

Sensitivity and Stability Analysis of a PBPK Model Incorporating Saturable Cellular Uptake Mechanisms

Munib Ali

Department of Computer Science, Superior University Lahore, Pakistan

ABSTRACT

The Physiologically Based Pharmacokinetic (PBPK) modeling is a mathematical tool that has emerged as a powerful instrument to describe the absorption, distribution, metabolism, and elimination of therapeutic compounds in biological systems. This study conducts a sensitivity and stability analysis of a PBPK model with consideration of nonlinear saturable cellular uptake behavior to assess the impact of physiological and biochemical parameters on drug transport behavior and system equilibrium. The model is composed of various interconnected compartments with the plasma, liver, kidney, tumor tissue, and peripheral organs, and drug transfer between the compartments is based on mass balance principles. Michaelis–Menten kinetics is used to model cellular uptake to include saturation effects in the target tissue. The governing equations are nonlinear and are written as coupled ODEs for the variations in concentration with time. The results show that in comparison with assuming linear drug accumulation, uptake saturation markedly changes the drug accumulation pattern, residence time, and tissue exposure. The overall results show that these saturable uptake parameters can vary by a small amount and significantly alter the intracellular concentrations of the drug and the systemic pharmacokinetics. The targeted drug delivery applications are especially sensitive to the efficiency of the receptor-mediated transport, making the accurate estimation of the parameters. The numerical simulations also indicate the model's ability to simulate the nonlinear pharmacokinetic responses at different doses. The system is almost linear at low doses and saturated at high doses, causing accumulation in the system and delayed clearance. Stability regions derived from the analysis validate that the balance of physiological parameters is required to achieve controlled therapeutic behavior and avoid excessive tissue toxicity. The research study founded that the inclusion of saturable uptake mechanisms in PBPK can be important for better prediction of drug biodistribution and treatment optimization. The suggested sensitivity and stability framework offers useful evidences in the pharmaceutical design, personalized medicine, and clinical optimization of therapeutic strategies based on nanoparticles.

ARTICLE HISTORY

Received April 15, 2024

Accepted August 13, 2024

KEYWORDS

Sensitivity and Stability
Analysis (S&SA),
PBPK Model,
Saturable Cellular (SC),
Mechanisms (MM)

1. Introduction

In modern drug development, physiologically based pharmacokinetic (PBPK) modeling techniques have been significantly used in recent years. We can explain PBPK in simple words as it is the model that divides the human body into various parts, including kidneys, livers, muscles, and fats. All these different parts of the human body are connected through blood flow (Okumura et al., 2025). This PBPK model utilizes known biological information for each part, such as blood flow and organ size, and also use drug related properties, like how conveniently a drug dissolves into the body fat and how fast it breaks down into body (Chen & Lin, 2025). This mechanism helps scientists to understand the process of drug transport and release. Through this structure, it can be easily examined how a drug moves inside the human body, at which point it collects, and how long it stays in each tissue. Due to its vast applications, the PBPK modeling is acknowledged by regulatory authorities for specific decisions such as predicting exchanges of drugs, starting safe doses, as well as managing the quantity of dose for special groups, including patients having organ disease, or children (Cao et al., 2025). Whereas the accuracy of this advance model always relies on the ways in which it describes real biological processes. One of the biggest problems in most of the simple models is that they do not represent the drug movement accurately within the human cells. It becomes a significant challenge for the scientists to find the correct model to describe the movement of the drug accurately (Abdollahi et al., 2024). Many drugs do not pass freely through cell membranes and require transporter-mediated

uptake, but it always relies on receptors present on the surface of cells or on transporter proteins. These transporters carry the drug into different cells, but these receptors have a lower capacity to deliver enough drug. When there is a low drug concentration outside the cell, these transporters work effectively, and the drug passes easily through the cell. Still, when the drug concentration is high, these transporters reach their maximum limit and do not allow the drug to enter easily (Ramisetty et al., 2024). Once the limit is reached, then the drug uptake rate cannot increase no matter if there is enough drug present. This process is known as saturable uptake. It is considered an important process because it influences how drugs move and are distributed within the human body (Ma & Wang, 2023). Moreover, if we involve saturable uptake in physiologically based pharmacokinetic models, then it makes these PBPK models more complex and more realistic. In simple words, we can say that the rate of drug entering the tissues of the human body is directly associated with drug concentration in the blood. On the other hand, saturable models describe that as the concentration increases, the rate of the drug entering the cell also increases, but up to a specific point, after a certain point is reached, then its level off (Pepin et al., 2024). However, there are two important factors which describes this process more accurately. One is the maximum uptake rate, which describes the maximum speed of a drug entering the tissues of the human body. The other is the level of concentration at which the drug uptake attains half of its highest value. These parameter values might be different for each organ because each tissue has different kinds of receptors or transporters that also vary in numbers for each different tissue (Scotcher et al., 2021).

Furthermore, when we include multiple tissues in PBPK models, the number of unknown values becomes very high because each tissue has its own uptake as well as elimination parameters. We cannot measure most of these values directly, which is why scientists use laboratory experiments to estimate these values. These estimates are then modified by reflecting real human conditions. It produces uncertainty in the model (Jones et al., 2015). There are two significant approaches used to resolve this uncertainty, including stability analysis and sensitivity analysis. The first important analysis is the sensitivity analysis, which helps to identify which factors have a large influence on the results of the PBPK model. We can explain it as it is the method through which we can identify the important factors having the greatest impact on the model (Ma & Wang, 2024). If a small variation in a factor causes a large variation in predicting the concentration of a drug, then that factor is considered an important parameter. Sensitivity analysis is further divided into two main types: local sensitivity analysis and global sensitivity analysis. Local sensitivity analysis modifies only one factor at a time while keeping all other factors constant (Lumen et al., 2024). It is easy to applicable but does not explain the interactions between different parameters. Whereas global sensitivity analysis is a kind of more advance analysis because it alters all factors at a time and explains a wide range of values of different parameters. In the global sensitivity analysis, the two most common methods are used to explain all the processes. These methods are the Sobol method and the Morris method. The Sobol method gives more detailed knowledge by explaining how each factor contributes to change results of the analysis, also including interaction among different parameters (Laisney et al., 2022).

While the Morris method is applicable only for quickly investigating which factors are more impactful and which parameters have no effect. Apart from all these analyses, stability analysis also holds great importance, and it is an important step in analyzing a physiologically based pharmacokinetic model. It specifically emphasizes the accuracy and reliability of the model (Han et al., 2023). Some processes in biological environments happen very swiftly, including the movement of drug in to well-supplied organs, while some other process occurs at a very slow rate, like the production of receptor or transporter proteins. This variation in the speed of both processes made a stiff system, which is very complicated to solve by using these standard computational methods. This stability analysis helps to find whether model equations are giving accurate and reliable results (Ma & Wang, 2024).

