

AI AUGUMENTED PBPK MODELLING: TRANSFORMING PHARMACOKINETIC PREDICTION AND DRUG DEVELOPMENT

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ABSTRACT

Physiologically based pharmacokinetic (PBPK) modeling is widely used to predict drug absorption, distribution, metabolism, and excretion using mechanistic representations of human physiology. PBPK models support informed decision-making in drug development, regulatory evaluation, and risk assessment; however, their application is often limited by extensive data requirements, parameter uncertainty, and challenges in estimating drug-specific inputs, particularly at early stages of development. Artificial intelligence (AI) and machine learning (ML) have recently emerged as valuable complementary tools that can address these limitations. By learning complex, non-linear relationships from molecular descriptors, in vitro data, and simulation outputs, AI-based models enable rapid prediction of key pharmacokinetic parameters. The integration of AI with PBPK modeling has led to hybrid AI-PBPK frameworks that combine the physiological interpretability of mechanistic models with the predictive efficiency and scalability of data-driven approaches. This review provides an overview of AI-driven approaches in PBPK modeling, covering fundamental PBPK principles, commonly used AI and ML techniques, and strategies for integrating machine learning outputs into PBPK simulations. Key applications in drug development, including pharmacokinetic prediction, drug-drug interaction assessment, formulation optimization, and special population analysis, are discussed. The review also highlights current challenges related to data quality, model interpretability, and regulatory acceptance, and outlines future perspectives for advancing AI-assisted PBPK modeling.

KEYWORDS: Artificial intelligence; machine learning; physiologically based pharmacokinetic modeling; hybrid AI-PBPK frameworks; pharmacokinetic parameter prediction; *In vitro*-in vivo extrapolation (IVIVE); toxicokinetic modeling; special population pharmacokinetics.

INTRODUCTION

Understanding the pharmacokinetic behaviour of drugs within the human body is a central objective of pharmaceutical research, as it directly influences drug efficacy, safety, and therapeutic outcomes. Drug absorption, distribution, metabolism, and excretion (ADME) are governed by complex and interrelated physiological and biochemical processes that vary across individuals and disease states. Conventional pharmacokinetic approaches, including non-compartmental and compartmental modeling, have been widely used to describe drug concentration–time profiles; however, these methods are largely empirical and often lack physiological interpretability. As a result, their predictive capability is limited when extrapolating across species, dosage regimens, routes of administration, or special populations.^[1,11]

Physiologically based pharmacokinetic (PBPK) modeling has emerged as a mechanistic alternative that overcomes many of these limitations. PBPK models represent the body as a series of anatomically and physiologically realistic compartments connected by blood flow, enabling simulation of drug disposition in individual organs and tissues [11,13]. These models integrate system-specific parameters, such as organ volumes and blood flow rates, with drug-specific properties, including solubility, lipophilicity, and metabolic clearance. Because of this mechanistic foundation, PBPK modeling allows rational extrapolation from preclinical data to humans and has become an important tool in drug development, clinical pharmacology, and regulatory decision-making.^[7,11]

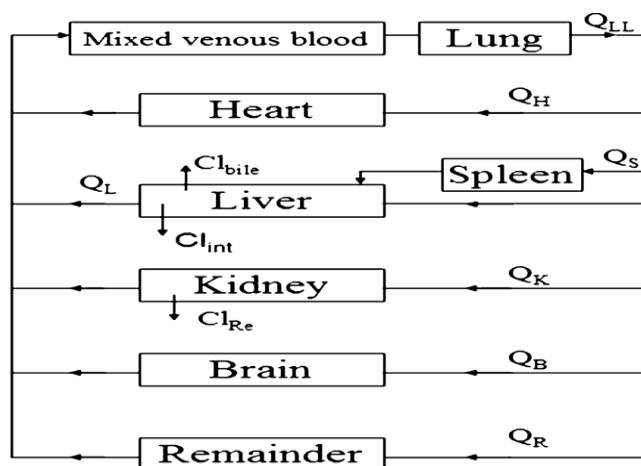


Fig. 01: Schematic representation of a PBPK model.

Over the past decade, PBPK modeling has gained increasing acceptance by regulatory agencies for applications such as dose selection, prediction of drug-drug interactions (DDIs), evaluation of special populations, and risk assessment of chemicals.^[7,8] Nevertheless, the development and implementation of PBPK models remain challenging. Reliable PBPK simulations require a large number of input parameters, many of which are difficult to measure experimentally, particularly during early stages of drug discovery. Uncertainty in parameter estimation, data gaps, and model identifiability issues can affect predictive performance and limit the routine application of PBPK approaches.^[1,5]

In parallel with advances in PBPK modeling, artificial intelligence (AI) and machine learning (ML) techniques have rapidly evolved and are increasingly being applied across pharmaceutical sciences. ML algorithms are particularly well suited for analyzing complex, high-dimensional datasets and identifying non-linear relationships that are difficult to capture using traditional statistical methods. In pharmacokinetics, ML and deep learning models have been successfully

employed to predict key parameters such as clearance, volume of distribution, bioavailability, and half-life directly from molecular structure and in vitro data.^[10,14] These developments have created new opportunities to accelerate drug development by reducing experimental burden and enabling earlier pharmacokinetic assessment.

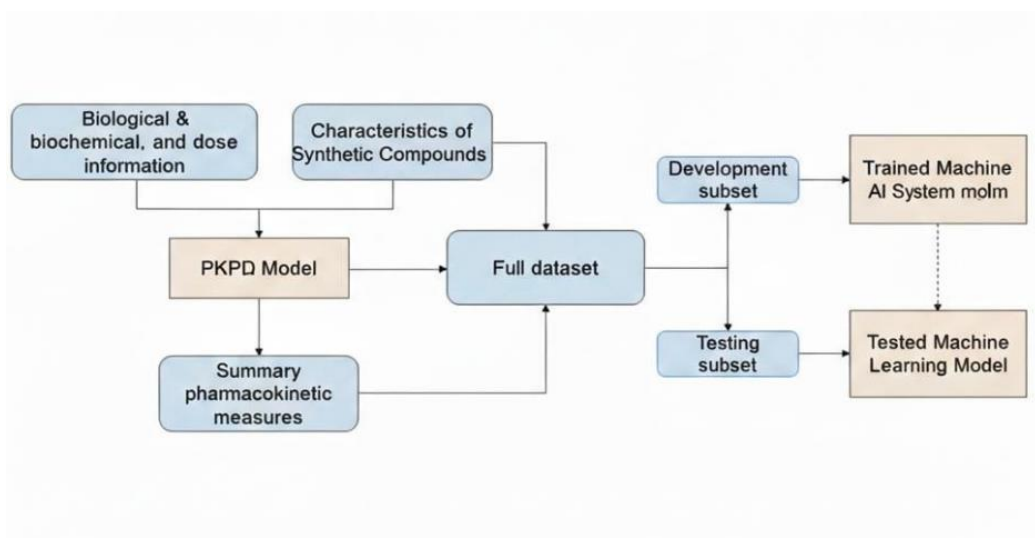


Fig. 02: AI and machine learning techniques used in pharmacokinetics.

