for example, to prevent unwanted nanoparticles remaining in the body). In this paper, there is finding that Faria et al. (2019) established a solid mathematical foundation of symbolising cell-particle interactions. Inspired by the model of Faria et al. (2019), we developed a detailed mathematical for the analysis of nanoparticle transport through the liver. We present numerical solutions to the model and reveal the impact of immune cells in the liver.

General Liver-Particle Transportation Structure

The graph below helps illustrate how nanoparticles transport through the liver to the bile duct and finally excrete the human body.

- **Kupffer Cells:** localized in the blood vessel of the liver, take in particles by endocytosis.
- **Fenestrae:** Windows between each endothelial cell, particles can easily travel through if they are larger than the fenestrae.
- **Endothelial Cells:** As a single-layer barrier of the vessel, they control fluid and particles into and out of a tissue/blood.
- **Hepatocyte Cells:** Main cells in the liver, take up particles in liver tissue, then deliver them to the bile duct.

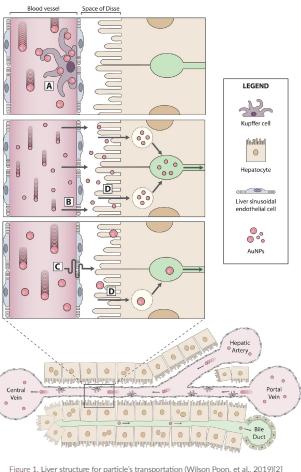


Figure 1. Liver structure for particle's transportation (Wilson Poon, et al., 2019)[2]

Cell&Fluid-Particle Association Model

$$f_{FluidsCell}(Fluid, Cell) = SC_{cell} \cdot r_{cell} \cdot \frac{P_{cell_capacity} - C_{Cell}(t)}{P_{cell_capacity}} \cdot C_{Fluid}(t) \quad (1)$$

$$f_{CellsFluid}(Cell, Fluid) = SC_{cell} \cdot r_{cell_out} \cdot C_{Cell}(t) \quad (2)$$

$$f_{FluidsFluid}(FluidA, FluidB) = r_A \cdot r_B \cdot \frac{Size_{fenestrae} \cdot C_{FluidA}(t)}{Size_{Particle}} \quad (3)$$

Where f_{XtoY} representing rate of particles moving from X compartment to Y. $C_{Cell}(t)$ is the concentration of that compartment at time t. SC_{cell} is the surface coverage of the cell in who r_{in} and r_{out} are rates of particles in/out/diffusion of the specific compartment part. For example, when representing particles moving from the blood to the space of disse, $f_{FluidsCell}$ can be used. The change of particle concentration in the blood or the space of disse is related to each fluid's specific rate of association with the particles (r_A and r_B), size of the particles ($Size_{Particle}$). Specifically, $f_{FluidsCell}$ is a removal rate of particles from the blood. The CCC model by Faria et al. (2019) has research successfully takes our understanding of cell-particle association from a quantitative level to a next level that enable us for quantitative analysis.

Liver Transportation Mathematical Model

The follow diagram shows the connections between different components of the liver and body. For the purpose of this model, the particles are injected into the blood and finally excrete the body through bile duct.

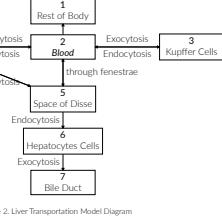


Figure 2. Liver Transportation Model Diagram

Mathematical Ordinary Differential Equations

After drawing the connection diagram we can construct a mathematical model based on the cells/fluid-particle association model. Each equation represents the change of particle concentration in each body part. For example, the change of particle concentration in **Kupffer Cells** consists of the rate that particles enter the Kupffer cells minus the rate that the cells emit the Kupffer cells and return back to the blood.

$$\frac{dC_{Blood}}{dt} = -r_{Body}(Blood) * Blood(t) + f_{CellsFluid}(Kupffer, Blood) - f_{FluidsCell}(Blood, Kupffer) + f_{CellsFluid}(Endothelial, Blood) - f_{FluidsCell}(Blood, Endothelial) + f_{FluidsFluid}(Space, Blood) - f_{FluidsFluid}(Blood, Space) \quad (4)$$

$$\frac{dC_{Kupffer}}{dt} = f_{FluidsCell}(Blood, Kupffer) - f_{CellsFluid}(Kupffer, Blood) \quad (5)$$

Full Model and Simulation Scenarios

Only two of seven ODE equations and a single simulated scenario has been shown due to the limited space. For the full model, please click [here](#).

[Source Code](#)

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Results

By setting up some initial values, I coded a python program using advanced Euler method iteratively, the full model is now solved. To analyse the impact of Kupffer cells been kept or removed, some diagnostic plots have been drawn,

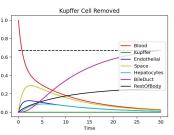
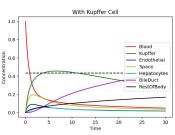



Figure 3. Kupffer Cell Removed

Figure 4. With Kupffer Cell

Figure 5: Liver structure for particle's transportation

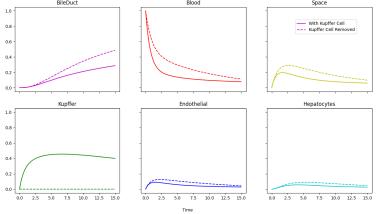


Figure 5. Liver structure for particle's transportation

From Figure 5, it is interesting that particles in the blood may get to the BileDuct more effectively if the Kupffer Cells, the "devourers", are removed by making $SC_{KupfferCell}$ equals zero. However, although Kupffer cells may retain particles to slow down the rate of particle excretion process, they could lead to less particle outflow to the rest of the body as most particles are been kept in Kupffer Cells in Blood.

Conclusions

A quantitative mathematical model of nanoparticles transportation through the liver has been developed. It would be fascinating if experimental data can be obtained for model fitting. A more detailed model could lead to further biomedical research towards nanoparticle applications.