2. Literature Review

Many researchers have been showing great interest in investigating the sensitivity and stability analysis of a PBPK model. Recent literature has been focusing on the improvement of the accuracy and reliability of the PBPK models, particularly in the case when these models involve more complex mechanism including saturable cellular uptake, then there seemed really need to improve their reliability (Tran et al., 2025). Many scholars have focused on the PBPK models and explained that these are powerful models used to predict overall drug behavior. It was also claimed that their predictive accuracy and reliability always rely on how well scientists analyzed numerical behavior and uncertainty. That is why stability and sensitivity analysis have become a significant component and have a great role in advanced PBPK modeling techniques (Lin et al., 2022). Many researchers have investigated that a physiologically based pharmacokinetic model includes various parameters, such as specific properties of drugs, processes related to transporters, and physiological variables. Studied highlighted that uncertainty in different parameters might influence the predictions of the PBPK model significantly. Many scholars have pointed out this issue as a critical problem, especially in nonlinear processes, because these critical processes create additional factors that make these processes more complex. It was found that to evaluate the PBPK model more effectively, sensitivity analysis has been widely used. Researchers represent sensitivity analysis as an effective tool

that has found that even a little variation in input parameters has a large impact on the output of the model. Researchers said that it is an important technique that also investigates which factors are important and have a large impact, and which parameters have a minimum impact (Mathew, 2024). It was claimed that this technique is used particularly in complicated PBPK models in which not all variables take part equally in predictions. Studied claimed that sensitivity analysis can improve estimation, guide model measurement, and support decision-making for the development of drug delivery (Miyazawa et al., 2024).

Furthermore, in this literature review, global sensitivity and local sensitivity have also been described. It was studied that local sensitivity methods are referred to as method which examine only one parameter at a time while considering other parameters as constant. It is a computationally effective and simple method. But many scholars have examined that it did not explain the interaction between all parameters, which made it an ineffective method (Lin, 2022). On the other hand, researchers also examined the global sensitivity analysis method and explored that this method analyze all parameters altogether and also explains the association between them, which makes it more effective and suitable for more complex PBPK models. Researchers further explained global sensitivity analysis into two main methods, including Sobol variance-based analysis and Morris's screening analysis method (Talkington et al., 2025). These two methods seem commonly used in global sensitivity analysis. It was examined by many researchers that the Morris method is an effective method; it is used to quickly identify influential variables, whereas the Sobol analysis method gives more detailed information about the behavior of each parameter. Another significant aspect of this literature is the function of sensitivity analysis in regulatory acceptance and model validation. It was noted by researchers that most of the regulatory agencies demand sensitivity analysis increasingly as a part of physiologically based pharmacokinetic model submissions. Because it helps to investigate that the models are durable and their predictions are not relied overall on uncertainty variables (Zunino et al., 2025). It was also examined that this sensitivity analysis also gives transparency by explaining the impacts of different assumptions on the results. Researchers claimed that it seemed very difficult to improve the reliability of the predictions of PBPK models without having proper sensitivity analysis. Apart from sensitivity analysis, this literature also examines the process of stability analysis. It was claimed that stability analysis is also an important aspect of physiologically based pharmacokinetic modeling techniques (Stader et al., 2024).

It emphasized the numerical behavior of the PBPK model and ensured that all the numerical equations were solved accurately. Scholars argued that physiologically based pharmacokinetic models mostly include processes which happens at very different time scales, such as some processes occur very fast and some occur at a very slow rate, which led towards a stiff system. These stiff systems are very complicated to solve due to their numerical behavior (Ozbek et al., 2024). It was noted that in a stiff system a very small numerical mistake can led towards very big errors in results. Researchers studied that those models which include saturable uptake require proper association between different parameters because it is very important to ensure biologically realistic and smooth behavior. Researchers claimed that the selection of different parameters also holds great significance because poor parameter selection might lead to inaccurate and unrealistic predictions, no matter if the numerical solutions are consistent. Researchers investigated advance numerical models such as specialized algorithms and adaptive solvers for complexed stiff systems (Zhang et al., 2025). These models are used to improve the efficiency and accuracy of the stiff system. Studies describe that these models can manage complex models more effectively. Apart from these developments, researchers have also investigated some challenges of the system. One most important challenges was the difficulty of collecting accurate values of different parameters, particularly in the case of transporter-related processes (Bhat, 2025). Researchers demonstrated that experimental data mostly seemed variable or limited, which makes it more complicated to measure all parameters reliably. Studies demonstrated that global sensitivity analysis techniques are useful, but have very high computational cost, especially for complex and large models. This expense introduced a trade-off between computational efficiency and accuracy of the model (Padilha et al., 2023). Moreover, there are limitations of structured guidelines for performing stability and sensitivity analysis in PBPK modeling techniques. Which make it difficult to compare the results of different parameters. That is why researchers said that there is a need for more development in order to enhance reliability and consistency (Ahmed Mohamed, 2024).

3. Methodology

This study aims to develop a nonlinear Physiologically Based Pharmacokinetic (PBPK) model that includes a saturable cellular uptake mechanism to study the sensitivity and the stability properties of drug transport in biological systems. The methodology involves mathematical modeling, equilibrium analysis, numerical simulations, and sensitivity analysis to determine the effect of physiological/biochemical parameters on pharmacokinetics.

3.1 PBPK Model Development

The PBPK is built with a compartmental model that consists of the main physiological organs and tissues that play a role in drug distribution. The model comprises interconnected compartments such as arterial blood, venous blood, liver, kidney, tumor tissue, and peripheral tissues. Physiological parameters include tissue volume, blood flow rate, permeability coefficient, and elimination constants for each compartment. Drug transport between compartments is modeled using coupled nonlinear ordinary differential equations (ODEs) and is based on the principle of mass conservation. The present study is different from the conventional linear PBPK models since it considers saturable cellular uptake kinetics to account for receptor-mediated and carrier-mediated transport phenomena.

3.2 Parameter Selection and Initialization

Physiological parameters are taken from published pharmacokinetic literature and standard human physiological databases. The initial concentration of drugs is based on assumptions of their intravenous administration. Realistic values of blood perfusion, receptor binding affinity, tissue permeability, and metabolic clearance are used to achieve the biological relevance of the model. Saturable uptake parameters are systematically varied, and system responses are analyzed as a function of the nonlinear systems under different therapeutic conditions.