The integration of AI and ML with PBPK modeling represents a natural and promising progression in pharmacokinetic science. Rather than replacing mechanistic PBPK models, AI-driven approaches can complement them by providing rapid and data-driven predictions of drug-specific parameters required for PBPK simulations.^[1,5] For example, ML models have been used to estimate tissue partition coefficients, intrinsic clearance, permeability, and protein binding, which can then be incorporated into PBPK frameworks to simulate systemic exposure.^[24,25] This hybrid modeling paradigm combines the interpretability of PBPK models with the predictive efficiency of AI, enabling more robust and scalable pharmacokinetic predictions.

Recent studies have demonstrated the value of AI-assisted PBPK modeling across a range of applications. In drug development, hybrid ML–PBPK models have shown improved performance in predicting human pharmacokinetics and DDIs compared with standalone approaches.^[3,6] In addition, AI-enhanced PBPK frameworks have been applied to pharmacodynamic prediction, formulation optimization, and assessment of nanoparticle and advanced drug delivery systems, where traditional modeling approaches may be insufficient.^[4,6] These advances highlight the flexibility of AI-driven PBPK modeling in addressing emerging challenges in modern therapeutics.

Beyond pharmaceutical applications, AI-PBPK integration has gained importance in toxicology and human health risk assessment. PBPK models are widely used to support in vitro–in vivo extrapolation (IVIVE) and chemical safety evaluation; however, parameter uncertainty and limited experimental data often restrict their applicability. Machine learning techniques can support high-throughput toxicokinetic screening and improve parameter estimation, thereby enhancing the reliability of PBPK-based risk assessments.^[34,35] Such approaches are particularly relevant for environmental chemicals and industrial compounds, where experimental human data are scarce.^[21,22]

Despite its growing promise, the integration of AI into PBPK modeling presents several challenges. Data quality, standardization, and representativeness remain critical concerns, as ML models are highly dependent on the datasets

used for training.^[9,20] Moreover, many advanced ML and deep learning models function as “black boxes,” raising concerns regarding interpretability and transparency, especially in regulatory contexts where mechanistic understanding is essential.^[32] Ensuring biological plausibility, robust validation, and generalizability of AI-assisted PBPK models is therefore crucial for their broader acceptance and implementation.

The rapid expansion of research at the interface of AI, ML, and PBPK modeling, there is a clear need for comprehensive reviews that synthesize current methodologies, applications, and limitations. A structured overview of AI-driven approaches in PBPK modeling can help researchers and practitioners understand how data-driven methods are reshaping pharmacokinetic modeling while preserving mechanistic integrity. Such reviews also provide guidance on best practices and highlight future research directions needed to support responsible and effective adoption of AI in PBPK frameworks.^[1,5]

In this context, the present review provides an overview of AI-driven approaches in PBPK modeling, focusing on fundamental PBPK principles, commonly used AI and ML techniques, strategies for integrating data-driven models with mechanistic frameworks, and key applications in drug development, toxicology, and regulatory science. The review further discusses current challenges and future perspectives, emphasizing the importance of interpretability, data integration, and interdisciplinary collaboration to advance PBPK modeling in the era of artificial intelligence.

FUNDAMENTALS OF PHARMACOKINETICS:

Pharmacokinetics describes how a drug moves through the human body over time and provides a quantitative understanding of drug exposure following administration. It focuses on four key processes-absorption, distribution, metabolism, and excretion (ADME) which together determine the concentration of a drug at its site of action and its duration of effect. A clear understanding of pharmacokinetic principles is essential for optimizing dosage regimens, ensuring therapeutic efficacy, and minimizing adverse effects in clinical practice.^[11,27]

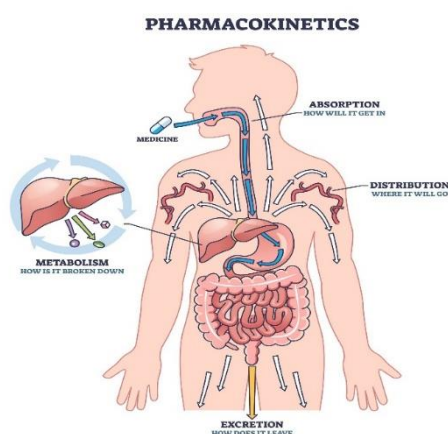


Fig 03: Fundamental processes of pharmacokinetics (ADME).

Absorption

Absorption refers to the process by which a drug enters the systemic circulation from its site of administration. The extent and rate of absorption depend on factors such as drug solubility, permeability, formulation characteristics, and physiological conditions at the absorption site. For orally administered drugs, gastrointestinal transit time, pH, enzymatic activity, and transporter expression play important roles in determining bioavailability. Variability in these

factors can lead to significant differences in drug exposure among individuals.^[13,27] Understanding absorption mechanisms is therefore critical for predicting oral bioavailability and optimizing formulation strategies.

Distribution

Once absorbed, a drug distributes from the bloodstream into various tissues and organs. Drug distribution is influenced by tissue blood flow, membrane permeability, plasma protein binding, and tissue composition. Lipophilic drugs tend to accumulate in fatty tissues, whereas hydrophilic compounds are often confined to extracellular fluids. The apparent volume of distribution is a key pharmacokinetic parameter that reflects the extent to which a drug partitions between plasma and tissues. Mechanistic understanding of tissue distribution is particularly important for predicting drug concentrations at target sites and avoiding accumulation in non-target organs.^[30,31]

Metabolism

Drug metabolism involves enzymatic biotransformation processes that convert parent compounds into metabolites, often facilitating elimination. The liver is the primary site of drug metabolism, with cytochrome P450 enzymes playing a central role in oxidative reactions. However, metabolism can also occur in other organs, including the intestine, kidneys, and lungs. Metabolic clearance is a major determinant of systemic drug exposure and is subject to variability due to genetic polymorphisms, disease states, and drug–drug interactions. Accurate characterization of metabolic pathways is therefore essential for predicting pharmacokinetic behaviour and ensuring safe drug use.^[7,15]