Acknowledgements

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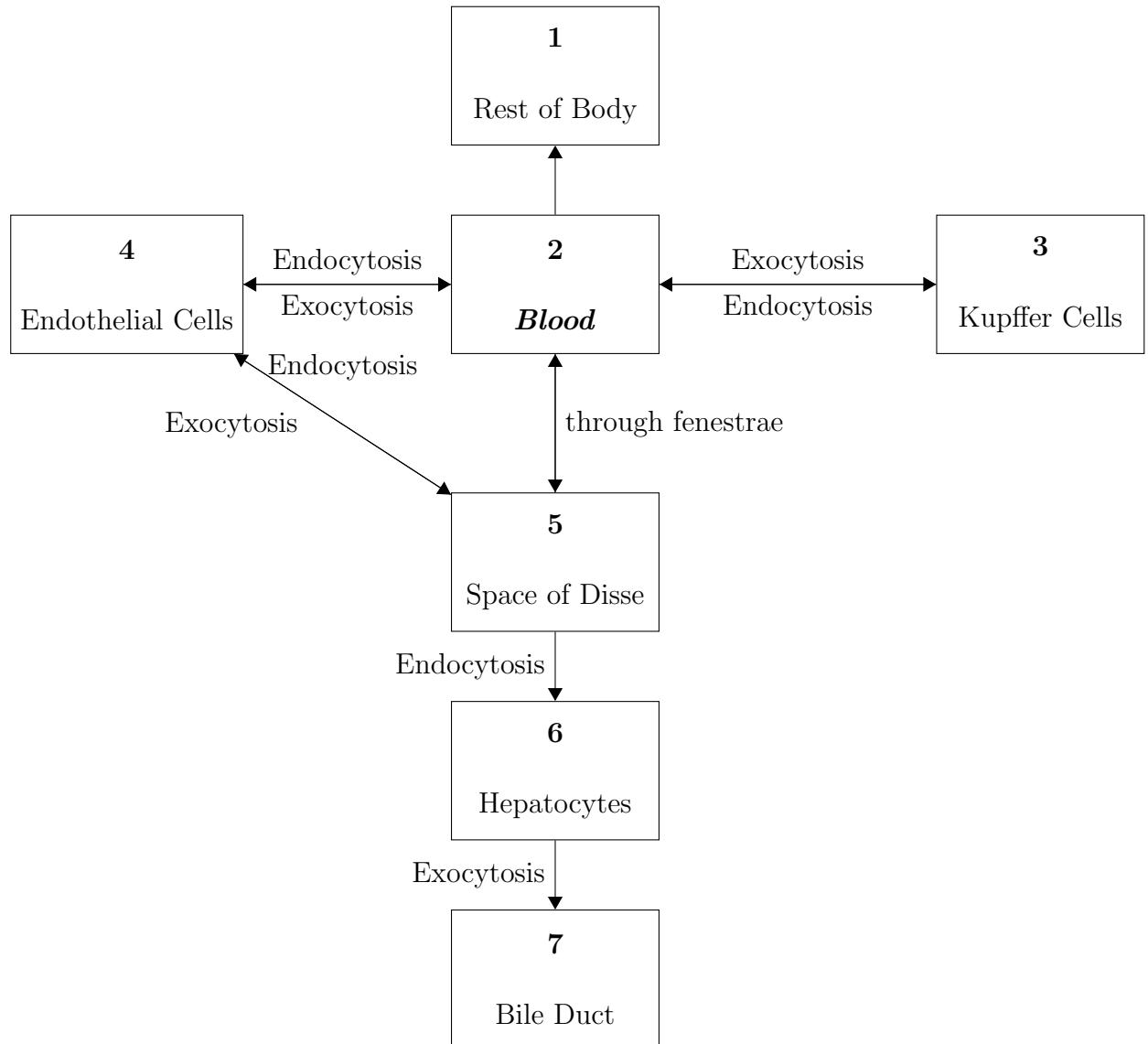
[1] Qiong Dai Mattias Björnemann Stuart T. Johnston Kristian Kempe Frank Caruso Edmund J. Campina Matthew Fung Nöl Reviving cell-particle association in vitro: A quantitative method to compare particle performance. *Journal of Controlled Release*, 2020, 330, 121-128.

[2] Ben Onyany Benjamin R. Kingston Jamie L.Y. Wu Stefan Wilhelm Warren C.W. Chan Wilson Poon, Yi-Nan Zhang. Elimination pathways of nanoparticles. *ACS Nano*, 13:5785–5796, 2019.

For coding detail, please navigate to [GitHub Page](#). For a brief overview of the project, please navigate to [Poster Link](#). Go to the References: [1] [2]

2 Illustration Diagram

Assumptions: Continuous Mixing so Dosimetry effect can be neglected.



Endocytosis = Eat, Exocytosis = spit out

Endocytosis + Exocytosis = Transcytosis

3 Full Model Equations

3.1 Kinetic Models

$$f_{FluidtoCell}(Fluid, Cell) = SC_{cell} \cdot r_{cell} \cdot \frac{P_{cell_capacity} - C_{Cell}(t)}{P_{cell_capacity}} \cdot C_{Fluid}(t) \quad (1)$$

$$f_{CelltoFluid}(Cell, Fluid) = SC_{cell} \cdot r_{cell_out} \cdot C_{Cell}(t) \quad (2)$$

$$f_{FluidtoFluid}(FluidA, FluidB) = r_A \cdot r_B \cdot \frac{Size_{fenestrae}}{Size_{Particle}} \cdot C_{FluidA}(t) \quad (3)$$

$f_{toCell}(Fluid, Cell)$: the cell kinetic model of particles moving from fluid to cell.

SC : surface coverage of the cells in current Fluid.

r_{cell} : rate of cell association.

u : particle concentration.

$P_{capacity}$: carrying capacity of cells for particles

$Cell(t)$: current number of associated particles in cell.

$Fluid(t)$: current number of particles in fluid

$r_{exchange}$: default exchange rate.

3.2 Liver Transportation Model

$$\frac{dRestOfBody}{dt} = r_{RestOfBody} * C_{Blood}(t) \quad (4)$$

$$\begin{aligned} \frac{dC_{Blood}}{dt} = & -r_{OutofBody} * C_{Blood}(t) + f_{CelltoFluid}(Kupffer, Blood) - f_{FluidtoCell}(Blood, Kupffer) \\ & + f_{CelltoFluid}(Endothelial, Blood) - f_{FluidtoCell}(Blood, Endothelial) \\ & + f_{FluidtoFluid}(Space, Blood) - f_{FluidtoFluid}(Blood, Space) \end{aligned} \quad (5)$$

$$\frac{dC_{Kupffer}}{dt} = f_{FluidtoCell}(Blood, Kupffer) - f_{CelltoFluid}(Kupffer, Blood) \quad (6)$$

$$\begin{aligned} \frac{dC_{Endothelial}}{dt} = & f_{FluidtoCell}(Blood, Endothelial) - f_{CelltoFluid}(Endothelial, Blood) \\ & + f_{FluidtoCell}(Space, Endothelial) - f_{CelltoFluid}(Endothelial, Space) \end{aligned} \quad (7)$$

$$\begin{aligned}
\frac{dC_{Space}}{dt} = & f_{FluidtoFluid}(Blood, Space) - f_{FluidtoFluid}(Space, Blood) \\
& + f_{CelltoFluid}(Endothelial, Space) - f_{FluidtoCell}(Space, Endothelial) \\
& - f_{FluidtoCell}(Hepatocytes, Space) \quad (8)
\end{aligned}$$