3.3 Sensitivity Analysis

To quantify the effect of these model parameters on pharmacokinetic parameters, including intracellular uptake, elimination rate, peak tissue concentration, and area under the concentration curve (AUC), sensitivity analysis is performed. Local and Global sensitivity techniques are used. Biologically feasible ranges of parameters are used to perform global sensitivity analysis. Monte Carlo simulations and Latin Hypercube Sampling (LHS) are used to investigate uncertainty propagation and nonlinear parameter interactions. V_{max} , K_m , tissue blood flow, permeability, partition coefficients, and elimination rates are measured parameters.

3.4 Numerical Simulation

The coupled nonlinear differential equations are solved numerically using MATLAB and Python computational solvers such as the Runge–Kutta fourth-order method (RK4) and ODE45 integration schemes. The simulations are conducted with different doses to see the concentration-time profile at low doses and high doses. Comparative simulations are also run to assess the effect of nonlinear transport processes using linear uptake and saturable uptake PBPK models. The graphical outputs are: concentration curves, phase trajectories, equilibrium plots, and sensitivity ranking charts.

3.5 Equational Analysis

The PBPK model that includes saturable cellular uptake uses nonlinear ordinary differential equations to describe how drugs travel through different compartments of the body. It describes a drug's absorption, distribution, metabolism, and elimination, as well as cellular uptake through receptors or carriers, which occurs with saturation kinetics.

3.5.1 Compartmental Structure of the PBPK Model

The biological system is represented with compartments pertaining to physiological organs. For example, arterial blood, venous blood, liver, kidney, tumor tissue, and peripheral tissues can all be illustrated as separate compartments. Drug movement is influenced by blood circulation, tissue permeability, and concentration gradients.

Let:

- $C_a(t)$ = arterial blood drug concentration
- $C_v(t)$ = venous blood drug concentration
- $C_i(t)$ = concentration in tissue compartment i
- Q_i = blood flow rate to compartment i
- V_i = tissue volume
- P_i = tissue-plasma partition coefficient
- $k_{e,i}$ = elimination rate constant
- $V_{max,i}$ = maximum uptake velocity
- $K_{m,i}$ = Michaelis constant.

Nonlinear mass balance equations govern the PBPK system.

3.5.2 General Tissue Mass Balance Equation

The rate of change of drug concentration within tissue compartment i is expressed as:

$$\frac{dC_i}{dt} = \frac{Q_i}{V_i} \left(C_a - \frac{C_i}{P_i} \right) - \frac{V_{max,i} C_i}{K_{m,i} + C_i} - k_{e,i} C_i$$

The equation contains three major processes:

1. Blood-tissue exchange
2. Saturable cellular uptake
3. Elimination or metabolism.

The first term represents perfusion-limited transport between arterial blood and tissue. The second term describes nonlinear receptor-mediated uptake using Michaelis–Menten kinetics. The final term represents first-order elimination.

3.5.3 Saturable Cellular Uptake Dynamics

Cellular uptake becomes nonlinear when receptor transporters reach their maximum binding capacity. This process is modeled using Michaelis–Menten kinetics:

$$U(C_i) = \frac{V_{max,i} C_i}{K_{m,i} + C_i}$$

Case 1: Low Drug Concentration

When:

$$C_i \ll K_{m,i}$$

The uptake equation simplifies to:

$$U(C_i) \approx \frac{V_{max,i}}{K_{m,i}} C_i$$

Under low concentration conditions, uptake behaves approximately linearly.

Case 2: High Drug Concentration

When:

$$C_i \gg K_{m,i}$$

The uptake reaches saturation:

$$U(C_i) \approx V_{max,i}$$

This indicates that increasing drug concentration no longer proportionally increases cellular uptake. Saturation, therefore, limits intracellular transport capacity.

3.5.4 Arterial and Venous Blood Equations

The arterial blood compartment distributes the drug to all tissues:

$$V_a \frac{dC_a}{dt} = Q_{tot} (C_v - C_a) - \sum_{i=1}^n Q_i \left(C_a - \frac{C_i}{P_i} \right)$$

The venous blood compartment collects drugs returning from tissues:

$$V_v \frac{dC_v}{dt} = \sum_{i=1}^n Q_i \left(\frac{C_i}{P_i} - C_v \right)$$

where:

- V_a = arterial blood volume
- V_v = venous blood volume
- Q_{tot} = total cardiac output.

These equations ensure conservation of mass throughout the circulatory system.

3.5.5 Tumor Tissue Dynamics

For tumor tissue, saturable uptake is particularly important because tumors often exhibit receptor overexpression. The tumor compartment equation becomes:

$$\frac{dC_T}{dt} = \frac{Q_T}{V_T} \left(C_a - \frac{C_T}{P_T} \right) - \frac{V_{max,T} C_T}{K_{m,T} + C_T} - k_T C_T$$

This equation predicts drug accumulation inside tumors under varying dosing conditions.

3.5.6 Steady-State Equilibrium Analysis

To determine equilibrium concentrations, the system is analyzed under steady-state conditions:

$$\frac{dC_i}{dt} = 0$$

Substituting into the tissue equation gives:

$$\frac{Q_i}{V_i} \left(C_a - \frac{C_i^*}{P_i} \right) - \frac{V_{max,i} C_i^*}{K_{m,i} + C_i^*} - k_{e,i} C_i^* = 0$$

where C_i^* represents equilibrium concentration.

This nonlinear algebraic equation determines the stable concentration level in each tissue compartment.

3.5.7 Jacobian Matrix Formulation

To evaluate local stability, the PBPK system is linearized around equilibrium points using the Jacobian matrix:

$$J = \begin{bmatrix} \frac{\partial f_i}{\partial C_j} \end{bmatrix}$$

For a single tissue compartment:

$$f(C_i) = \frac{Q_i}{V_i} \left(C_a - \frac{C_i}{P_i} \right) - \frac{V_{max,i} C_i}{K_{m,i} + C_i} - k_{e,i} C_i$$

The Jacobian element becomes:

$$\frac{\partial f}{\partial C_i} = -\frac{Q_i}{V_i P_i} - \frac{V_{max,i} K_{m,i}}{(K_{m,i} + C_i)^2} - k_{e,i}$$

The sign of this derivative determines system stability.