Excretion

Excretion is the process by which drugs and their metabolites are removed from the body, primarily through renal and biliary pathways. Renal excretion involves glomerular filtration, active tubular secretion, and passive reabsorption, while biliary excretion contributes to faecal elimination. The overall rate of drug elimination is commonly described by clearance, a fundamental pharmacokinetic parameter that integrates metabolic and excretory processes. Clearance directly influences drug half-life and dosing frequency, making it a critical factor in dosage regimen design.^[11,27]

Key Pharmacokinetic Parameters

Several quantitative parameters are used to describe pharmacokinetic behaviour, including clearance, volume of distribution, bioavailability, and half-life. These parameters provide a simplified yet informative summary of complex physiological processes. While traditional pharmacokinetic models estimate these parameters empirically from concentration–time data, their interpretation often lacks direct physiological meaning. This limitation has motivated the development of mechanistic modeling approaches, such as physiologically based pharmacokinetic models, which link pharmacokinetic parameters to underlying biological processes.^[11,16]

PRINCIPLES OF PBPK Modelling:

Physiologically based pharmacokinetic (PBPK) modeling is a mechanistic approach used to describe and predict the time-dependent distribution of drugs within the human body by explicitly incorporating physiological structure and biological processes. Unlike traditional compartmental pharmacokinetic models, which rely on empirical fitting of concentration–time data, PBPK models are constructed using realistic representations of human anatomy and physiology. This mechanistic nature enables PBPK models to provide biologically meaningful predictions across different populations, dosing regimens, and clinical scenarios.^[11,13]

Physiological Representation of the Human Body

At the core of PBPK modeling is the division of the body into individual compartments that correspond to real organs and tissues, such as the liver, kidneys, lungs, gastrointestinal tract, brain, muscle, and adipose tissue. Each compartment is characterized by physiological parameters including tissue volume, blood flow rate, and tissue composition. These compartments are interconnected through systemic circulation, allowing drugs to move dynamically between organs in a manner that reflects human physiology.^[11,30] This structural framework forms the foundation for simulating drug disposition at both systemic and organ-specific levels.

Integration of Drug Specific Properties

PBPK models integrate drug-specific physicochemical and biochemical properties to describe how a compound behaves within the physiological system. Key properties include molecular weight, lipophilicity, solubility, ionization characteristics, plasma protein binding, and intrinsic metabolic clearance. These parameters determine tissue partitioning, permeability, and elimination processes. By explicitly linking drug characteristics to physiological compartments, PBPK models provide mechanistic insight into how formulation changes or molecular modifications can influence pharmacokinetic outcomes.^[13,31]

Modeling of Absorption Processes

Drug absorption in PBPK modeling is represented using mechanistic descriptions of drug entry into systemic circulation based on the route of administration. For oral drugs, PBPK models account for gastrointestinal transit, dissolution, intestinal permeability, first-pass metabolism, and transporter-mediated processes. These factors collectively determine the rate and extent of drug absorption. Such mechanistic absorption models enable prediction of bioavailability and allow evaluation of formulation effects, food interactions, and interindividual variability.^[7,13]

Distribution and Tissue Partitioning

Drug distribution within PBPK models is governed primarily by tissue blood flow and tissue-to-plasma partition coefficients. Partitioning reflects the affinity of a drug for different tissues and is influenced by tissue composition and drug lipophilicity. Mechanistic equations are used to describe perfusion-limited or permeability-limited distribution, depending on the physicochemical properties of the drug. This detailed representation enables PBPK models to predict tissue-specific concentrations, which are critical for understanding efficacy and toxicity.^[30,31]

Metabolism and Elimination Mechanisms

PBPK models explicitly incorporate metabolic and excretory pathways to describe drug elimination. Hepatic metabolism is commonly modeled using enzyme-specific clearance parameters, particularly for cytochrome P450-mediated reactions. Renal elimination is described through processes such as glomerular filtration, active secretion, and tubular reabsorption. By integrating these mechanisms, PBPK models can simulate changes in drug exposure due to enzyme inhibition, induction, organ impairment, or drug–drug interactions.^[7,8]

Population Variability and Special Populations

One of the major strengths of PBPK modeling is its ability to account for physiological variability across populations. Age-related changes, disease conditions, genetic polymorphisms, and differences in body composition can be incorporated by modifying system-specific parameters. This feature allows PBPK models to predict pharmacokinetics

in special populations such as paediatrics, geriatrics, pregnant women, and patients with hepatic or renal impairment, often in situations where clinical data are limited or unavailable.^[7,11]

Predictive and Translational Capability

Because PBPK models are grounded in biological mechanisms, they support extrapolation across species, doses, and exposure scenarios. This makes PBPK modeling particularly valuable for translating preclinical data to humans and for predicting outcomes under untested conditions. Regulatory agencies increasingly recognize PBPK models as reliable tools for supporting clinical pharmacology decisions, including dose justification, labelling recommendations, and drug-drug interaction risk assessment.^[8,10]

LIMITATIONS & CHALLENGES OF TRADITIONAL PBPK MODELLING

Physiologically based pharmacokinetic (PBPK) modeling has become an important tool in modern drug development and regulatory science due to its mechanistic foundation and predictive capability. However, despite its advantages, traditional PBPK modeling approaches are associated with several limitations that can restrict their applicability, particularly during early drug discovery and in data-limited scenarios. Recognizing these challenges is essential for understanding the motivation behind the integration of artificial intelligence and machine learning techniques with PBPK frameworks.^[1,11]

1. Extensive Data Requirements

PBPK models require extensive physiological and drug-specific inputs such as tissue partitioning, clearance, permeability, and protein binding. These data are often unavailable in early development, leading to reliance on assumptions or literature values and increased uncertainty.^[11,13]

2. Parameter Uncertainty and Identifiability Issues

The large number of model parameters can result in identifiability issues, where different parameter sets produce similar outcomes, reducing confidence in biological accuracy and extrapolation.^[5,9]

3. Time Consuming Model Development

Model building, calibration, and validation are labour-intensive and require specialized expertise, limiting routine use when rapid decision-making or compound screening is needed.^[1,9]

4. Limited Predictive Performance in Early Development

PBPK performance may be reduced during early drug discovery due to sparse experimental data, making early compound prioritization challenging.^[1,11]