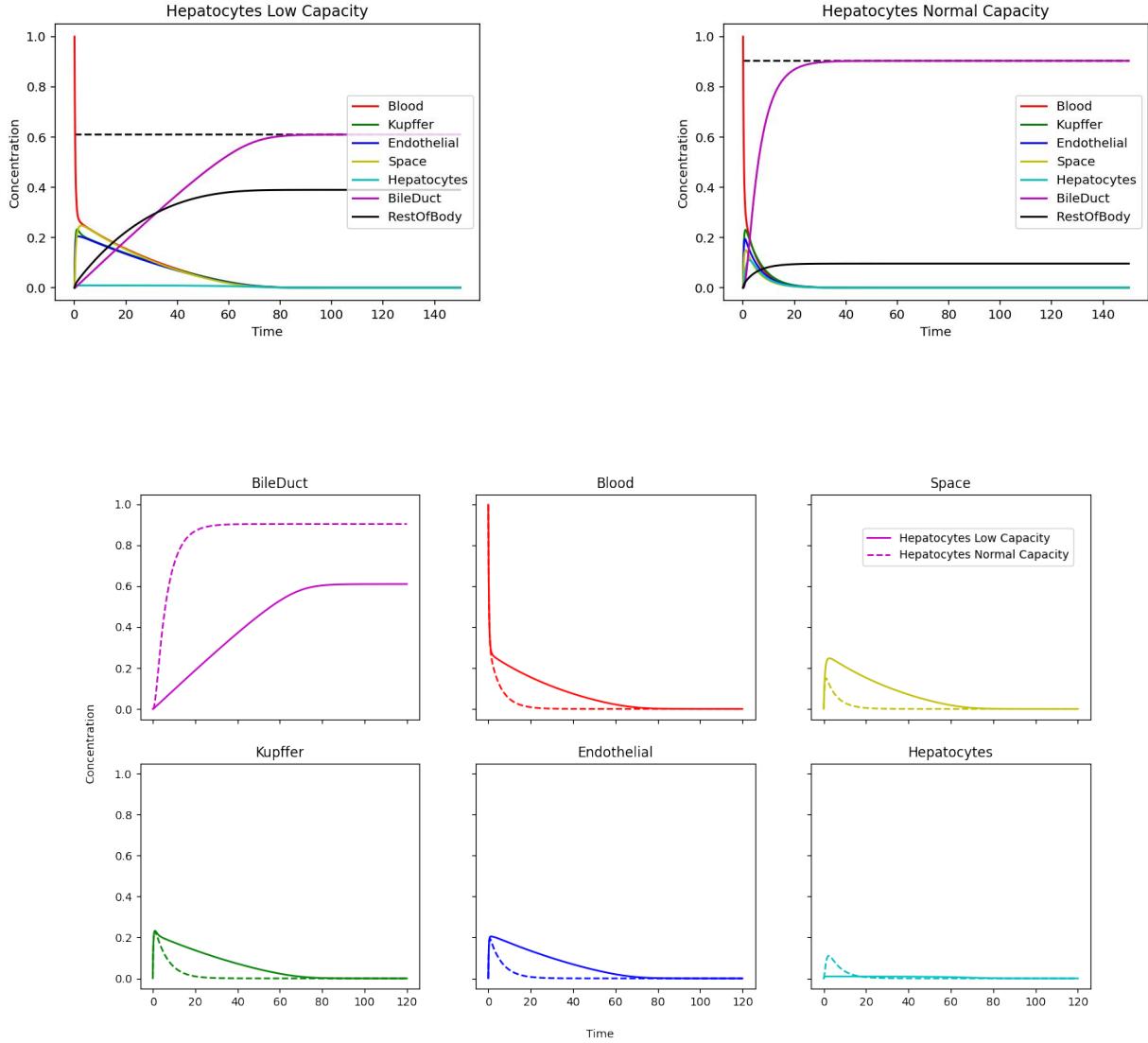
$$\frac{dC_{Hepatocytes}}{dt} = f_{FluidtoCell}(Space, Hepatocytes) - f_{CelltoFluid}(Hepatocytes, BileDuct) \quad (9)$$

$$\frac{dC_{BileDuct}}{dt} = f_{CelltoFluid}(Hepatocytes, BileDuct) \quad (10)$$

4 Scenarios Analysis

Exploring different Scenarios with program.