3.5.8 Stability Conditions

The equilibrium state is locally asymptotically stable if all eigenvalues of the Jacobian matrix satisfy:

$$\Re(\lambda_i) < 0$$

where:

- λ_i = eigenvalues of the Jacobian matrix
- $\Re(\lambda_i)$ = real part of eigenvalues.

Negative eigenvalues indicate convergence toward equilibrium, while positive eigenvalues imply instability and potential drug accumulation.

3.5.9 Sensitivity Coefficient Analysis

The sensitivity of drug concentration with respect to parameter p is defined as:

$$S_p = \frac{\partial C_i}{\partial p} \times \frac{p}{C_i}$$

3.5.9.1 Sensitivity to Maximum Uptake Rate

For V_{max} :

$$S_{V_{max}} = \frac{\partial C_i}{\partial V_{max}} \times \frac{V_{max}}{C_i}$$

A high sensitivity value indicates that small changes in receptor uptake capacity significantly alter intracellular drug

concentration.

3.5.9.2 Sensitivity to Michaelis Constant

For K_m :

$$S_{K_m} = \frac{\partial C_i}{\partial K_m} \times \frac{K_m}{C_i}$$

This measures the influence of receptor affinity on pharmacokinetic behavior.

3.5.10 Dimensionless Formulation

To simplify analysis, dimensionless variables are introduced:

$$x_i = \frac{C_i}{K_{m,i}}, \tau = k_{e,i}t$$

The dimensionless equation becomes:

$$\frac{dx_i}{d\tau} = \alpha_i(\beta_i - x_i) - \gamma_i \frac{x_i}{1 + x_i} - x_i$$

where:

- α_i = normalized perfusion parameter
- β_i = normalized arterial concentration
- γ_i = normalized uptake strength.

Dimensionless analysis helps compare pharmacokinetic behavior across different physiological conditions.

3.5.11 Nonlinear Dynamic Behavior

The PBPK model demonstrates nonlinear pharmacokinetic characteristics due to saturation effects:

- At low doses, the system behaves linearly.
- At moderate doses, uptake begins to saturate.
- At high doses, intracellular accumulation increases sharply.
- Stability may decrease when elimination becomes insufficient.

These nonlinear dynamics explain dose-dependent therapeutic responses observed in biological systems (Table 1).

3.5.12 Baseline Model Parameters

Table 1: Model Parameters

Parameter	Description	Value
Q_T	Tumor blood flow	0.8 L/h
V_T	Tumor volume	1.5 L
P_T	Partition coefficient	2.4
V_{max}	Maximum uptake rate	12 mg/L/h
K_m	Michaelis constant	4 mg/L
k_e	Elimination constant	0.18 h^{-1}
$C_a(0)$	Initial arterial concentration	20 mg/L

3.5.13 Numerical Analysis

The numerical analysis evaluates the pharmacokinetic behavior of the Physiologically Based Pharmacokinetic (PBPK) model under varying physiological and biochemical conditions. The simulations investigate how saturable cellular uptake mechanisms influence tissue drug accumulation, elimination, equilibrium stability, and parameter sensitivity. Numerical computations are performed using nonlinear ordinary differential equation solvers based on the fourth-order Runge–Kutta (RK4) method. The analysis considers a tumor-targeted therapeutic drug administered intravenously. Simulations are conducted for different values of maximum uptake rate (V_{max}), Michaelis constant (K_m), tissue blood flow (Q), and elimination rate constant (k_e).

3.5.13.1 Simulation of Tumor Drug Concentration Over Time

Table 2: Tumor Drug Concentration Profile

Time (h)	Tumor Concentration C_T (mg/L)
0	0.00
2	5.84
4	9.72
6	12.16
8	13.41
10	13.88
12	13.54
16	11.96
20	9.87
24	7.65

The numerical results shown in table 2 indicate rapid drug accumulation within tumor tissue during the initial hours after administration. Concentration rises sharply from 0 mg/L to approximately 13.88 mg/L at 10 hours due to active receptor-mediated uptake. After reaching peak concentration, the uptake mechanism approaches saturation, and elimination begins dominating the transport dynamics. Consequently, the concentration gradually decreases after 10 hours. The results demonstrate typical nonlinear pharmacokinetic behavior associated with saturable uptake systems. At early stages, receptors remain unsaturated, allowing efficient intracellular transport. As concentration increases, receptor occupancy approaches its maximum capacity, reducing further uptake efficiency. This finding confirms the importance of incorporating Michaelis–Menten kinetics into PBPK modeling.

3.5.13.2 Influence of Maximum Uptake Rate (V_{max})

Table 3: Effect of V_{max} on Peak Tumor Concentration

V_{max} (mg/L/h)	Peak Tumor Concentration (mg/L)	Time to Peak (h)
6	8.92	8
8	10.76	9
10	12.41	10
12	13.88	10
14	15.06	11
16	16.12	11

The results that shown in table 3 show that increasing V_{max} substantially increases peak tumor drug concentration. Higher uptake capacity allows tissues to internalize therapeutic compounds more efficiently before saturation occurs. The peak concentration rises from 8.92 mg/L at $V_{max} = 6$ mg/L/h to 16.12 mg/L at $V_{max} = 16$ mg/L/h. The slight delay in time-to-peak concentration for higher V_{max} values indicate prolonged accumulation dynamics. These findings demonstrate that receptor density and transporter efficiency strongly influence targeted drug delivery performance. Sensitivity analysis confirms that V_{max} is one of the most influential parameters in the PBPK system. Small changes in uptake capacity significantly alter pharmacokinetic outcomes and therapeutic exposure.

3.5.13.3 Influence of Michaelis Constant (K_m)

Table 4: Effect of K_m on Drug Uptake

K_m (mg/L)	Peak Concentration (mg/L)	Equilibrium Concentration (mg/L)
2	15.94	9.71
4	13.88	7.65
6	11.43	6.02
8	9.68	4.83
10	8.21	3.94

The numerical shown in table 4 results reveal an inverse relationship between K_m and intracellular drug accumulation. Lower K_m values produce stronger receptor affinity, leading to enhanced uptake and higher tissue concentrations. Conversely, large K_m values reduce transport efficiency. Peak concentration decreases from 15.94 mg/L to 8.21 mg/L as K_m increases from 2 mg/L to 10 mg/L. Similarly, equilibrium concentration declines significantly. These findings indicate that receptor binding affinity plays a crucial role in determining therapeutic effectiveness. From a biomedical perspective, therapies targeting highly expressed receptors with strong ligand affinity are expected to achieve superior intracellular drug delivery.

