DOI: 10.12923/cipms-2025-0020 Curr. Issues Pharm. Med. Sci., Vol. 38, No. 2, Pages 125-131

Current Issues in Pharmacy and Medical Sciences
Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA

journal homepage: https://czasopisma.umlub.pl/curipms

Harnessing machine learning for predictive pharmacokinetics: revolutionizing drug development and personalized medicine

Lukasz Dudarski*

Student – Logistics major, Pomeranian Higher School in Starogard Gdanski, Poland

ARTICLE INFO

Received 02 June 2024
Accepted 12 December 2024

Keywords:
absorption, distribution, metabolism, excretion (ADME),
machine learning (ML)
pharmacokinetics (PK).

ABSTRACT

Despite extensive existing literature on the role of machine learning (ML) in pharmacokinetics and drug development, there remains a gap in understanding its real-world implementation challenges, especially across diverse populations. This review aims to bridge this gap by focusing on specific case studies that illustrate the practical impact of ML on addressing the limitations of traditional pharmacokinetic (PK) methods. By leveraging large datasets and sophisticated algorithms, ML techniques provide improved predictions of absorption, distribution, metabolism, and excretion (ADME) processes, offering an individualized approach to patient care. Unlike traditional PK modeling, ML allows for the handling of large-scale, multidimensional data, improving the prediction accuracy for diverse patient populations. This review delves into recent advancements in ML applications for PK, emphasizing their impact on early-stage drug discovery, dose optimization, and tailoring personalized treatment plans. Specific case studies illustrate the advantages of ML over conventional approaches, particularly in addressing the variability in drug responses among patients. The challenges and opportunities of using ML in PK modeling are discussed, highlighting the potential of these techniques to revolutionize pharmaceutical sciences.

INTRODUCTION

Pharmacokinetics (PK) is a foundational component of drug development, providing insights into how drugs are absorbed, distributed, metabolized and excreted in the human body. Conventional PK studies have relied on compartmental models, ranging from simple one-compartment models, to more sophisticated structures, so as to predict drug behavior. However, these traditional approaches face significant limitations, particularly when applied to complex patient populations. Factors such as age, genetics, comorbidities and concurrent medications introduce high inter-individual variability, which cannot be fully captured by traditional PK models [1-3].

Machine learning (ML), a subset of artificial intelligence, represents a paradigm shift in PK modeling. ML uses advanced algorithms, such as neural networks, support vector machines (SVMs) and random forests (RFs), to detect complex patterns within large-scale datasets, which would be impractical for traditional models to handle. The flexibility and computational power of ML allow for the incorporation of diverse data sources, including Electronic Health Records (EHR), molecular databases and clinical trial results, making it possible to model drug responses more accurately [4]. While many reviews discuss ML in PK modeling, they often lack specific real-world implementation challenges and outcome-based comparisons. This manuscript bridges these gaps by providing detailed case studies and highlighting how ML can overcome practical limitations faced by traditional PK methods. This review focuses on the role of ML in overcoming traditional PK challenges by exploring practical examples of how ML-driven approaches enhance drug development processes. Through highlighting the measurable impact of ML on drug discovery and personalized treatment, this review seeks to provide a fresh perspective on the transformative potential of ML in pharmacokinetics.

Despite the growing body of literature on the use of ML in pharmacokinetics, there are significant challenges in real-world implementation that remain under-explored. This review aims to bridge this gap by focusing on practical case studies that illustrate the complexities of applying ML techniques in diverse patient populations, an area often overlooked by existing reviews.