4.1 Hepatocytes Reach Max Capacity



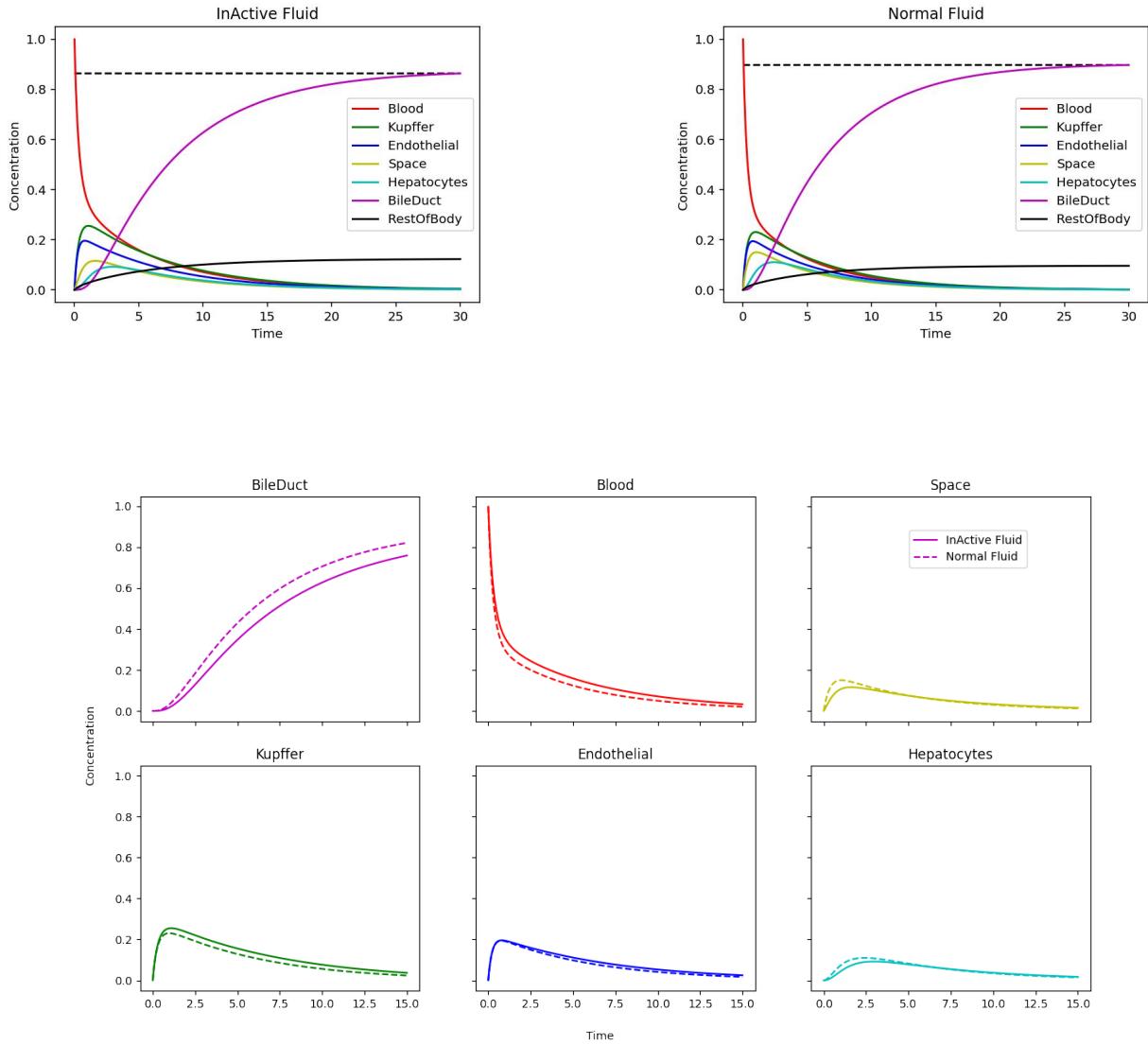
If we model the Hepatocytes with its capacity removed(it never stores any particles). The result is very interesting.

As the graph suggests, the particle concentration in the bile duct indicating a linear increase. It is believed that the rate of that in BileDuct is the same as the rate going out of Hepatocytes.

It also indicates that the actual rate of liver-particle association through different parts are varying across the board. Generally except for the blood and the bile duct, the particles rushes into each part of the liver, making them populated. After the concentration of particles in Blood decrease around a certain amount of value, the process reverse: each liver part's concentration goes down and they are functioning like balloon to become less saturated.

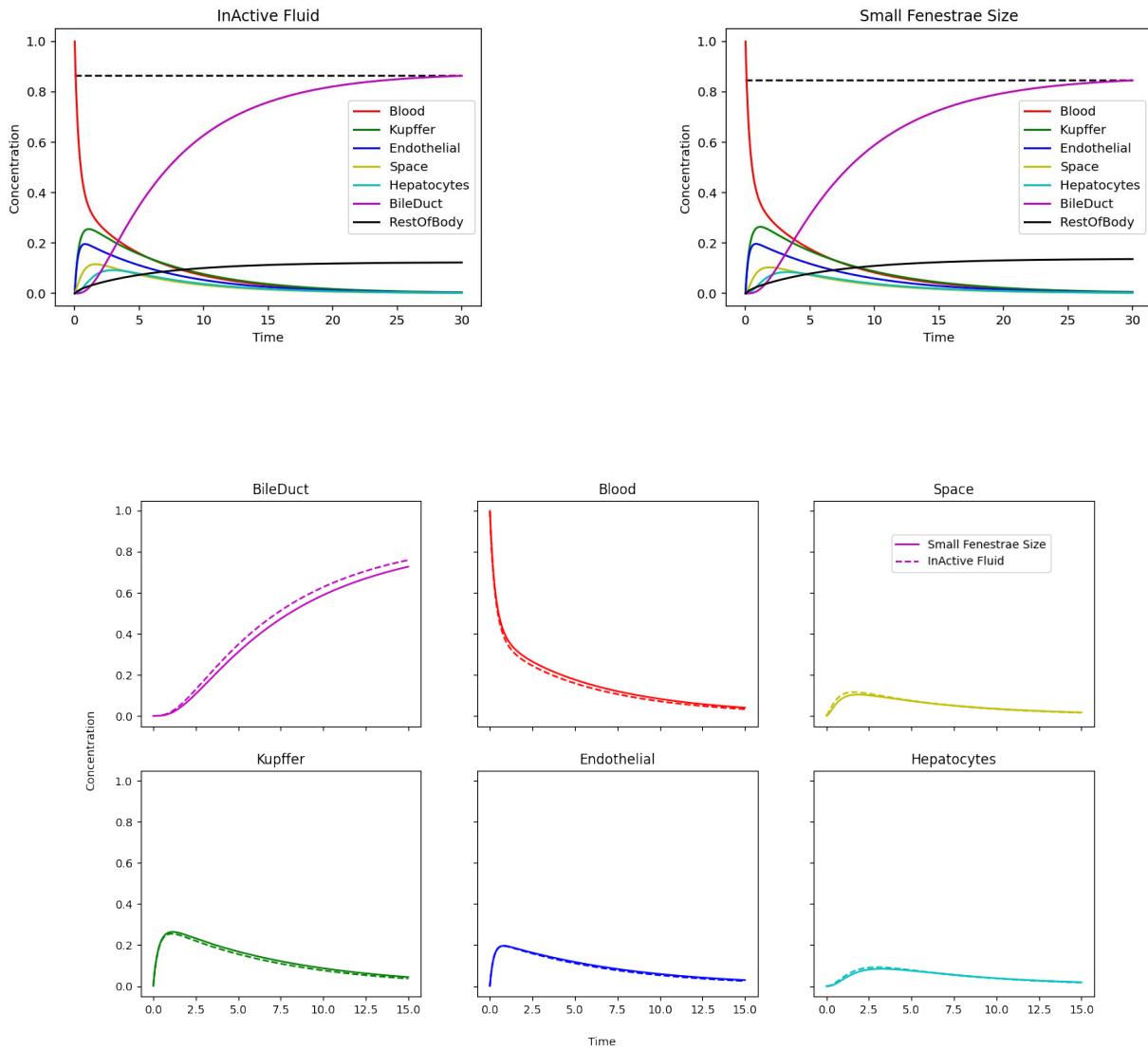
4.2 Between Fluid Transportation

4.2.1 InActive Fluid VS Normal Fluid



When making body fluid less active (with less particle association rate), it appears to directly affect the particle transportation through the fenestrae since between fluid transportation mainly rely on fenestrae. As the graph suggested, fenestrae transmission takes an important role in particle association as there's significant change of concentration in the bile duct.