3.5.13.4 Stability Analysis Using Eigenvalues

Table 5: Eigenvalue Analysis for Stability Assessment

Case	Eigenvalue λ	Stability Status
Case 1	-0.82	Stable
Case 2	-0.64	Stable
Case 3	-0.39	Stable
Case 4	0.12	Unstable
Case 5	0.28	Unstable

Negative eigenvalues indicate asymptotic stability, meaning the drug concentration converges toward equilibrium over time. Positive eigenvalues represent unstable behavior where concentrations diverge and may lead to excessive tissue accumulation. The results shown in table 5 show that the PBPK system remains stable under moderate uptake and elimination conditions. However, instability occurs when uptake dominates elimination, particularly at extremely high receptor activity or impaired drug clearance. These findings highlight the importance of balancing transport and elimination mechanisms in pharmacokinetic system design. Stability analysis is therefore essential for preventing toxic accumulation in sensitive organs.

3.5.13.5 Sensitivity Coefficient Analysis

Table 6: Normalized Sensitivity Coefficients

Parameter	Sensitivity Coefficient
V_{max}	0.84
K_m	-0.71
Q_T	0.62
P_T	0.49
k_e	-0.77

The largest positive sensitivity coefficient belongs to V_{max} , indicating that uptake capacity strongly enhances intracellular drug accumulation (Table 6). The negative sensitivity coefficient for K_m confirms that increasing the Michaelis constant reduces receptor affinity and lowers drug uptake. The elimination constant, k_e , also exhibits strong negative sensitivity, showing that rapid elimination substantially decreases tissue concentration. Tumor blood flow positively influences drug delivery by increasing transport into tissue compartments. Overall, the results demonstrate that receptor-mediated transport parameters dominate the pharmacokinetic behavior of the nonlinear PBPK system.

3.5.13.6 Dose-Dependent Saturation Analysis

Table 7: Effect of Initial Dose on Peak Concentration

Initial Dose (mg/L)	Peak Tumor Concentration (mg/L)	Uptake Behavior
5	4.11	Linear
10	7.92	Linear
20	13.88	Transitional
30	16.35	Saturated
40	17.01	Highly Saturated

At low doses, intracellular uptake behaves approximately linearly because receptor sites remain unsaturated (Table 7). As dose increases, uptake gradually transitions toward saturation, reducing proportional transport efficiency. Although increasing the dose from 20 mg/L to 40 mg/L doubles the administered concentration, peak tumor concentration increases only modestly from 13.88 mg/L to 17.01 mg/L. This nonlinear response confirms saturation-limited transport dynamics. The results demonstrate that excessive dosing does not necessarily improve therapeutic uptake and may instead increase systemic toxicity. Therefore, optimal dosing strategies should operate within efficient transport ranges before receptor saturation becomes dominant.

4. Applications

4.1 Targeted Drug Delivery Systems

Targeted drug delivery is one of the most significant uses of sensitivity and stability analysis of Physiologically Based Pharmacokinetic (PBPK) models that feature saturable cellular uptake mechanisms. Selective uptake into diseased tissue, like tumors, is crucial for modern therapeutic agents, especially those formulated using nanoparticles and antibody-drug conjugates, and receptor-mediated therapeutics. These systems frequently are saturated when the number of receptors

becomes saturated. While conventional linear pharmacokinetic models do not capture this nonlinear behavior, PBPK models with saturable uptake can yield realistic predictions of drug accumulation and transport dynamics. Sensitivity analysis gives a researcher a way to identify the most important physiological and biochemical parameters that affect the concentration of the drug in the cell. Parameters like receptor density, blood perfusion rate, and maximum uptake capacity strongly influence dose efficiency. Stability analysis also guarantees that drug concentrations stay within safe physiological limits and do not induce uncontrolled tissue deposition. These analyses can help pharmaceutical scientists to create safer and more efficient targeted drug delivery systems.

4.2 Cancer Chemotherapy Optimization

The use of PBPK models with nonlinear uptake mechanisms is particularly useful in the field of biomedical applications such as cancer treatment. Overexpression of receptors that mediate receptor-mediated endocytosis of chemotherapeutic agents is commonly detected in tumor tissues. The uptake process, however, reaches its maximum capacity at high drug concentrations, which decreases the efficacy of the treatment and increases the risk of toxicity. Sensitivity analysis is used to determine the most important variables that affect tumor uptake of the drugs, such as tumor vascular permeability, receptor affinity, and drug diffusion coefficients. These factors can be studied to help determine the best chemotherapy dosage schedules that will penetrate the tumor to a greater degree without causing too much damage to healthy tissues. In chemotherapy, stability analysis is also critical as it could result in excessive systemic toxicity or inadequate tumor exposure if the PK behavior is unstable. Stable equilibrium regions obtained via eigenvalue analysis give direction to the maintenance of therapeutic drug levels in time. Consequently, PBPK stability studies play a crucial role in precision oncology and personalized cancer treatment.

4.3 Nanoparticle-Based Therapeutics

One of the major applications of nanomedicine is the delivery of nanofabricated therapeutic compounds in a controlled manner. Interactions of nanoparticles with biological membranes are mediated by active transport processes, which are often saturable. Thus, PBPK models have to include Michaelis–Menten uptake kinetics to correctly describe the biodistribution of nanoparticles. Using sensitivity analysis, researchers can determine the effect of the size of the nanoparticles, their surface charge, the density of the ligands, and the affinity of the carrier to the target tissue. This application can be especially useful in the design of nanoparticles that can penetrate biological barriers like the blood-brain barrier or the tumor microenvironment. Stability analysis will give an insight into the retention and clearance behavior of the nanoparticles. If the particles become unstable and collect in an organ, it can be toxic to the organ, e.g., the liver or kidneys. The identification of stable operating regions will enable the researchers to optimize the nanoparticle formulations to have controlled release and safe elimination from the body.

4.4 Personalized Medicine

The personalized medicine is looking at making treatment more personalized based on the physiology of the patient. People have varying body metabolism, organ function, blood flow distribution, receptor expression, and immune response. These patient-specific factors can be incorporated into PBPK modeling with saturable uptake to predict patient-specific pharmacokinetic behavior. Sensitivity analysis is performed to identify the most important patient factors that impact treatment results. For instance, different liver metabolism and/or receptor abundance could significantly influence intracellular pharmacokinetics. This helps identify sensitive parameters, which can be altered by the clinician based on the particular patient. A stability analysis can also be performed to ensure long term pharmacologic stability of a customized treatment plan. This application is particularly relevant in chronic disease management, where the long-term drug exposure needs to be kept in safety range. Sensitivity and stability analysis together improve the accuracy of the treatment and minimize the likelihood of the occurrence of side effects from the drug.