5. Challenges in Capturing Biological Complexity

Conventional PBPK models may inadequately capture complex processes such as transporter effects, non-linear kinetics, disease-related changes, and formulation-dependent absorption.^[7,13]

6. Variability and Population Specific Limitations

Accurately representing interindividual differences arising from genetics, disease states, or environmental factors remains difficult, particularly when population-specific data are limited.^[7,11]

7. Regulatory and Practical Constraints

Model complexity, transparency issues, and limited standardization across platforms can complicate regulatory review and broader acceptance of PBPK outputs.^[8,10]

INTRODUCTION TO ARTIFICIAL INTELLIGENCE & MACHINE LEARNING:

Artificial intelligence (AI) and machine learning (ML) have emerged as transformative technologies across many scientific disciplines, including pharmaceutical sciences. These approaches enable computers to analyse large volumes of data, recognize patterns, and make predictions or decisions with minimal human intervention. In pharmaceutical research, where experimental processes are often complex, time-consuming, and resource-intensive, AI and ML offer efficient, data-driven solutions to support drug discovery, development, and evaluation.^[9,15]

Artificial intelligence refers to the broad field of computer science focused on developing systems capable of performing tasks that normally require human intelligence, such as learning, reasoning, pattern recognition, and problem solving. AI systems are designed to adapt to new information and improve their performance over time, making them suitable for complex scientific applications.^[15]

Machine learning is a key subset of AI that emphasizes algorithms capable of learning relationships directly from data rather than relying on predefined rules. In ML, models are trained using experimental or simulated datasets to identify links between input variables and outcomes. Once trained, these models can make predictions for new data, making ML particularly useful for pharmaceutical applications involving large and high-dimensional datasets.^[9,14]

Types of Machine Learning

1. Supervised Learning

Supervised learning involves training machine learning models using labelled datasets, where both input variables and known outcomes are provided. The algorithm learns the relationship between inputs and outputs, allowing it to predict outcomes for new data. In pharmaceutical sciences, supervised learning is widely used to predict properties such as drug solubility, pharmacokinetic parameters, toxicity, and bioavailability based on molecular descriptors or experimental measurements.

2. Unsupervised Learning

Unsupervised learning deals with unlabelled data, where the algorithm identifies hidden patterns or structures without predefined outcomes. These methods are useful for grouping similar compounds, identifying data trends, or reducing dimensionality in complex datasets. In pharmaceutical research, unsupervised learning supports tasks such as chemical space exploration, patient stratification, and identification of novel drug candidates with similar characteristics.

3. Deep Learning

Deep learning is an advanced subset of machine learning that uses multi-layered neural networks to model highly complex and non-linear relationships. These models are particularly effective when working with large datasets, such as molecular structures, biological images, or omics data. In pharmaceutical sciences, deep learning has shown strong potential in applications including structure activity relationship prediction, pharmacokinetic modeling, image-based analysis, and virtual screening

AI and ML have become increasingly relevant across the pharmaceutical development pipeline. In early drug discovery, these techniques enable rapid screening of large compound libraries and prediction of drug-like properties prior to experimental validation. In formulation development and manufacturing, AI supports optimization of excipient selection, process parameters, and quality attributes.^[9,24]

In pharmacokinetics and pharmacodynamics, AI-based models assist in predicting key parameters and complement mechanistic approaches such as physiologically based pharmacokinetic (PBPK) modeling. AI-driven methods are also increasingly applied in toxicology, risk assessment, and regulatory science to support in vitro–in vivo extrapolation and safety evaluation.^[1,5,19] Overall, the integration of AI and ML into pharmaceutical sciences promotes a more predictive, efficient, and knowledge-driven approach to drug development.^[15]

AI and ML TECHNIQUES USED IN PBPK MODELLING:

The integration of artificial intelligence (AI) and machine learning (ML) techniques into physiologically based pharmacokinetic (PBPK) modelling has significantly enhanced the ability to estimate drug-specific parameters and improve model predictability. These techniques complement mechanistic PBPK frameworks by learning complex relationships between molecular properties, experimental data, and pharmacokinetic outcomes, particularly in situations where experimental information is limited.

1. Linear and Non-Linear Regression

Linear and non-linear regression methods represent some of the earliest and most widely used machine learning techniques in pharmacokinetics. These approaches are used to establish mathematical relationships between molecular descriptors or experimental inputs and pharmacokinetic parameters such as clearance and volume of distribution. While linear regression assumes simple relationships between variables, non-linear regression allows modeling of more complex biological processes. In PBPK modelling, regression techniques are often applied as baseline predictive tools or for parameter refinement due to their simplicity, transparency, and ease of interpretation.^[9,15]

2. Random Forest

Random forest is an ensemble learning method that constructs multiple decision trees and combines their predictions to improve accuracy and reduce overfitting. This technique is particularly effective in handling non-linear relationships and high-dimensional datasets commonly encountered in pharmacokinetic studies. In PBPK modelling, random forest algorithms have been used to predict tissue partition coefficients, intrinsic clearance, and other drug-specific inputs required for model construction. Their robustness and ability to rank variable importance make random forest models valuable for parameter selection and uncertainty reduction.^[14,26]

3. Support Vector Machines (SVM)

Support vector machines are supervised learning algorithms that identify optimal boundaries between data points in high-dimensional space. SVMs are well suited for pharmacokinetic prediction tasks where datasets may be relatively small but complex. In the context of PBPK modelling, SVMs have been applied to predict absorption, distribution, and metabolic parameters using molecular descriptors and in vitro data. Their strong generalization capability makes them useful for extrapolating pharmacokinetic behaviour across diverse chemical structures.^[10,14]

4. Artificial Neural Networks (ANN)

Artificial neural networks are computational models inspired by biological neural systems and are capable of learning non-linear relationships through interconnected layers of nodes. ANNs have been widely used in PBPK-related research to predict pharmacokinetic parameters such as clearance, bioavailability, and volume of distribution. Compared to traditional regression methods, ANNs can capture more complex interactions between variables, making them suitable for modelling multifactorial pharmacokinetic processes. However, their interpretability may be limited, requiring careful validation when integrated into PBPK frameworks.^[9,26]

5. Deep Learning Models

Deep learning models are advanced neural network architectures that contain multiple hidden layers, enabling them to model highly complex and non-linear relationships. These models are particularly effective when large datasets are available and have demonstrated strong performance in predicting pharmacokinetic parameters directly from molecular structure or high-dimensional descriptors. In PBPK modelling, deep learning approaches are increasingly used to enhance parameter prediction, support virtual compound screening, and improve scalability of PBPK workflows. Despite their predictive power, challenges related to data requirements and model transparency remain important considerations.^[26,32]

The application of AI and ML techniques in PBPK modelling has expanded in recent years. The Table 01 summarizes the commonly used techniques and their use in PBPK modelling.