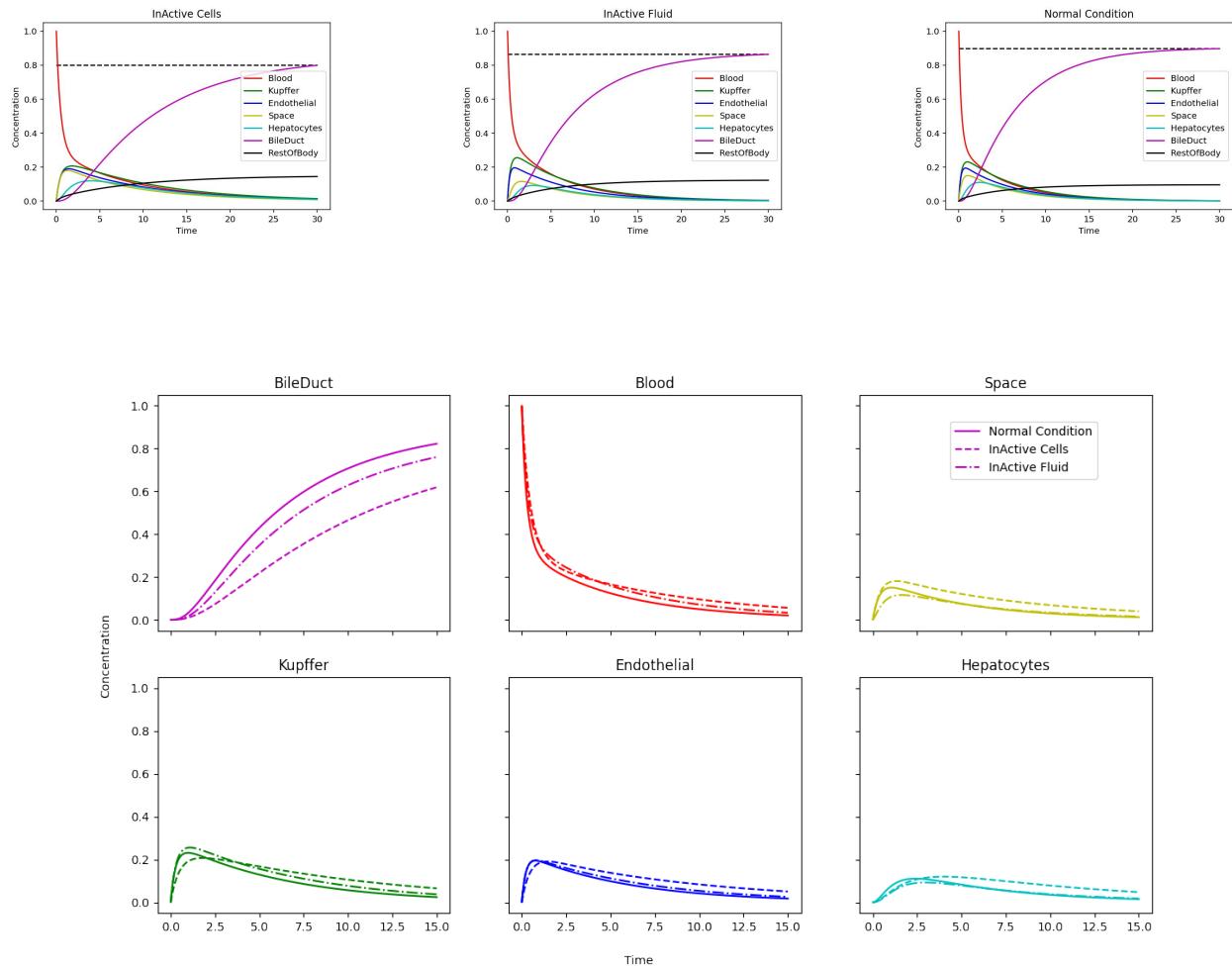
4.2.2 InActive Fluid VS Fenestrae Size



[Be aware that the fenestrae size changes may lead to change in Surface Coverage SC parameter] Discussed Above: - Assume Surface_Coverage is not affected by Fenestrae_Size