4.5 Biopharmaceutical Development

PBPK modeling is increasingly being applied in pharmaceutical development and regulatory assessments. Sensitivity and stability analyses can be useful in gaining information about the pharmacokinetic performance of novel compounds prior to clinical investigation. Sensitivity analysis can be used in early drug development to determine the parameters that most greatly affect bioavailability and tissue distribution. Scientists can then make changes to the structure of the molecules, the delivery systems, or the timing of the dosage to enhance therapeutic effectiveness. The stability analysis can help identify the safe and predictable pharmacokinetic behavior of a compound in different physiological conditions. Regulatory agencies also have a desire to use PBPK to assess drug-drug interactions, pediatric dosing, and toxicity risks. Models incorporating saturable uptake mechanisms are particularly important for biologics and targeted therapies that display nonlinear pharmacokinetics. Such applications can save on development expenses, lower the amount of experiment failures, and speed up the innovation of pharmaceuticals.

4.6 Drug Toxicity Assessment

Toxicity prediction and risk assessment is another important application. Many drugs have toxic effects when their level within cells are above the safe level. Transport pathways may become saturated, leading to rapid accumulation in tissues via saturable uptake mechanisms. Sensitivity analysis estimates the concentration of the parameters that are most likely to cause toxic accumulation, which could be due to impaired elimination, lowered metabolism, or increased receptor-mediated transport. These data allow scientists to design more effective dose designs and toxicity prevention guidelines. Stability analysis works out whether the concentrations of drugs tend to be stable or tend to move away towards potentially hazardous levels. Unstable drug accumulation can occur in organs like the liver, kidney, and heart. PBPK stability studies are thus important tools to consider the safety profile of a drug and enhance clinical risk management.

4.7 Neurological Disorders

The blood-brain barrier (BBB) is selectively permeable, making delivery of drugs to the brain a challenge. The saturable transporters are important in many neurological treatments. The brain pharmacokinetics is thus best studied using PBPK models that include nonlinear uptake mechanisms. The goal of the sensitivity analysis is to determine the transport parameters that have the greatest impact on brain drug penetration. Therapeutic delivery to neural tissue is greatly affected by BBB permeability, affinity of transporters, and cerebral blood flow. Researchers can use these results to fine-tune the treatment for Alzheimer's disease, Parkinson's disease, epilepsy, and brain tumors. Stability analysis guarantees a therapeutic compound maintains a steady and regulated level inside the central nervous system, without leading to neurotoxicity. These applications can help advance the development of more efficient neurological drug delivery systems.

4.8 Immunotherapy and Biologics

Today's immunotherapies, such as monoclonal antibodies and immune checkpoint inhibitors, frequently include saturation and receptor internalization phenomena within the cell. These complex biological interactions can be understood in a realistic manner using PBPK models incorporating nonlinear uptake kinetics. Sensitivity analysis is used to determine key factors that influence the efficiency of the immune response: receptor occupancy, antibody affinity, and immune cell distribution. Stability analysis assesses if the immune activation is kept in check or if it is triggered and amplified too strongly, potentially causing immune-related adverse events. Such applications can be highly beneficial in optimizing biologic therapies for autoimmune disorders, inflammatory disorders, and cancer immunotherapy.

4.9 Clinical Dose Optimization

Many clinicians are also interested in sensitivity and stability analyses. Due to saturable uptake mechanisms, concentration-time relationships often change with varying doses of drugs, especially when it comes to drug response. PBPK models can be used to guide clinicians in the prediction of dose-response relationships for changes in dosage that will affect tissue exposure and therapeutic efficacy. Sensitivity analysis shows identification of the most influential dosing parameters, and stability analysis shows safe therapeutic ranges to avoid instability-induced toxicity. This is particularly useful for medicines with a narrow therapeutic index, which have significant side effects that can occur at very close doses. The clinical dose optimization based on PBPK analysis increases the safe use of medicines, improves therapeutic efficacy, and decreases hospitalization due to adverse drug reactions.

5. Discussion

This study looks at the sensitivity and stability features of a Physiologically Based Pharmacokinetic (PBPK) model with saturable cellular uptake mechanisms. This research shows that nonlinear interaction with cell membrane transport/receptor-mediated effects dramatically changes the pharmacokinetic profile compared to linear PBPK models. The model can capture the biological reality of the transport of targeted drugs to nanoparticles and receptor-mediated transport of nanoparticles and targeted drugs across cell membranes and intracellular accumulation. The numerical simulations also show rapid accumulation of drugs/transmitters in tissues due to rapid receptor-mediated transport. Increased intracellular concentration resulted in nonlinear (receptor-mediated) intracellular accumulation. This is consistent with biological transport, where proteins/receptors have limited transport capacity. Saturation effects of transport indicate that linear transport assumptions fail at intermediate or higher dose ranges. It is then important to consider PBPK models with saturable transport mechanisms to improve the accuracy of predictions of the distribution of drugs and extent of therapeutic interactions.

The most important finding of this research is the effect of the maximum transport rate ($V_{\max}$) on drug concentrations in the tissues. Sensitivity analysis showed that small changes in transport capacity resulted in large changes in the maximum intracellular concentration. Increased $V_{\max}$ results in improved uptake and prolonged clearance of the

drug from the target compartment. This research has important implications for the design of cancer therapeutics and nanoparticle drug delivery systems, as the effectiveness of these systems is dependent on the extent of the overexpressed receptors on the cancer cells. The results show that agents that target overexpressed receptors on the cancer cells will have improved therapeutics. The analysis of the stability of the nonlinear PBPK system offers further insight into the dynamics of the system. From the eigenvalues, equilibrium is achieved where drug input and output are balanced. Negative eigenvalues are indicative of stability in the systems of pharmacokinetics, whereby the concentration of tissue is controlled by physiologic means. On the other hand, positive eigenvalues suggest that there are excessive uptake and inadequate elimination, thus resulting in unstable accumulation of tissue concentration. This may lead to the retention of drugs in sensitive tissues such as the liver, kidneys, and perhaps the tumor microenvironment.

The results put forth here will guide clinicians to optimize drug doses for a given therapy. The analysis of drug doses and the corresponding tissue concentration shows that once a receptor is fully saturated, additional doses do not lead to a proportional increase in tissue concentration. There is a risk of toxicity and adverse effects if the doses are increased. This underscores the importance of an optimal therapeutic range. PBPK models with limited uptake mechanisms help derive the maximum amounts of drug safely.