Table 01: Artificial Intelligence and Machine Learning Techniques Used in PBPK Modelling.

Technique	Description	Use in PBPK Modelling	Main Strength	Key Limitation	Reference
Linear & Non-linear Regression	Uses mathematical equations to relate inputs and outputs	Uses multi-layer neural networks for advanced pattern learning	Easy to interpret and transparent	Limited ability to capture complex biological behaviour	[9,15]
Random Forest	Combines many decision trees to improve prediction	Predicts tissue partitioning, clearance, and permeability for PBPK models	Handles non-linear data and reduces overfitting	Interpretation of results can be challenging	[14,26]
Support Vector Machines (SVM)	Separates data using optimal boundaries in high-dimensional space	Used to predict absorption and metabolism-related parameters	Performs well with small and complex datasets	Requires careful parameter and kernel selection	[10,14]
Artificial Neural Networks (ANN)	Mimics brain-like learning through interconnected nodes	Predicts pharmacokinetic parameters for PBPK simulations	Captures complex, non-linear relationships	Limited interpretability ("black-box")	[9,26]
Deep Learning Models	Uses multi-layer neural networks for advanced pattern learning	Enables large-scale and high-accuracy PBPK parameter prediction	High predictive power for complex datasets	Needs large data and high computation	[10,26]

As shown in Table 01 each modeling approach presents its own set of strengths and constraints. Consequently, selecting an appropriate technique should be driven by the specific goals of the modelling objective, data availability, and the need for mechanistic interpretability.

INTEGRATION OF AI & ML WITH PBPK Models:

The integration of artificial intelligence (AI) and machine learning (ML) with physiologically based pharmacokinetic (PBPK) models represents a significant advancement in pharmacokinetic modeling. Traditional PBPK models are mechanistic and physiologically interpretable but often limited by extensive data requirements and parameter uncertainty. AI and ML techniques complement these models by enabling efficient, data-driven prediction of key inputs and by supporting scalable and automated model development. Together, these approaches form hybrid frameworks that combine biological realism with predictive efficiency.^[1,5]

AI Based Prediction of PBPK Input Parameters

One of the most impactful roles of AI and ML in PBPK modeling is the prediction of drug-specific input parameters required for model construction. Parameters such as intrinsic clearance, tissue-to-plasma partition coefficients, permeability, and plasma protein binding are essential for PBPK simulations but are often difficult to measure experimentally. Machine learning models trained on molecular descriptors, in vitro data, and historical datasets can predict these parameters rapidly and with reasonable accuracy [10,14,26].

By providing early estimates of PBPK inputs, AI based prediction enables PBPK models to be developed at earlier stages of drug discovery, even when experimental data are limited. This approach reduces experimental burden and supports rapid screening and prioritization of candidate compounds. Importantly, these AI-generated parameters can be refined iteratively as new experimental data become available, improving model reliability over time.^[1,5]

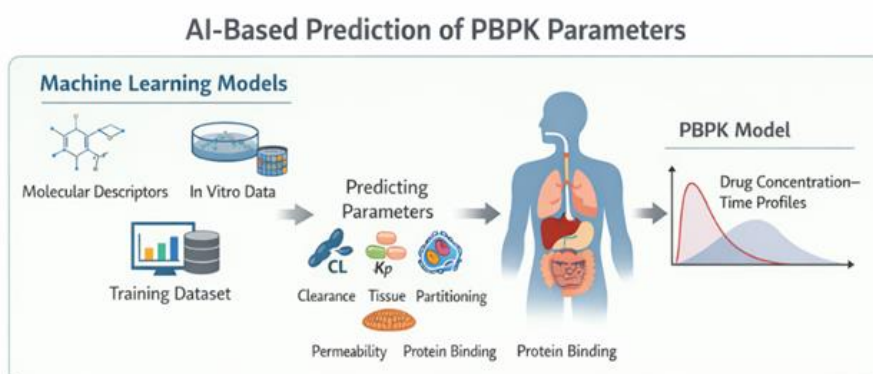


Fig 04: AI based prediction of drug specific input parameters for PBPK modeling.

Hybrid ML PBPK Frameworks

Hybrid ML PBPK frameworks combine data-driven prediction with mechanistic simulation to leverage the strengths of both approaches. In these frameworks, machine learning models are used to estimate uncertain or missing parameters, while PBPK models use these inputs to simulate drug concentration time profiles across tissues and populations. This integration preserves the physiological interpretability of PBPK models while enhancing their predictive performance and scalability.^[2,5]

Hybrid approaches have demonstrated improved accuracy in predicting human pharmacokinetics and drug-drug interactions compared with standalone ML or PBPK models. They are particularly useful for complex scenarios such as special populations, nanoparticle-based drug delivery systems, and formulation dependent absorption, where purely mechanistic or purely data-driven methods may be insufficient.^[2,4]

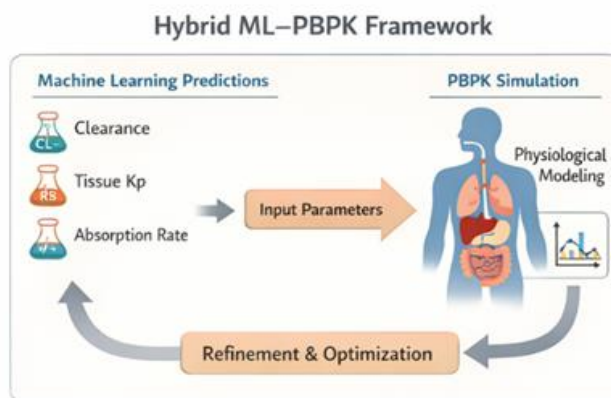


Fig. 05: Hybrid ML-PBPK modeling framework.