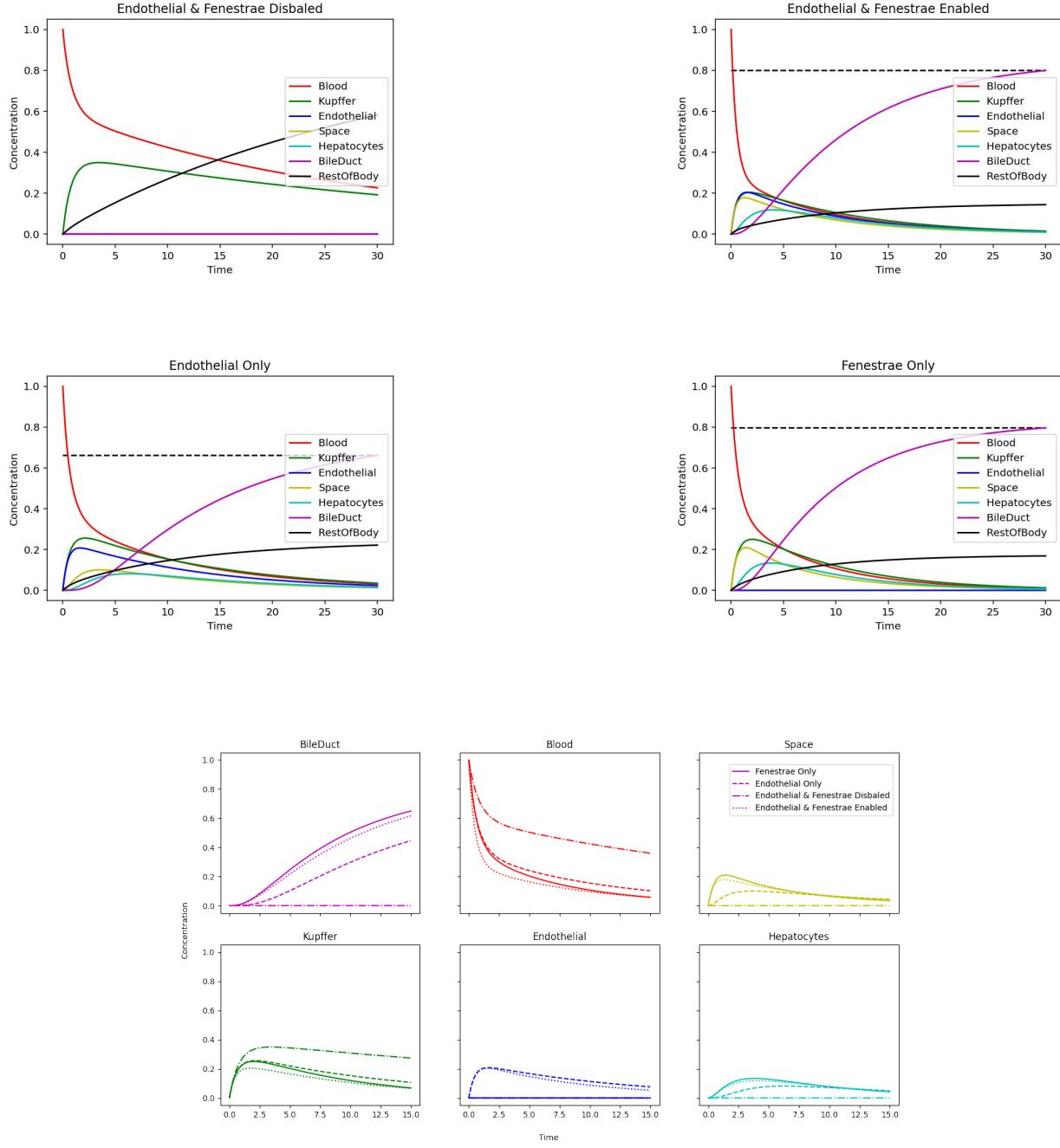
Since the impact of fenestrae size depends on particle size as well, it needs further experiment data to analyse. However, the analysis above does suggest fenestrae size and the rate of association of fluids do have impact of the transportation process between fluid.

4.2.3 InActive Fluid VS InActive Cells



If Cells are more likely inactive, which means they have lower rate_{in} and rate_{out}, most likely the whole process is been slowed down. It can be seen that more particles will remain in cells if the fluid is inactive or the Cells are inactive. Therefore, there are significantly more particles in Space of Disse in "inactive Cell Model" as the fenestrae transmission is not affected. Generally, the cells' performance may have large impact on the transportation than fluid's.

4.2.4 Endothelial VS Fenestrae Size



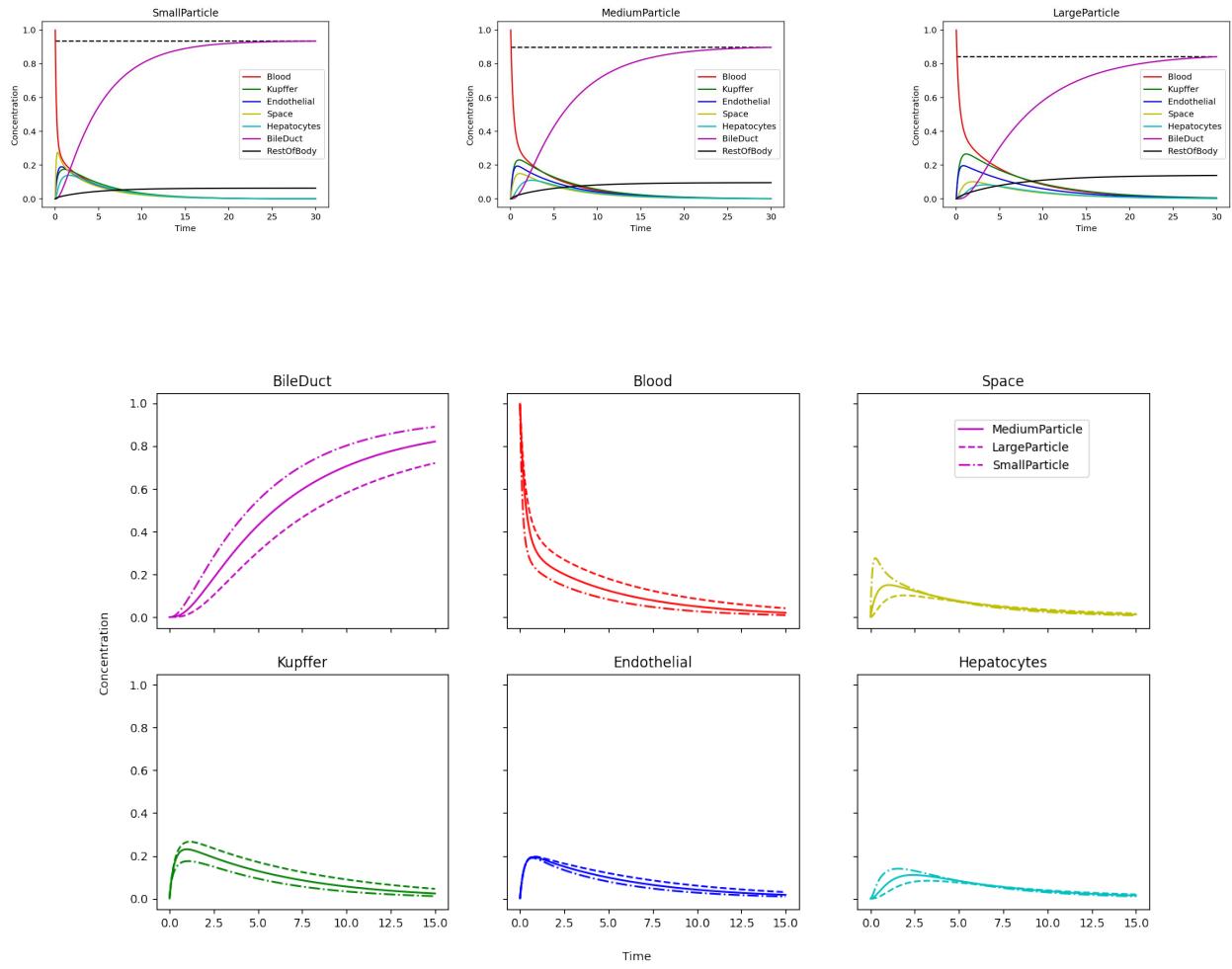
In this part, I tried to explore one of the factor's effect — Endothelial

By making Endothelial Cell incapacitated ($r_{in}=r_{out}=0$), with the help of Fenestrae only, our particles can easily going to the bile duct with a little less effectiveness.

