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REVIEW ARTICLE

Computational Pharmacokinetics in Drug Development: A Critical, Question-Centred Review of Modelling Platforms, Validation, and Regulatory Applications

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Abstract

Computational pharmacokinetics (PK) has become an important component of modern drug development, extending beyond the description of drug exposure toward prediction, simulation, dose optimization, and support for regulatory decision-making. This critical, question-centered review examines how major computational approaches differ in their applications, data requirements, assumptions, and capacity to address specific drug-development questions. Conventional noncompartmental analysis remains useful for summarizing observed exposure and supporting comparative pharmacokinetic and bioequivalence studies. Population pharmacokinetic and nonlinear mixed-effects models provide a framework for characterizing interindividual variability, identifying influential covariates, evaluating external predictive performance, and supporting model-informed dosing. Programmable pharmacometrics further enables flexible model development, simulation, automation, and reproducible workflows through R-based and other computational environments. Physiologically based pharmacokinetic and mechanistic models provide a more detailed representation of drug disposition and are increasingly applied to drug–drug interaction assessment, special populations, bioequivalence, and clinical or regulatory extrapolation. Recent developments in high-throughput modeling, automated workflows, and applications to biologics, antisense oligonucleotides, cellular therapies, and antibody–drug conjugates are broadening the scope of computational PK. However, increasing model complexity does not necessarily ensure greater predictive value. Model credibility remains dependent on data quality, appropriate assumptions, transparent reporting, uncertainty assessment, and meaningful internal and external validation. Overall, computational PK is most informative when the modeling strategy is selected according to the scientific question and intended decision rather than the capabilities of a particular software platform. Future progress should emphasize reproducibility, standardized evaluation, external validation, and appropriate integration of emerging computational methods into drug-development practice

Keywords: Pharmacokinetics, Pharmacometrics modelling, Pharmacokinetic software, Population pharmacokinetics, Nonlinear mixed-effects modeling

1. Introduction

Pharmacokinetic (PK) analysis is an essential part of drug development because concentration–time data provide the basis for understanding drug exposure, disposition, and variability. These analyses also support decisions that extend beyond the observed study conditions, including dose selection, formulation development, assessment of drug–drug interactions (DDIs), and prediction in populations that may not have been directly studied. As drug-development programs have become increasingly data-intensive, computational methods have consequently expanded from relatively simple calculations to more complex approaches for estimation, simulation, and prediction [1,2]. Noncompartmental analysis (NCA) continues to have an important role in describing observed drug exposure and remains widely applicable to bioavailability and bioequivalence studies. Population pharmacokinetic (PopPK) and nonlinear mixed-effects (NLME) models provide a framework for quantifying interindividual variability and evaluating the influence of patient characteristics and other covariates on PK parameters. Physiologically based pharmacokinetic (PBPK) models take a different approach by incorporating physiological characteristics, drug-specific properties, and mechanistic processes to support extrapolation across conditions [3,4]. At the same time, programmable pharmacometric environments have made it possible to combine model development, simulation, diagnostics, and data processing within reproducible computational workflows [5]. The growing number of available platforms has created a practical problem for investigators. Similar PK questions can often be approached using several software environments, yet the availability of a particular function does not establish that the resulting model is scientifically appropriate or sufficiently predictive. Model performance depends on factors such as the quality and structure of the underlying data, assumptions about biological processes, parameter identifiability, model specification, sampling design, and the way model predictions are evaluated. Thus, software selection should be considered in relation to the scientific question and intended use rather than on the basis of functionality alone. This distinction is particularly relevant when computational PK is used to support clinical or regulatory decisions. Regulatory guidance from the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recognizes the potential value of PBPK and model-informed approaches while emphasizing appropriate model development, qualification, reporting, and evaluation for the intended context of use [6,7]. More recently, the ICH M15 framework has provided broader principles for the planning, evaluation, documentation, and communication of model-informed drug-development evidence [8]. These developments emphasize that computational predictions require an appropriate evidentiary basis before they are used to support consequential development decisions. Despite this progress, comparisons of computational PK technologies are often presented primarily in terms of software capabilities or individual applications. Such descriptions provide limited information about when a particular approach is scientifically appropriate, how reliably its predictions can be transferred to new datasets or populations, and what evidence is needed to establish credibility. External-validation and cross-platform studies are particularly informative in this regard because they can reveal differences between apparent model fit and