Workflow of AI Augmented PBPK Modelling

An AI augmented PBPK modeling workflow typically begins with the collection of molecular, physicochemical, and experimental data for a given compound. These data are used to train machine learning models that predict key pharmacokinetic parameters. The predicted parameters are then integrated into a PBPK model, which simulates systemic and tissue-specific drug exposure under various dosing and physiological conditions.^[1,5]

The outputs generated by the PBPK simulations such as concentration–time profiles or exposure metrics can be further used to refine ML models or validate predictions. This iterative feedback loop allows continuous model improvement and supports uncertainty analysis and sensitivity assessment. Such workflows enable efficient exploration of multiple scenarios, making AI-augmented PBPK modeling a powerful tool for drug development, toxicology, and regulatory decision-making.^[3,6]

PHARMACOKINETIC PARAMETER PREDICTION FOR PHARMACEUTICAL COMPOUNDS:

Physiologically based pharmacokinetic (PBPK) models play a central role in predicting the absorption, distribution, metabolism, and excretion (ADME) behaviour of pharmaceutical compounds. By integrating physiological information with drug-specific properties, PBPK models can simulate concentration–time profiles in plasma and various tissues, thereby supporting dose selection and optimization.^[1,11] In addition to system-specific physiological parameters, PBPK modeling requires several critical drug-related inputs, including absorption rate constants for extravascular administration, tissue-to-plasma partition coefficients (Kp), fraction unbound in plasma (fu), and clearance (Cl).^[11,13]

Traditionally, these parameters are obtained through in vivo animal studies, in vitro experiments, or mechanistic calculations. However, all these approaches depend heavily on compound-specific experimental data and are often time-consuming, costly, and limited during early drug development.^[11] In recent years, advances in artificial intelligence (AI) and machine learning (ML) have enabled structure-based prediction of key pharmacokinetic parameters, allowing PBPK models to be developed even in the absence of extensive experimental data. These AI-driven approaches reduce reliance on animal studies and also support toxicity assessment for newly emerging compounds. The following sections summarize progress in AI- and ML-based prediction of absorption, distribution, metabolism, and excretion parameters relevant to PBPK modelling.^[1,5]

Prediction of Absorption Parameters

Oral absorption characteristics, including bioavailability and gastrointestinal absorption rate constants, are essential inputs for PBPK modeling. Numerous quantitative structure–activity relationship (QSAR) models have been developed to predict absorption-related parameters using data from in vitro assays, such as human intestinal and epithelial cell lines, as well as in vivo studies.^[14] A wide range of ML techniques—including artificial neural networks, support vector machines, multivariate adaptive regression splines, and regression-based approaches—have been applied for this purpose.^[14,15]

Early absorption models were often based on small datasets, which limited their predictive reliability.^[15] To overcome this limitation, large curated databases of human intestinal absorption data were developed, enabling more robust classification models that could distinguish well-absorbed from poorly absorbed compounds with high accuracy.^[16,17] Subsequent studies using ensemble learning and random forest algorithms further improved predictive performance, while more recent gradient boosting approaches have demonstrated strong correlations between predicted and observed membrane permeability values.^[18,26]

Prediction of Distribution Parameters

Tissue-to-plasma partition coefficients (K_p) are critical PBPK inputs that describe the extent of drug distribution and accumulation in tissues at steady state. Experimental determination of K_p values using animal studies is costly and time-consuming, motivating the development of in silico prediction methods [30]. Mechanistic models based on tissue composition and physicochemical properties such as lipophilicity and plasma protein binding have been widely used for this purpose.^[30,31]

In parallel, ML-based approaches—including support vector machines, decision trees, and random forest models—have been developed to predict K_p values using molecular descriptors.^[21,22] More recently, hybrid ML–PBPK platforms have demonstrated that ML-predicted K_p values can improve the accuracy of simulated pharmacokinetic outputs such as area under the curve, maximum concentration, and volume of distribution compared with traditional mechanistic approaches.^[20]

Prediction of Metabolism Parameters

Drug metabolism is a key determinant of pharmacokinetic behavior and plays a central role in PBPK modeling. Metabolic processes are complex and involve multiple enzyme systems, particularly cytochrome P450 enzymes and conjugation pathways.^[15] Several ML-based classification models have been developed to predict whether compounds undergo specific metabolic pathways.

Hybrid approaches that integrate traditional ML algorithms with deep learning methods, such as graph-based neural networks, have demonstrated improved performance by effectively capturing molecular structure features.^[23] These models have achieved high accuracy in classifying metabolic pathway involvement, while other approaches have focused on pairing compounds with specific metabolic routes relevant to PBPK model development.^[24]

Prediction of Enzymatic Kinetic Parameters

Michaelis–Menten parameters, including the Michaelis constant (K_m) and maximum metabolic rate (V_{max}), are essential for describing enzyme-mediated metabolism in PBPK models. Experimental determination of these

parameters is often labour-intensive, prompting the use of QSAR and ML-based prediction methods.^[27] Artificial neural networks and non-linear regression models have been successfully applied to predict K_m and V_{max} values for multiple cytochrome P450 enzymes, showing improved predictive accuracy compared with conventional regression approaches.^[27,28]

Prediction of Excretion and Clearance Parameters

Clearance is a fundamental pharmacokinetic parameter representing the overall elimination of a compound from the body. Several ML-based models have been developed to predict intrinsic, renal, and total clearance using human pharmacokinetic datasets and in vitro data.^[29] Random forest models have consistently shown superior performance compared with other ML and regression-based approaches in clearance prediction.^[29,33]

More recently, deep learning models that treat chemical structures as graph data have been introduced to further improve clearance prediction. These approaches automatically extract relevant structural features and have demonstrated improved performance over conventional ML models and traditional in vitro–in vivo extrapolation methods. Importantly, explainable deep learning frameworks have also been proposed to address interpretability concerns associated with black-box ML models.^[26,34]

Table 02: Various Representative Studies Using Artificial Intelligence and Machine Learning to Predict ADME Properties Relevant to PBPK Modeling.

ADME Aspect	Parameter Predicted	Type of Data Used	AI / ML Methods Applied	Key Outcomes
Absorption	Human intestinal absorption (HIA)	Numerical values describing chemical structure, molecular size, polarity, and solubility	Neural networks, support vector machines, regression models, genetic algorithms	ML models were able to reliably predict whether a drug can be well absorbed through the intestine
Absorption	Drug permeability	Two- and three-dimensional molecular descriptors	Machine learning regression and classification models	Predictions showed strong agreement with experimental absorption data
Distribution	Tissue–plasma partition coefficient (K_p)	Molecular structure details and physicochemical properties	Support vector machines, decision trees, random forests	AI models successfully estimated how drugs distribute between blood and tissues
Metabolism	Enzyme-related metabolism (e.g., CYP pathways)	Structural and physicochemical drug characteristics	Machine learning classification models	High prediction accuracy showed ML is very effective for metabolism prediction
Elimination	Renal clearance	Molecular size, polarity, and charge-related features	Regression-based ML techniques	Models could estimate kidney elimination with good reliability