* **Corresponding author**
e-mail: ld49643@amu.edu.pl

HARNESSING MACHINE LEARNING FOR PREDICTIVE PHARMACOKINETICS: REVOLUTIONIZING DRUG DEVELOPMENT AND PERSONALIZED MEDICINE

PK is a fundamental framework of drug development that aims to explain drug behavior in the body. Conventionally, PK studies relied on both simple one-compartment models and more complicated ones. Mechanisms of drug behavior are, in many instances, poorly described, especially in complex patient populations. Though helpful, these conventional and clinical approaches have certain constraints in providing accurate drug responses amongst different populations and physiological statuses [1]. Some of the challenges experienced by applied PK studies result from the high inter-individual variability in patients, including age, genetics, other diseases and other medications that the patients could be taking. They include issues related to power, sample size, generalizability and the inability to explain all the variations in drug action in diverse individuals [3]. These restrictions prevent the full utilization of PK data in designing targeted therapeutic strategies that meet the needs of individual persons. Examples of studies where machine learning was applicable include Predictive analytics, facial recognition and financial accuracy.

Despite these challenges, the approach of ML brings a shift in the PK modeling methodologies. These ML techniques are very flexible and efficient in detecting many patterns in such huge-sized data sets for further PK studies, which are very helpful in overcoming existing weak points in such works. ML algorithms can advance research data by incorporating information from clinical trials, EHR and molecular data to further understand the kinetics and dynamics of drugs. Consequently, ML in PK modeling is innovative. It is pointed out as being an outlier from currently acceptable approaches towards delineating the action of drugs and, by extension, provides a data-driven solution to enhance precision [4]. Other useful approaches for detecting non-linear associations between the PK and other pharmacokinetic variables or their interdependencies include neural networks, support vector machines and random forests [5]. ML methods can also be applied through predictability enhancements or optimizations and adaptation during the training and cross-validation cycles within the same model or as an approach to problems that are representative of real-world pharmacological systems.

Furthermore, the combination of ML and PK modeling is not limited to the extension of the typical methodologies of pharmacokinetics. However, it opens new opportunities for progress in drug development and the application of personalized medicine. In addition, ML helps researchers to understand the action mechanisms of drugs, such as absorption, distribution, metabolism or elimination, enabling differentiation of which drug candidates should be pursued at an early stage of the development pipeline [6]. Beyond the aforementioned, Ml can be employed to optimize the dosing regimens in clinical trials - making trials run faster, better and safer for the patient [7]. Thus, the integration and application of ML within PK modeling remain a significant step forward in pharmaceutical sciences.

While several reviews discuss the application of ML in pharmacokinetics, this paper focuses on specific pharmacokinetic challenges and opportunities in personalized medicine. In it, I highlight unique advantages of ML over traditional methods, particularly in diverse population studies and early-stage drug discovery, providing an innovative perspective compared to established methodologies. While numerous reviews have explored ML applications in pharmacokinetics and personalized medicine, they often lack a focus on real-world implementation challenges and specific outcomes across diverse patient populations. This manuscript aims to bridge this gap by spotlighting not only the theoretical potential of ML but also practical challenges and specific case studies that demonstrate ML's measurable impact on drug development efficiency and treatment personalization.

METHODOLOGY

The paper categorizes existing approaches for predictive pharmacokinetics by applying three main criteria. The above approaches include ML, the specific pharmacokinetic problems addressed, and the types of populations studied. The first category classifies approaches into various ML techniques. Examples include neural networks, SVMs, and RFs. The above approaches showcase the ability to model complex relationships in drug absorption and excretion (ADME).

The second category identifies key pharmacokinetic challenges. Examples include modeling drug-drug interactions and predicting drug behavior in special populations. The third category examines how different population characteristics influence machine learning model performance. The above characteristics include genetic background and comorbidities. The approach provides a comprehensive understanding of how ML techniques can offer a more structured framework for comparing existing studies and results.

Neural networks are highly effective in capturing complex, non-linear relationships within pharmacokinetic data, allowing for more accurate predictions of drug behavior in diverse populations. RFs, through ensemble learning, offer robustness in handling high-dimensional data, which is crucial in predicting drug interactions and individual patient responses. SVMs, on the other hand, excel in classification tasks, making them suitable for identifying patient subgroups with unique pharmacokinetic profiles.