predictive performance. Recent applications also show that computational PK is expanding into high-throughput mechanistic modeling, advanced therapeutic modalities, and increasingly automated workflows, creating new opportunities as well as new requirements for model evaluation and reproducibility. Accordingly, this review examines computational PK from a question-centered perspective. Rather than ranking software platforms, it considers how conventional NCA, PopPK/NLME modeling, programmable pharmacometrics, and PBPK approaches have been applied to contemporary drug-development problems. Particular attention is given to the relationship between the scientific objective, data requirements, model assumptions, validation strategy, reproducibility, and intended decision context [9]. The review also considers emerging applications and identifies areas where stronger external validation, standardized benchmarking, transparent computational workflows, and decision-specific performance criteria are needed. Unlike reviews focused on individual methods, this review connects these approaches with their practical applications.

2. Review methodology

This study was conducted as a structured critical narrative review of computational pharmacokinetics in drug development. A structured literature search was conducted using PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. Search terms included “computational pharmacokinetics,” “PBPK,” “population pharmacokinetics,” “NLME,” “PK simulation,” “virtual bioequivalence,” “model validation,” “artificial intelligence,” and “machine learning,” along with major computational PK platforms. Relevant studies were selected based on their contribution to computational PK modeling, prediction, simulation, validation, software applications, or drug development. Research articles were prioritized, while relevant reviews and FDA/EMA documents provided methodological context.Selected literature was screened by title, abstract, and full text and critically synthesized according to computational approach, application, findings, validation, and limitations. The review followed the general principles of high-quality narrative reviews described by SANRA.

Rather than ranking software platforms, the review compares approaches according to the research question, data requirements, modeling assumptions, validation strategy, and intended use in drug development. No quantitative meta-analysis was performed.

3. Conventional pharmacokinetic analysis

Noncompartmental analysis (NCA) remains a fundamental approach for describing observed pharmacokinetic profiles. It provides key parameters such as C_{max}, T_{max}, AUC, and elimination half-life without requiring a predefined compartmental structure. This makes NCA particularly useful in early clinical studies, formulation development, bioavailability, and bioequivalence (BE) assessment [10]. Commercial platforms such as Phoenix WinNonlin provide standardized workflows for NCA, while open-source tools have also been developed to support reproducible analysis. The development of the R packages NonCompart and ncar demonstrated that NCA results could be reproduced using programmable workflows [11].

Recent applications demonstrate the continued role of conventional PK analysis in drug development. Phoenix WinNonlin has been used for BE assessment and evaluation of food-related changes in drug exposure [12,13]. Conventional PK analysis has also been applied to characterize plasma and cerebrospinal fluid exposure and to evaluate clinical PK in healthy subjects [14,15]. Formulation and food effects, PK variability, and comparative bioequivalence have subsequently been investigated using similar approaches [16–18].

The integration of validated bioanalytical methods with PK analysis is also important. A validated LC–MS/MS method using SFOD microextraction was developed for lazertinib quantification in rat plasma and applied to PK analysis [19]. Similarly, a validated LC–MS/MS method was developed for simultaneous quantification of talazoparib and enzalutamide in rat plasma with subsequent pharmacokinetic application [20]. These studies highlight the importance of reliable concentration measurements as the basis for PK characterization.

NCA offers several practical advantages, including simplicity, limited structural assumptions, and established application in comparative PK studies. However, it is primarily descriptive and provides limited information on the mechanisms underlying PK variability. Its usefulness is also reduced when datasets are sparse or when nonlinear processes, population variability, or extrapolation to unstudied conditions must be addressed. Such questions are more appropriately investigated using population PK/NLME or mechanistic PBPK approaches.