APPLICATIONS OF AI-DRIVEN PBPK MODELLING:

The integration of artificial intelligence (AI) and machine learning (ML) with physiologically based pharmacokinetic (PBPK) modelling has significantly broadened the practical applications of pharmacokinetic analysis. By combining mechanistic physiological knowledge with data-driven prediction, AI-driven PBPK models improve efficiency, scalability, and predictive confidence across pharmaceutical development and toxicological risk assessment.^[1,5]

1. Drug Discovery and Early Development

In early drug discovery, experimental pharmacokinetic data are often limited, which restricts the application of conventional PBPK models. AI-based methods enable rapid prediction of key drug-specific parameters such as clearance, tissue distribution, and absorption directly from molecular structure or in vitro data. These predicted inputs allow PBPK models to be developed at earlier stages, supporting compound screening, lead optimization, and early decision-making while reducing experimental workload and development timelines.^[1,9,10]

2. Dose Selection and Optimization

AI-enhanced PBPK models are increasingly applied to optimize dosing strategies by simulating concentration–time profiles under different dosing regimens. Machine learning approaches help refine uncertain parameters and improve model accuracy, enabling more reliable prediction of systemic and tissue exposure. This application is particularly valuable during clinical trial planning and for dose adjustment following formulation or route-of-administration changes.^[11,12]

3. Prediction of Drug-Drug Interactions

Assessment of drug-drug interactions (DDIs) is a critical requirement in drug development and regulatory evaluation. AI-driven PBPK models improve DDI prediction by enabling efficient estimation of enzyme and transporter related parameters and supporting large scale simulation of interaction scenarios. These hybrid models allow systematic evaluation of interaction risks across populations and dosing conditions, reducing the need for extensive clinical DDI studies.^[3,7]

4. Special Populations and Personalized Medicine

AI-assisted PBPK modelling plays an important role in predicting pharmacokinetics in special populations such as paediatrics, geriatrics, pregnant individuals, and patients with organ impairment. Machine learning methods can incorporate demographic and physiological variability to generate virtual populations, improving extrapolation and supporting personalized dosing strategies in populations where clinical data are limited.^[7,11]

5. Advanced Drug Delivery and Formulation Development

Modern drug delivery systems, including nanoparticles and modified-release formulations, present challenges for traditional PBPK models due to complex absorption and distribution behaviour. AI-driven approaches help capture formulation-dependent effects by learning relationships between formulation attributes and pharmacokinetic outcomes. When integrated with PBPK models, these methods enhance prediction of absorption profiles, tissue targeting, and release kinetics.^[4,24]

6. Toxicology and Chemical Risk Assessment

Beyond pharmaceuticals, AI-driven PBPK modelling is widely applied in toxicology and environmental health sciences. These models support high-throughput toxicokinetic screening of non-pharmaceutical chemicals by estimating internal exposure from external doses. AI-based parameter prediction enables PBPK models to be applied to large chemical inventories, supporting risk assessment while reducing reliance on animal testing.^[18,19]

ROLE OF AI IN POPULATION PBPK MODELLING:

Population physiologically based pharmacokinetic (PBPK) modelling is designed to describe variability in drug exposure across individuals by accounting for differences in physiology, biology, and external influences. Traditional population PBPK approaches typically rely on predefined parameter distributions and simplifying assumptions, which may not fully capture real-world heterogeneity. The integration of artificial intelligence (AI) and machine learning (ML) has enhanced population PBPK modelling by enabling data-driven characterization of variability, uncertainty, and population structure.^[5,7]

1. Inter Individual Variability

AI plays a crucial role in improving the representation of inter-individual variability in population PBPK models. Drug pharmacokinetics can vary substantially due to factors such as age, body composition, genetic polymorphisms, disease state, organ function, and environmental exposure. Machine learning algorithms are capable of identifying complex, non-linear relationships among these factors by learning directly from clinical, demographic, and biological datasets. When incorporated into PBPK frameworks, AI-derived relationships enable more accurate prediction of variability in absorption, distribution, metabolism, and excretion across individuals, beyond what can be achieved using conventional statistical approaches.^[9,11]

2. Virtual Populations

The generation of virtual populations is a key application of AI in population PBPK modelling. Traditional methods often construct virtual populations by sampling physiological parameters from assumed distributions, which may overlook correlations between parameters. AI-based approaches can learn realistic parameter distributions and dependencies from real-world data, allowing the creation of virtual populations that better reflect human diversity. These AI-informed virtual populations improve PBPK-based predictions for specific subgroups, such as paediatric and geriatric populations or patients with hepatic or renal impairment, and support personalized dosing and risk assessment.^[7,11]

3. Sensitivity and Uncertainty Analysis

Sensitivity and uncertainty analysis are essential for understanding the robustness and reliability of population PBPK model predictions. AI-driven methods enhance these analyses by efficiently exploring large parameter spaces and identifying the most influential parameters affecting pharmacokinetic outcomes. Machine learning techniques can rank parameter importance and detect interactions that drive variability, guiding experimental prioritization and model refinement. In addition, AI-assisted uncertainty quantification supports probabilistic interpretation of PBPK outputs, improving confidence in population-level predictions and regulatory decision-making.^[5,9]

SOFTWARE TOOLS & PLATFORMS SUPPORTING AI-PBPK MODELLING

The practical implementation of AI-driven physiologically based pharmacokinetic (PBPK) modelling relies heavily on advanced software platforms that support mechanistic simulation, data-driven analysis, and seamless integration of artificial intelligence (AI) and machine learning (ML) techniques. In recent years, a wide range of PBPK platforms, AI/ML tools, and hybrid integration frameworks have emerged to facilitate efficient model development, validation, and application across pharmaceutical and toxicological domains.

1. PBPK Platforms

Dedicated PBPK software platforms provide the mechanistic foundation required for simulating drug absorption, distribution, metabolism, and excretion across tissues and populations. These platforms incorporate detailed physiological descriptions, organ-specific parameters, and dosing scenarios, enabling simulation of concentration–time profiles under various clinical and experimental conditions.