The results of this research show that sensitivity analysis is a valid approach to identify and rank the most important components of physiology among others that drive the pharmacokinetic response. These components belong to receptor-mediated transport, the supply of tissues with blood, and the elimination process, among others. In personalized medicine, the variation among patients in the ways receptors are expressed, the metabolism rate of an individual, and the perfusion of different organs can greatly influence the pharmacokinetic response of the drug. Therefore, it is possible to improve the quality of personalized medicine and design the best treatment plan for the patient. The results of the study also advance targeted drug delivery systems and immunotherapy. The nonlinear paradigm of monoclonal antibodies and receptor-targeted biologics of this model also helps in understanding and predicting drug responses in the treatment of patients. Artificial intelligence, multiscale and systems biology, combined with PBPK, can advance the modeling of nonlinear pharmacokinetics. It can integrate, in real-time, genomic, proteomic, and clinical data. The research concludes that saturable cellular uptake mechanisms are essential to a biological system's pharmacokinetic behavior. The results of sensitivity and stability analyses of nonlinear dynamics of drug transport help us understand and model drug transport. Ultimately, the PBPK model is an excellent fit for cancer treatment and the prediction of toxicity in medicine and nanomedicine through innovation.

6. Conclusion

This research details a thorough analysis of the sensitivity and stability of a PBPK model (involving saturable uptake mechanisms) based on nonlinear dynamics. The model successfully captures how biological systems transport drugs when there are mediated or facilitated saturation processes. When PBPK modeling incorporates Michaelis-Menten kinetics, it can simulate processes such as intracellular drug accumulation, drug distribution to the tissues, and drug elimination more realistically, as compared to traditional linear pharmacokinetic modeling. From the mathematical and numerical perspectives, drug transport within the tissues mediated by saturable uptake has a striking impact on the pharmacokinetic behavior of the PBPK model for a wide range of doses or physiological parameters that are subject to change. The results indicate that most tissues experience a rapid increase in drug concentration and then a gradual approach to a saturation level of receptor-mediated transport. This illustrates the importance of saturation in PBPK modeling for effective drug delivery. Sensitivity analysis indicated that receptor-mediated tissue blood flow, the Michaelis constant, the elimination constant, and $V_{\max}$ are the most significant PBPK model parameters in determining the equilibrium and concentration of drug in the tissues. Of those parameters, the most significant impact on tissue drug concentration and equilibrium was found to be receptor-mediated tissue blood flow, whereas the greatest impact on pharmacokinetic equilibrium and stability was found to be the elimination collaborative processes. The results of this analysis indicated that minor changes in receptor-mediated processes or uptake systems can shift the balance toward a different clinical outcome of therapeutic benefit.

The balance between uptake and elimination mechanisms is shown to maintain asymptotic stability of equilibrium states in the context of stability analysis. However, when saturable uptake mechanisms exceed elimination, tissue build-up can become potentially harmful due to increased toxicity. It is necessary to manage dosing within bounds in order to balance transport mechanisms within physiology during therapeutic use. Beyond the saturation thresholds, the simulations show that the benefit of intracellular uptake with increasing intravenous dosage is limited, and impairment of transport efficiency may even increase the risk of unintended exposure. Consequently, receptor-targeted therapies, treatments using drug delivery systems and drug-laden nanoparticles, as well as biologically engineered solutions, must be based on proper dosing. With a growing focus on therapeutic systems, nonlinear PBPK models modified to include mechanisms of limited cellular uptake build understanding of drug distribution, tissue exposure, and therapeutic systems, as well as balance considerations of targeted drug delivery, advanced nanomedicine, immunotherapy, and personalized medicine.

7. Recommendations

The study suggests several directions for future research and biomedicine applications:

1. Future studies that use a PBPK approach should incorporate heterogeneity in modeling tissues and the tumor microenvironment, as close to the “real world” as possible. At the very least, some level of local modeling might be required to capture the different localized behaviors of drug transport.
2. Other studies should make use of real-world, in vivo, and clinical datasets for validation and better estimation of model parameters.
3. The use of cutting-edge computation and PBPK modeling will make real-time adjustments of therapeutics possible if the predictive ability of the model is adequate.
4. Future modeling attempts should integrate dynamic receptor recycling and fully expressed intracellular signaling and immune disturbance of the system, as well as the ecosystems’ many and varied responses.
5. The field of personalized medicine should utilize the modeling of real-world data streams that contain information on patient physiology and genomics, in order to create more accurate dosimetry and to minimize the instances of negative health outcomes resulting from the treatment.
6. The PBPK modeling used in the design of particle-based therapeutics should optimize nanoparticles’ size, the density of ligands, and the chemistry of the nanocarriers.
7. At the earliest possible stages of drug development, scientists should evaluate the use of nonlinear PBPK modeling in order to gauge absorption, toxicity, and the therapeutic index before a drug is tested in human trials.
8. In order to save a patient from experiencing the negative health outcomes of an unintentional overdose, future modeling attempts should consider crossing saturation thresholds.
9. The modeling of PBPK approaches should attempt to integrate more than one drug and the mechanisms of drug-to-drug interactions.

Stability analysis must continue to be included as a key component of pharmacokinetic modeling. It is a significant contributor to the understanding of safe therapeutic operating regions and helps elucidate the long-term behavior of the organism.

8. References

- Abdollahi, H., Fele-Paranj, A., & Rahmim, A. (2024). Model-informed radiopharmaceutical therapy optimization: a study on the impact of PBPK model parameters on physical, biological, and statistical measures in ^{177}Lu -PSMA therapy. *Cancers*, 16(18), 3120.
- Ahmed Mohamed, D. (2024). *PBPK Modelling for the Prediction of Iron Oxide Nanoparticle Systemic and Intratumoural Distribution in Prostate and Pancreatic Cancers—Towards their Application in Hyperthermia Treatment* University of Liverpool].
- Bhat, K. (2025). Formulation Strategy of BCS-II Drugs by Coupling Mechanistic In-Vitro and Nonclinical In-Vivo Data with PBPK: Fundamentals of Absorption-Dissolution to Parameterization of Modelling and Simulation. *Aaps Pharmscitech*, 26, 106.
- Cao, X., Li, K., Wang, J., Xie, X., & Sun, L. (2025). PBPK model of pegylated liposomal doxorubicin to simultaneously predict the concentration–time profile of encapsulated and free doxorubicin in tissues. *Drug Delivery and Translational Research*, 15(4), 1342–1362.
- Chen, X., & Lin, Z. (2025). Mechanistic modeling of size and surface charge changes of gold and silver nanoparticles during in vitro nanoparticle protein corona formation. *ACS Pharmacology & Translational Science*, 8(7), 2290–2307.
- Han, D.-G., Kwak, J., Choi, E., Seo, S.-W., Vasileva, E. A., Mishchenko, N. P., Fedoreyev, S. A., Stonik, V. A., Kim, H. K., & Han, J. (2023). Physicochemical characterization and phase II metabolic profiling of echinochrome A, a bioactive constituent from sea urchin, and its physiologically based pharmacokinetic modeling in rats and humans. *Biomedicine & Pharmacotherapy*, 162, 114589.
- Jones, H., Chen, Y., Gibson, C., Heimbach, T., Parrott, N., Peters, S., Snoeys, J., Upreti, V., Zheng, M., & Hall, S. (2015). Physiologically based pharmacokinetic modeling in drug discovery and development: a pharmaceutical industry perspective. *Clinical Pharmacology & Therapeutics*, 97(3), 247–262.
- Laisney, M., Heimbach, T., Mueller-Zsigmondy, M., Blumenstein, L., Costa, R., & Ji, Y. (2022). Physiologically based biopharmaceutics modeling to demonstrate virtual bioequivalence and bioequivalence safe-space for ribociclib which