Table 1. Recent applications of conventional pharmacokinetic analysis and noncompartmental analysis in drug development

Technology	PK application	Population/dataset	Key finding	Ref.
NonCompart / ncar	NCA	Reference PK datasets	Reproduced WinNonlin NCA results	[10]
Phoenix WinNonlin	Bioequivalence	Healthy volunteers	NCA supported BE assessment	[11]
Phoenix WinNonlin	Food-effect PK	Healthy subjects	Quantified food-related exposure changes	[12]
Phoenix WinNonlin	Plasma PK	Human subjects	NCA characterized systemic exposure	[13]
Phoenix WinNonlin	BE / food effect	Healthy volunteers	Supported formulation and food comparisons	[14]
Phoenix WinNonlin	BE variability	BE trials	Quantified PK variability	[15]
Phoenix WinNonlin	Bioequivalence	38 PK-evaluable subjects	Fenofibrate BE demonstrated	[16]
Phoenix WinNonlin	Bioequivalence	Healthy subjects	90% CIs met BE criteria	[17]
Phoenix WinNonlin	BE / NCA	50 women	Supported comparative PK	[18]
LC–MS/MS + SFOD	Lazertinib PK	Rat plasma	Validated method applied to PK analysis	[19]

Technology	PK application	Population/dataset	Key finding	Ref.
LC–MS/MS	Talazoparib + enzalutamide PK	Rat plasma	Validated simultaneous quantification and PK analysis	[20]

4. Population pharmacokinetics and nonlinear mixed-effects modeling

Population pharmacokinetic (PopPK) and nonlinear mixed-effects (NLME) modeling provide a framework for describing typical pharmacokinetic behavior while accounting for interindividual variability. These approaches also allow demographic, clinical, and physiological factors to be incorporated as covariates, helping to explain differences in drug disposition and support individualized dosing.

4.1. Population PK model development

NONMEM remains an important platform for PopPK and NLME analysis, with Monolix and Phoenix NLME providing alternative modeling environments. Recent applications demonstrate the use of these platforms across critically ill patients, pediatric populations, transplantation, and newer therapeutic modalities. Covariate-based models have been used to examine factors such as renal function, body size, and extracorporeal support, thereby improving the interpretation of PK variability [21,22].

Population modeling is particularly valuable when conventional PK analysis cannot adequately describe variability between patients. For example, renal function and extracorporeal membrane oxygenation were evaluated as determinants of meropenem disposition in critically ill patients, while renal function was incorporated into polymyxin B modeling to support dose optimization [23,24].

4.2. External validation and predictive performance

An important limitation of PopPK models is that good performance in the original development dataset does not necessarily guarantee reliable prediction in another population. External evaluation of a gentamicin model demonstrated differences in predictive performance between critically ill populations [25]. Similarly, externally evaluated meropenem models showed variable predictive performance in critically ill adults [26].

External validation has also been applied to evaluate population differences and optimize sampling strategies. A darunavir PopPK model was externally evaluated together with optimal sampling design, while piperacillin modeling examined interethnic variability using an independent population [27,28]. Evaluation of gentamicin models across pediatric age groups further emphasized the importance of developmental characteristics in model performance [29].

4.3. Model-informed and individualized dosing

PopPK models can provide a quantitative basis for individualized dose selection, particularly when PK variability is clinically important. External evaluation of published linezolid models demonstrated differences in predictive performance and highlighted the importance of model selection for clinical application [30]. A similar comparison of eight vancomycin models showed substantial variation in predictive performance across models [31].

Recent applications have extended PopPK-based dosing to vulnerable populations. A linezolid model developed in premature neonates was used for dose optimization, while a tacrolimus model in kidney transplant recipients was used to develop a dosing algorithm [32–33].

4.4. Expansion to new therapeutic modalities

PopPK/NLME methods are increasingly being applied beyond conventional small-molecule drugs. A population model for the antisense oligonucleotide AZD8233 characterized its PK behavior and variability using a large clinical dataset [34]. More recently, NLME modeling was applied to cellular kinetics in patients receiving idecabtagene vicleucel, demonstrating the potential of population approaches for emerging therapeutic modalities [35].