Machine Learning in PK Modeling

References were selected based on their relevance to the topics of machine learning applications in pharmacokinetics, drug development and personalized medicine. Criteria included peer-reviewed journals, recent publications (from 2021-2023), and articles that explore real-world applications [2]. Others include advancements in ML techniques within pharmaceutical sciences. The merging of machine learning techniques in pharmacokinetic modeling has brought a novel way of studying drug behavior in the human body. Pivotal to this shift in paradigm is the use of multiple types of data to train and improve ML algorithms to forecast drug ADME processes accurately [1]. In the context of ML-driven PK

modeling, Data Sources are essential since they represent the starting point for modeling. These data include clinical studies, EHRs and molecular databases. Clinical trials help human subjects analyze drug kinetic and dynamic properties in controlled conditions to determine drug effectiveness and risks [3]. On the other hand, EHRs depict patients' demographic information, clinical history, and treatment outcomes, giving valuable insights into drug effects in diverse groups of patients [4]. Genetic information about the drug and biomarker profile, along with others, enriches the occurrence of the ML models that depict causal relationships and the biological pathways that lead to drug interactions [5].

Algorithms and Techniques form the core of designing ML-based PK Modeling and Assessment. Such a development framework is critical in analyzing data derived from PK studies and establishing predictive models. Neural networks, SVMs, and RFs are the most relevant ML methods and models for PK data, which have independent edges in modeling the complex relativity of PK up to date [6]. For example, learning by the neural network can be done in the non-linear relationships and correlations of PK parameters, which help model complicated pharmacological systems and their description. This allows use of the data points from the new sets of groupings, which are categorized, for identifying the different populations with regard to the phenomena of drug response with SVMs. The high accuracy and versatility of RFs in prediction are attributed to ensemble learning through many decision trees. The model type, PK application, strengths and weaknesses are listed in Table 1.

Table 1. Model type, PK application, strengths and weaknesses

Model	Data Type	PK Applications	Strengths	Weaknesses
Neural Networks	EHR, Molecular Data	ADME, Personalized Dosing	High accuracy in complex relationships	Potential for overfitting
Support Vector Machines	Clinical Trial Data	Drug-drug Interactions	Good for classification	Sensitive to parameter tuning
Random Forests	EHR, Clinical Trial Data	Dosing Optimization, Toxicity Prediction	Robust handling of high-dimensional data	Interpretation challenges

Machine Learning Models and Their Applications in PK

In PK modeling using ML, Model Training and Validation are essential steps to build accurate and validated prediction models. The model training uses large-scale datasets from clinical trials or real-world data. Cross-validation methods help assess the model's generalizability to unseen data. ML model valuations use accuracy and F1-score metrics. Model training involves feeding a PK data set to an ML algorithm for the model to be trained to make an accurate prediction, and the model's parameters are adjusted through hit or trial to improve its ability to make a prediction [1]. Assessment of ML models entails establishing how suitable they are in predicting new data or within cross-validation folds, to guarantee high model accuracy [2]. In this regard, through the cross-validation of the ML models across the data sets, the possible overfitting can be mitigated, and thus, researchers can be be confident that the resulting predictive models are relevant for studying pharmacokinetic processes [5]. Table 2 provides a comparison of the attributes of traditional PK and ML techniques.

Table 2. Comparison of Traditional Pharmacokinetics (PK) and Machine Learning (ML) Techniques

Aspect	Traditional PK	Machine Learning (ML)
Data Sources	Limited to small-scale clinical trials and empirical models	Utilizes big data from EHR, molecular data, and clinical trials
Modeling Approach	Based on compartmental models	Incorporates flexible algorithms like neural networks and random forests
Aspect	Traditional PK	Machine Learning (ML)
Data Sources	Limited to small-scale clinical trials and empirical models	Utilizes big data from EHR, molecular data, and clinical trials
Modeling Approach	Based on compartmental models	Incorporates flexible algorithms like neural networks and random forests
Accuracy	Subject to high inter-individual variability	High accuracy in predicting complex, nonlinear relationships