However, when trying to make Endothelial cell function only (with fenestrae size = 0), by only making rate_in and rate_out high enough, can we compensate the loss of the help from the fenestrae, which means by making endothelial cell more effective, we can totally replace the effect of fenestrae transportation.

Moreover, by making r_{in} and r_{out} high enough, it is shown that the Endothelial cell may not be the threshold of particle's transportation anymore. Further adjustment to rate won't take affect to our model. This generally implies that when treating multi factor models like this, by improving single part of the model (improve single cell/fluid's performance) won't improve the effectiveness overall, it will always reach a threshold limited by other factors.

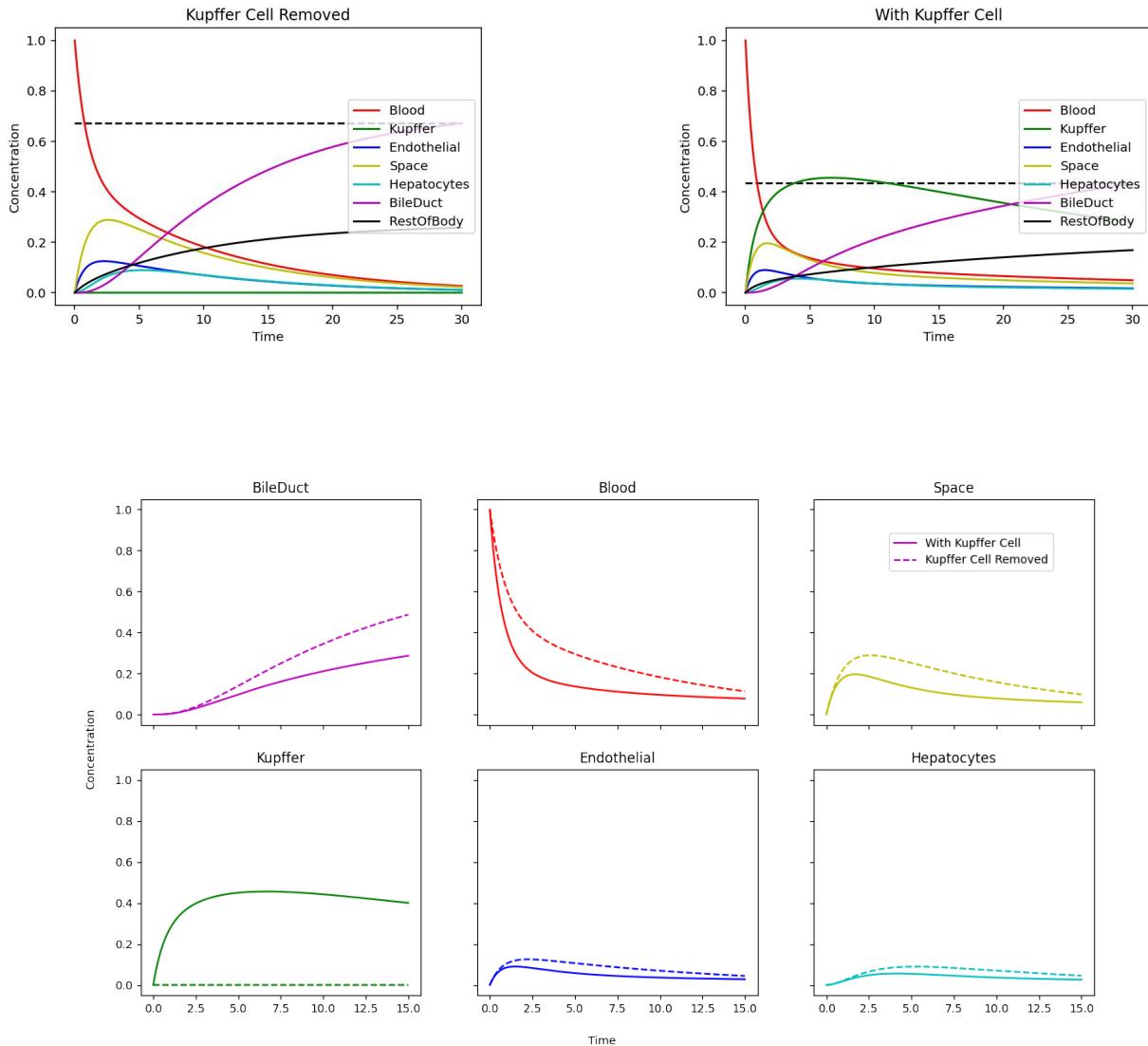
4.3 Particle Size Small VS Medium VS Large



Smaller Particles make the whole process faster. As the particles move faster through fenestrae within the blood and the space of disse. As a result, hepatocytes cells would be fully operating as the concentration in Space of Disse is higher.

With Larger Particles, they go through the fenestrae much more slowly and even been blocked out. Therefore the particles in the blood can only get to the space of disse by transcytosis across endothelial cells or finally overflow to the rest of the body.

4.4 Remove Kupffer Cells



By making Kupffer Cells surface coverage to 0, we removed the Kupffer Cells' effect.

Showing by graph, It is clear that removing Kupffer Cell may increase the overall association rate and more particles swarms into cells.