Table 2. Recent applications of population pharmacokinetics and nonlinear mixed-effects modeling in drug development, including model development, external validation, and individualized dosing

Technology	PK application	Population/dataset	Key finding	Ref.
NONMEM	Gentamicin PopPK	Critically ill adults	External performance varied between populations	[21]
NONMEM	Meropenem PopPK	ICU patients	Published models showed limited transportability	[22]
NONMEM + PopED	External validation	164 patients	Supported limited-sampling strategies	[23]
NONMEM	Prior-informed PopPK	Special populations	Prior information improved model stability	[24]
NONMEM	PopPK / dosing	Adults	Supported individualized dosing	[25]
NONMEM	PopPK	Critically ill patients	Renal function influenced clearance	[26]
NONMEM	Piperacillin PopPK	Critically ill patients	External validation addressed interethnic variation	[27]
NONMEM	Model evaluation	70 adults; 150 samples	Bayesian forecasting improved prediction	[28]
NONMEM	Gentamicin model validation	308 children; 512 samples	Developmental covariates improved prediction	[29]
NONMEM	AZD8233 PopPK	219 participants; 3,416 samples	Described nonlinear disposition	[30]
NONMEM	Vancomycin model evaluation	40 patients; 252 samples	Predictive performance varied across models	[31]
Phoenix NLME	Linezolid PopPK	Premature neonates	Supported dosing optimization	[32]

Technology	PK application	Population/dataset	Key finding	Ref.
Monolix	Dalbavancin PopPK	Chronic infection	Covariate and model diagnostics supported model evaluation	[33]
NONMEM	Tacrolimus PopPK	1,180 recipients; 13,427 concentrations	Developed dosing algorithm	[34]
Monolix	Cellular kinetics	225 ide-cel recipients	Extended NLME to cellular kinetics	[35]

5. Programmable pharmacometrics

Programmable pharmacometric tools have expanded the ability to perform PK modeling, simulation, visualization, and model evaluation within reproducible computational environments. R-based tools such as NonCompart, nlmixr2, rxode2, and mrgsolve, together with platforms such as Pumas, allow users to combine data processing, model specification, estimation, and simulation within scripted workflows.

The development of NonCompart and ncar demonstrated the feasibility of implementing conventional NCA within R and reproducing established PK calculations. Similarly, mrgsolve provides an R-based framework for solving ordinary differential equation models and has been applied to PK/PD and physiologically based simulations [36].

Open-source NLME tools have further extended programmable pharmacometrics to population modeling. Applications of nlmixr have demonstrated its use for PopPK analysis, while comparisons with established platforms have examined the consistency of model estimation and interpretation [37,38]. These approaches provide greater flexibility for modifying models and integrating analysis with other R-based statistical and visualization tools.

A major advantage of programmable workflows is interoperability. Model translation between platforms such as nlmixr2, rxode2, and NONMEM can facilitate independent evaluation and reuse of published models [39]. Similarly, automated pharmacometric workflows have been explored to reduce repetitive model-development tasks and improve computational efficiency [40,41].

Reproducibility is another important benefit. A population PK model library for caspofungin demonstrated how published models could be reimplemented and subjected to standardized quality-control procedures using programmable tools [42]. Such approaches can improve transparency and facilitate independent checking of model structure and performance.

Cross-platform evaluation also provides evidence regarding the practical equivalence of different computational environments. Nlmixr2 and NONMEM following external evaluation of gentamicin and tobramycin PopPK models and reported comparable population-level interpretation [43]. In another application, model-guided enoxaparin dosing in a neonatal intensive care setting demonstrated the use of programmable pharmacometric approaches for clinical dosing workflows [44].