Widely used PBPK platforms such as **Simcyp**, **PK-Sim**, **GastroPlus**, and **MATLAB**-based PBPK frameworks support population simulations, special population modelling, and drug-drug interaction assessment. These tools are commonly applied in drug development and regulatory submissions due to their mechanistic transparency and validation history. Although traditional PBPK platforms primarily rely on experimentally derived inputs, they increasingly allow the incorporation of AI-predicted parameters, thereby extending their applicability to early discovery and data-limited scenarios.^[7,8]

2. AI and Machine Learning Tools Used Alongside PBPK

AI and ML tools play a complementary role by enabling rapid prediction of drug-specific parameters and analysis of complex datasets. Open-source programming environments such as **Python** and **R** are widely used for developing ML models due to their extensive libraries for data processing, model training, and validation. ML frameworks including **TensorFlow**, **PyTorch**, and **scikit-learn** support the implementation of regression models, ensemble learning, neural networks, and deep learning architectures for pharmacokinetic parameter prediction.^[9,26]

These AI tools are frequently used to estimate PBPK input parameters such as clearance, tissue partition coefficients, permeability, and plasma protein binding directly from molecular structure or in vitro data. The predicted outputs are then integrated into PBPK platforms, enabling hybrid modelling workflows that combine mechanistic and data-driven approaches.^[1,5] In addition, AI tools support sensitivity analysis, uncertainty quantification, and optimization of PBPK model parameters.

3. Integration Frameworks for AI-PBPK Modelling

Integration frameworks bridge the gap between AI/ML tools and PBPK platforms by enabling automated data exchange, iterative learning, and model refinement. In such frameworks, ML models are trained using experimental or historical data to predict uncertain pharmacokinetic parameters, which are subsequently incorporated into PBPK simulations. Simulation outputs can then be used to retrain or validate ML models, creating a feedback loop that improves predictive performance over time.^[2,5]

Hybrid AI-PBPK frameworks have been implemented using custom pipelines that link ML environments with PBPK software through scripting interfaces, application programming interfaces (APIs), or shared data formats. These frameworks are particularly valuable for high-throughput screening, early drug discovery, nanoparticle-based drug delivery, and toxicokinetic risk assessment. By preserving physiological interpretability while enhancing scalability and efficiency, integrated AI–PBPK platforms support more informed decision-making in both pharmaceutical development and regulatory science.^[3,6]

CHALLENGES & LIMITATIONS OF AI INTEGRATED PBPK MODELLING:**1. Data quality and availability**

AI-assisted PBPK models require large, reliable datasets, but pharmacokinetic and ADME data are often limited, inconsistent, or poorly standardized, which can reduce prediction reliability.^[1,5]

2. Black box Nature and interpretability

Many ML and deep learning models lack transparency, making it difficult to explain how predictions are generated and to link results to biological mechanisms, which limits trust and usability.^[9,26]

3. Regulatory acceptance

Although PBPK modelling is increasingly accepted, regulatory confidence in AI-integrated models remains cautious due to concerns about validation, reproducibility, and model transparency.^[8,11]

FUTURE PERSPECTIVES OF AI-INTEGRATED PBPK MODELLING

The continued advancement of artificial intelligence (AI) and machine learning (ML) is expected to further transform physiologically based pharmacokinetic (PBPK) modelling. Emerging technologies and data-driven approaches are expanding the scope of PBPK applications beyond traditional simulation, enabling more dynamic, individualized, and clinically relevant modelling frameworks.^[1,5]

1. Digital Twins

Digital twins represent a promising future direction for AI-driven PBPK modelling. A digital twin is a virtual representation of an individual that integrates physiological, biochemical, and clinical data to simulate drug behaviour in a patient-specific manner. By combining PBPK models with AI algorithms that continuously learn from patient data, digital twins can predict individual drug exposure and treatment response more accurately. This approach has the potential to support individualized dosing strategies and real-time therapeutic decision-making, particularly in complex or high-risk patient populations.^[7,11]

2. Real-Time PBPK Simulations

Advances in computational power and AI algorithms are enabling the development of real-time PBPK simulations. Unlike traditional static PBPK models, real-time frameworks can update predictions dynamically as new clinical or physiological data become available. AI-driven parameter updating and rapid simulation capabilities allow PBPK models to adapt to changes in patient condition, dosing adjustments, or disease progression. This capability is especially valuable in critical care settings and adaptive clinical decision support systems.^[5,9]

3. Personalized Medicine

AI-integrated PBPK modelling is expected to play a central role in the advancement of personalized medicine. By incorporating individual-level data such as genetics, age, body composition, organ function, and disease state, AI-enhanced PBPK models can better predict variability in drug exposure and response. This approach supports tailored dosing regimens that maximize therapeutic efficacy while minimizing adverse effects. As patient-specific data become more accessible, personalized PBPK modelling is likely to become an integral part of precision pharmacotherapy.^[7,11]

4. AI-Driven Clinical Trial Design

AI-driven PBPK models are increasingly being explored as tools to improve clinical trial design and efficiency. These models can simulate drug exposure across virtual populations to inform dose selection, identify high-risk subgroups, and optimize inclusion criteria before trials begin. AI-assisted PBPK simulations can also support adaptive trial designs by predicting outcomes under different dosing or scheduling scenarios, potentially reducing trial size, cost, and failure rates. Such approaches may accelerate clinical development while improving patient safety.^[1,3]

CONCLUSION

Physiologically based pharmacokinetic (PBPK) modelling has become a cornerstone of modern drug development and chemical risk assessment by offering a mechanistic framework to understand drug disposition in the human body. The integration of artificial intelligence (AI) and machine learning (ML) has further strengthened PBPK modelling by addressing many limitations of traditional approaches, particularly those related to data gaps, parameter uncertainty, and model scalability. Together, AI and PBPK form a complementary partnership in which data-driven intelligence enhances mechanistic understanding.

AI-augmented PBPK models enable earlier and more efficient prediction of pharmacokinetic behaviour by supporting rapid estimation of key input parameters, improved representation of population variability, and high-throughput simulation of multiple scenarios. These capabilities have expanded PBPK applications across drug discovery, clinical development, toxicology, and regulatory decision-making, while reducing reliance on extensive experimental and animal studies. Importantly, the integration of AI has also facilitated the exploration of complex drug delivery systems, special populations, and non-pharmaceutical chemicals that are difficult to evaluate using conventional methods alone.

Despite these advances, challenges related to data quality, model interpretability, and regulatory acceptance remain. Addressing these issues through improved data curation, explainable AI approaches, and transparent validation strategies will be essential for broader adoption. Looking ahead, emerging concepts such as digital twins, real-time PBPK simulations, and AI-driven clinical trial design highlight the future potential of AI-integrated PBPK modelling to support personalized medicine and more efficient healthcare decision-making. Overall, the continued evolution of AI–PBPK frameworks is expected to play a transformative role in advancing predictive pharmacokinetics and shaping the next generation of drug development and precision therapeutics.

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