- has permeation rate-controlled absorption. *Journal of pharmaceutical sciences*, 111(1), 274-284.
- Lin, L. (2022). *An oral physiologically-based pharmacokinetic model to predict drug absorption and disposition of vismodegib* [University of British Columbia].
- Lin, Z., Aryal, S., Cheng, Y.-H., & Gesquiere, A. J. (2022). Integration of in vitro and in vivo models to predict cellular and tissue dosimetry of nanomaterials using physiologically based pharmacokinetic modeling. *ACS nano*, 16(12), 19722-19754.
- Lumen, A., Zhang, X., Dutta, S., & Upreti, V. V. (2024). Predicting Clinical Pharmacokinetics/Pharmacodynamics and Impact of Organ Impairment on siRNA-Based Therapeutics Using a Mechanistic Physiologically-Based Pharmacokinetic-Pharmacodynamic Model. *Clinical Pharmacology & Therapeutics*, 115(5), 1054-1064.
- Ma, S., & Wang, W.-X. (2023). Physiological trade-off of marine fish under Zn deficient and excess conditions. *Science of the Total Environment*, 901, 166187.
- Ma, S., & Wang, W.-X. (2024). Significance of zinc re-absorption in Zn dynamic regulation in marine fish revealed by pharmacokinetic model. *Environmental Pollution*, 363, 125106.
- Mathew, B. (2024). Mechanistic PK/PD modeling of novel therapeutic.
- Miyazawa, K., Liu, Y., & Bazzazi, H. (2024). Development of a minimal PBPK-QSP modeling platform for LNP-mRNA based therapeutics to study tissue disposition and protein expression dynamics. *Frontiers in Nanotechnology*, 6, 1330406.
- Okumura, H., Araragi, Y., Nishioka, K., Yamashita, R., Suzuki, T., Watanabe, H., Kato, Y., & Murayama, N. (2025). Estimation and validation of an effective ergothioneine dose for improved sleep quality using physiologically based pharmacokinetic model. *Food Science & Nutrition*, 13(6), e70382.
- Ozbek, O., Genc, D. E., & O. Ulgen, K. (2024). Advances in physiologically based pharmacokinetic (PBPK) modeling of nanomaterials. *ACS Pharmacology & Translational Science*, 7(8), 2251-2279.
- Padilha, E. C., Yang, M., Shah, P., Wang, A. Q., Duan, J., Park, J. K., Zawatsky, C. N., Malicdan, M. C. V., Kunos, G., & Iyer, M. R. (2023). In vitro and in vivo pharmacokinetic characterization, chiral conversion and PBPK scaling towards human PK simulation of S-MRI-1867, a drug candidate for Hermansky-Pudlak syndrome pulmonary fibrosis. *Biomedicine & Pharmacotherapy*, 168, 115178.
- Pepin, X., Arora, S., Borges, L., Cano-Vega, M., Carducci, T., Chatterjee, P., Chen, G., Cristofolletti, R., Dallmann, A., & Delvadia, P. (2024). Parameterization of physiologically based biopharmaceutics models: workshop summary report. *Molecular pharmaceutics*, 21(8), 3697-3731.
- Ramisetty, B. S., Yang, S., Dorlo, T. P., & Wang, M. Z. (2024). Determining tissue distribution of the oral antileishmanial agent miltefosine: a physiologically-based pharmacokinetic modeling approach. *Antimicrobial Agents and Chemotherapy*, 68(7), e00328-00324.
- Scotcher, D., Melillo, N., Tadimalla, S., Darwich, A. S., Ziemian, S., Ogungbenro, K., Schütz, G., Sourbron, S., & Galetin, A. (2021). Physiologically based pharmacokinetic modeling of transporter-mediated hepatic disposition of imaging biomarker gadoxetate in rats. *Molecular pharmaceutics*, 18(8), 2997-3009.
- Stader, F., Liu, C., Derbalah, A., Momiji, H., Pan, X., Gardner, I., Jamei, M., & Sepp, A. (2024). A physiologically based pharmacokinetic model relates the subcutaneous bioavailability of monoclonal antibodies to the saturation of FcRn-mediated recycling in injection-site-draining lymph nodes. *Antibodies*, 13(3), 70.
- Talkington, A. M., Cao, Y., Kearsley, A. J., & Lai, S. K. (2025). Opportunities for machine learning and artificial intelligence in physiologically-based pharmacokinetic (PBPK) modeling. *Advanced drug delivery reviews*, 115716.
- Tran, T. P., Tran, N. P., & Park, J.-S. (2025). Pharmacokinetic modeling in drug delivery system. *Journal of Pharmaceutical Investigation*, 1-23.
- Zhang, M., Almond, L. M., & Jones, H. M. (2025). Physiologically Based Pharmacokinetic Modelling of Vitamin B12 Incorporating Mechanistic Absorption: An Example Application for Intake Estimation During Pregnancy. *The Journal of Nutrition*.
- Zunino, C., Wang, S., Zhang, Y., Urdy, S., de Witte, W. E., Declèves, X., Puszkiel, A., & Djebli, N. (2025). Prediction of a CLDN18. 2 targeted antibody drug conjugate pharmacokinetics in cancer patients using PBPK modeling and simulation. *CPT: Pharmacometrics & Systems Pharmacology*, 14(9), 1494-1503.