Table 3. Recent applications of programmable pharmacometrics and open-source computational tools

Technology	Application	Dataset/context	Key finding	Ref.
mrgsolve	ODE simulation	PK/PD and PBPK examples	Enabled R-based mechanistic simulation	[36]
nlmixr	PopPK	Metformin case study	Demonstrated open-source NLME modeling	[37]
nlmixr / Monolix	PopPK comparison	Meropenem	Compared open-source and commercial workflows	[38]
Pharmpy	Pharmacometrics automation	Modeling workflows	Supported reusable computational workflows	[39]
nlmixr2 / rxode2 / NONMEM	Model interoperability	PK models	Demonstrated model translation between platforms	[40]
Automated PopPK tools	Model building	PopPK workflows	Evaluated automated model-selection strategies	[41]
nlmixr2 / NONMEM	External model evaluation	7 antibiotic models	Similar population-level interpretation	[42]
rxode2	Model reimplementation	Published PopPK models	Enabled reproducible model QC	[43]
Pumas	Model-guided dosing	Neonatal ICU	Applied computational dosing workflow	[44]

6. Physiologically based pharmacokinetic and mechanistic modeling

Physiologically based pharmacokinetic (PBPK) modeling integrates drug-specific properties with physiological and biochemical information to describe drug absorption, distribution, metabolism, and elimination. Unlike conventional PK and PopPK approaches, PBPK models can be used to simulate drug behavior under conditions that may not have been directly investigated clinically. This makes them particularly relevant to drug–drug interaction (DDI) assessment, formulation development, special populations, and regulatory decision-making.

A major application of PBPK has been the prediction of metabolic and transporter-mediated DDIs. Studies using Simcyp have evaluated CYP-mediated interactions and OATP transporter effects using combinations of clinical and in vitro data [45,46]. PBPK modeling has also been used to evaluate fedratinib and ivosidenib interactions, with model qualification supporting their application to clinical DDI assessment [47,48]. PBPK models can also support regulatory applications by integrating evidence from different experimental sources. PK-Sim for predicting CYP3A4-mediated interactions involving pirtobrutinib, illustrating how mechanistic modeling can contribute to drug-labeling decisions [49]. Similarly, PBPK analysis of ponatinib was used to characterize CYP3A4-mediated interactions in patients with cancer [50].

An important consideration is the influence of model assumptions and platform implementation on predictions. A cross-platform evaluation of simvastatin demonstrated that model development and predictive results could vary according

to the PBPK platform used [51]. This finding indicates that the biological assumptions, parameterization, and implementation of a model may be as important as the software environment itself.

PBPK applications have also expanded to formulation and clinical PK prediction [52]. GastroPlus to alpelisib, integrating formulation-related and clinical information. More recently, GastroPlus to predict the pharmacokinetics of NH130 across clinical dose groups [53]. These applications demonstrate the ability of PBPK models to connect drug properties and formulation characteristics with observed clinical exposure.

The scale of PBPK applications is also increasing. PBK modeling using more than 200 compounds and over 2,000 PK profiles, demonstrating the potential for mechanistic modeling to support larger-scale prediction [54]. However, the observed performance varied according to modeling strategy and compound characteristics, indicating that high-throughput implementation does not eliminate the need for compound-specific evaluation.

PBPK modeling has increasingly been applied to complex biological therapeutics. A cross-platform assessment using Simcyp, PK-Sim, and GastroPlus compared monoclonal antibody disposition and found greater consistency for serum predictions than for tissue distribution [55]. This highlights the additional uncertainty associated with mechanistic prediction of tissue exposure for large molecules.

Recent studies further demonstrate the application of PBPK to clinical DDI and advanced therapeutic modalities. A Simcyp model was used to predict the interaction between fezolinetant and CYP1A2 inhibitors and to support regulatory labeling information [56]. For antibody–drug conjugates, PK-Sim and MoBi to model CLDN18.2-targeted ADC pharmacokinetics in cancer patients, incorporating mechanistic processes to improve prediction [57,58].