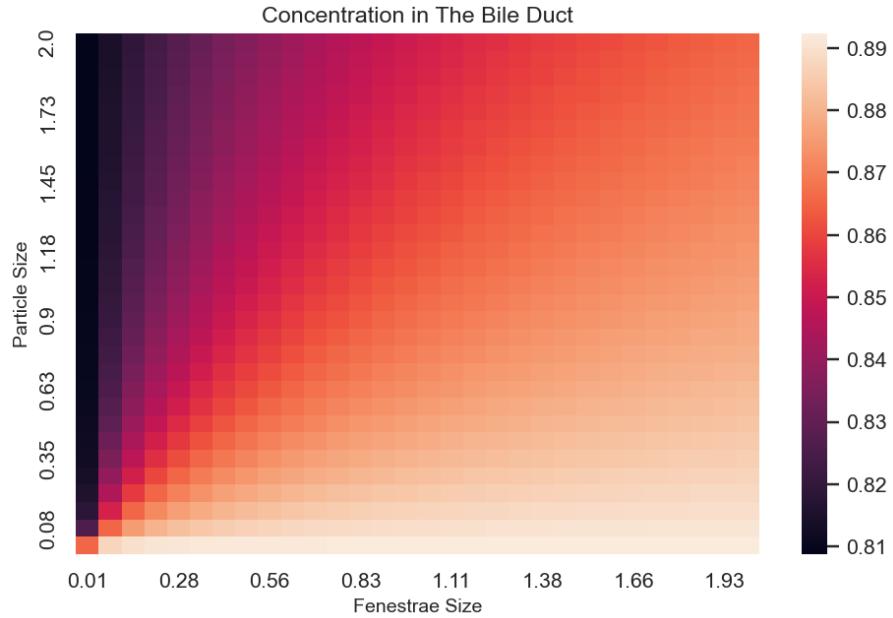
when Kupffer cell only takes particles, those particles will stuck in the Kupffer cells and it impeded the process of particle intake. While making Kupffer cells have even just a minor outflow rate (r_{out}), it increases the efficiency of transportation A LOT!

It also suggests the maximum capacity of each cell ($\text{max_capacity} = 1$) may not reach.

5 Contour Plot

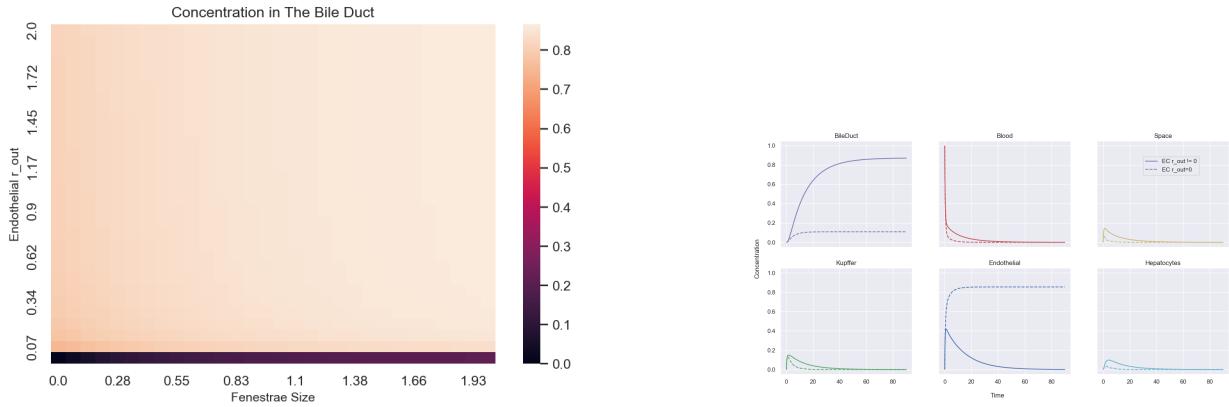
This section mainly focus on comparing different factor's effect on the transportation process. Use python to automatically solve for equilibrium state and compare the concentration in the bile duct.

5.1 Fenestrae Size VS Particle Size



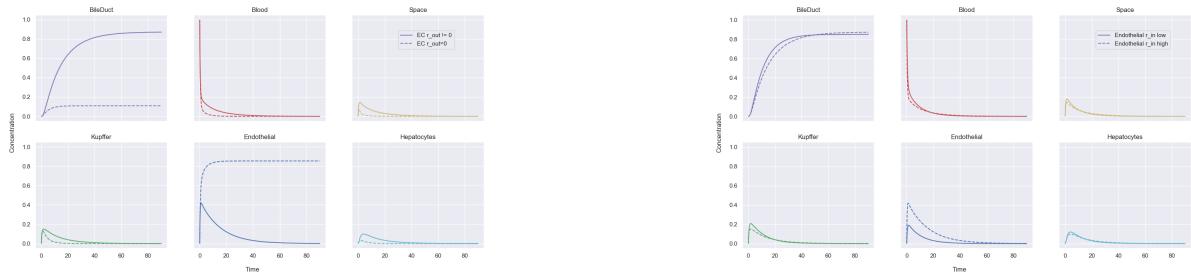
Comparing changing the size of particles VS size of Fenestrae. After the comparison, it is shown that when particle size is very small, the Fenestrae size may not have any effect on the transportation efficiency. But in general, if we change the size of particles to smaller ones, it may outperform we change the size of fenestrae to larger ones. Say if we change particle size the same amount of fenestrae size, the concentration change will be bigger for particle sizes change.

5.2 Fenestrae Size VS Endothelial rate_out



It seems that when r_{out} for EC are very low, the transportation process is hindered. The intuition behind this is that the EC capacity is very large so the particles are consistently associated with the ECs. Therefore they populated the ECs so none of them get into the bile duct. Also, it does show that the fenestrae size may have larger impact of the final concentration in the bile duct. The reason is that particles go through fenestrae directly but can be picked up and trapped in Endothelial Cells, so if less of them go through the fenestrae, more of them will end up been trapped in endothelial Cells.

5.3 Endothelial r_in VS Endothelial rate_out



Like said before, the ECs may keep those particles so when $r_{out}=0$, they end up keeping particles.

Additionaly, Interestingly, if the r_{out} is low enough, r_{in} and the change of concentration have a negative correlation. Otherwise they have a positive correlation!

In statistics, we call this, r_{in} and r_{out} have "interactions", Which means that change of r_{out} would change the relations between r_{in} and concentration.

To get a further understanding, the diagnostic plots have been drawn: and it seems that if ECs are efficient at exocytosis, the more they take, the more will end up in the bile duct. Otherwise, the less they take, the less particles been trapped in the ECs in the end.

References

- [1] Qiong Dai Mattias Björnmalm Stuart T. Johnston Kristian Kempe Frank Caruso Edmund J. Crampina Matthew Faria, Ka Fung Noi. Revisiting cell–particle association in vitro: A quantitative method to compare particle performance. *Journal of Controlled Release*, 307:355–367, 2019.
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