Table 4. Recent applications of physiologically based pharmacokinetic and mechanistic modeling for drug–drug interaction assessment

Technology	PK application	Population / dataset	Key finding	Ref.
Simcyp	CYP-mediated DDI	Clinical DDI datasets	Evaluated CYP modulator models	[45]
Simcyp	Transporter DDI	Phase I + in vitro data	Supported OATP-mediated DDI prediction	[46]
Simcyp	Metabolic DDI	Clinical + in vitro data	Supported DDI and labeling decisions	[47]
Simcyp	CYP3A4 induction	Cancer + clinical data	Platform qualification supported DDI prediction	[48]
PK-Sim	CYP3A4 DDI	Qualification datasets	Developed generic platform qualification framework	[49]
Simcyp + WinNonlin	Virtual BE	66-subject dataset	Explored variability propagation	[50]
Simcyp	Ponatinib DDI	Cancer PK	Predicted CYP3A4 interaction effects	[51]
Simcyp / PK-Sim	Cross-platform PBPK	Simvastatin	Platform choice affected model development	[52]
GastroPlus	Absorption / BE	Alpelisib	Integrated formulation and clinical data	[53]
GastroPlus	Clinical PK prediction	NH130 phase I	Verified predictions across dose groups	[54]
PK-Sim	High-throughput PBK	>200 compounds; >2,000 profiles	Demonstrated scalable human PK prediction	[55]
Simcyp / PK-Sim / GastroPlus	mAb disposition	IgG, adalimumab, infliximab	Tissue predictions varied across platforms	[56]
Simcyp	Fezolinetant DDI	Clinical + in vitro data	Supported labeling statements	[57]

7. Research gaps and future directions

Despite advances in computational PK, important gaps remain in external validation, model comparability, reproducibility, and prediction in emerging therapeutic modalities. Many models perform well in their development datasets but require broader evaluation in independent populations and clinical settings.

Standardized reporting of model assumptions, data requirements, validation procedures, and predictive performance would improve reproducibility and facilitate comparison across computational platforms.

The increasing use of PBPK, high-throughput modeling, automation, and AI-based methods provides opportunities for faster and broader PK prediction. However, these approaches require appropriate quality control, uncertainty assessment, and independent validation before routine application.

Future research should therefore focus on reproducible workflows, standardized model evaluation, stronger external validation, mechanistic modeling of complex therapies, and transparent integration of emerging computational methods into drug-development decisions.

8. Limitations

This review has several limitations. It was designed as a critical narrative review rather than a systematic review, and therefore the literature selection was not intended to be exhaustive. The available evidence also differs substantially across computational approaches, making direct comparison between technologies difficult.

Published studies may further differ in datasets, model structures, validation methods, and intended applications. Consequently, reported predictive performance should be interpreted within its specific study context rather than generalized across all drugs or populations.

Finally, emerging approaches such as high-throughput modeling, automation, and AI/ML have a shorter evidence base than established PK methods. Their broader clinical and regulatory utility therefore requires further independent validation and standardized evaluation.

9. Conclusion

Computational pharmacokinetics has evolved from conventional exposure analysis toward integrated approaches for variability assessment, mechanistic prediction, simulation, and model-informed drug development. NCA remains important for describing observed exposure and supporting comparative PK studies, whereas PopPK/NLME approaches provide greater insight into interindividual variability and individualized dosing. Programmable pharmacometrics adds flexibility, reproducibility, and opportunities for automation, while PBPK provides a mechanistic framework for extrapolation across drugs, populations, and clinical conditions.

The expanding application of these approaches to biologics, antibody–drug conjugates, cellular therapies, and high-throughput prediction creates new opportunities for drug development. At the same time, model credibility depends on appropriate assumptions, reliable data, transparent workflows, and meaningful validation. Future progress should therefore emphasize external validation, reproducibility, standardized evaluation, uncertainty assessment, and context-specific application rather than software capability alone.

Continued development and transparent integration of mechanistic and emerging computational approaches may strengthen the reliability and broader clinical and regulatory application of pharmacokinetic modeling.

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G.R.Y.: conceptualization, supervision, methodology, writing – original draft. R.G.: writing – review and editing. D.S.L.: methodology, resources. G.V.: investigation, resources.

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