Applications in Drug Development

ML is emerging as an industry-disrupting technology for optimizing compound development and dosing in clinical trials by adequately measuring the PK profiles. These applications of ML have been shown to significantly bring down the cost and timeline of drug development. For instance, ML models have reduced drug discovery timelines by nearly 30%, saving valuable resources in early-stage research [2]. Additionally, in oncology, personalized ML-driven dosing models have lessened chemotherapy toxicity by 20% while maintaining treatment efficacy [3]. One prominent area that will benefit significantly from ML application is Early-Stage Drug Discovery, where automatic systems predict the PK attributes of new compounds in the preclinical stage. Using the features of chemical structures and molecular descriptors, ML algorithms can estimate the major PK parameters: absorption, distribution, metabolism and excretion (ADME) and may aid in weighing the sets of suitable drug candidates with the desirable PK appropriate profiles [5]. This initial identification of lead compounds shortens the drug discovery channel, in which more resources can be directed to compounds that are most likely to pan out.

In addition, the application of ML approaches can improve dosing regimens within clinical trials, increase the efficiency of the trials, and reduce the risks associated with the tests conducted on patients. Conventional clinical trial strategies have a rigid dosing schedule derived from average population data, meaning the variation in participants' treatment responses may need to be captured better [1]. Considering all the patient parameters, such as demographic data, genetics, biomarkers and the medicines' PKs, ML algorithms can determine the dosing schedule for each patient. Through the dosing optimization techniques, the application of ML has benefits such as reducing side effects, enhancing treatment outcomes, and increasing the probability of subject recruitment and retention in clinical trials [4]. ML has significantly contributed to dose optimization in clinical trials. For example, ML algorithms have successfully been applied to predict patient responses to chemotherapy, enabling personalized dosing adjustments and minimizing side effects in cancer treatment [2].

Moreover, ML use has provided tangible improvements in early-stage drug discovery. For example, a study found that ML models reduced discovery timelines by nearly

30%, saving valuable resources [7]. Similarly, ML-driven PK models have enhanced personalized dosing in oncology, reducing chemotherapy toxicity by 20% while maintaining efficacy. Machine learning has demonstrated its value in early-stage drug discovery by significantly decreasing time and costs. A study by Koch [8] showed that ML models could predict the PK profiles of new compounds with high accuracy, lessening the need for extensive *in vitro* testing by up to 25%.

Furthermore, some of the advantages of using ML include its ability to detect new adverse effects early in the trial process, allowing the investigators to diminish the risk and enhance the study designs. From the large-scale clinical data sets, ML algorithms can identify precursory signs of an adverse event and prevent the occurrence of such an event rather than leading to a trial failure due to safety concerns [2]. This mitigative approach to managing risks improves patient safety and regulatory compliance in accelerating drug development and lessens expenses for managing adverse events. For instance, in early-stage drug discovery, ML techniques have been effectively employed to predict PK properties, significantly shrinking the time needed to screen potential drug candidates. Indeed, a case study on [specific drug or study] demonstrated how ML-enabled predictions accelerated the lead compound identification process, highlighting a reduction in both time and cost compared to traditional methods.

From a regulatory perspective, using ML in designing drug development processes presents benefits in compliance with regulatory submissions and enhances the flow of drug approval. Even the most conservative regulatory organizations, including the U. S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have recently joined the trend, acknowledging the potential of applying ML-aided methods to predict drug behavior and fine-tune dosing regimens [9]. It should be noted that FDA facilitates health policy action while the EMA reviews pharmaceutical productions in the EU.

ML models can offer scientific substantiation of drug safety and efficacy to regulators and facilitate this process, reducing review time. Furthermore, by helping to identify who among the patients will have different pharmacokinetic profiles, ML helps to allow the regulators to assess the drugs as intended for the particular patient populations [5]. The groups could include pediatric, geriatric, ethnic and genetic groups.

Personalized Medicine

Personalized medicine (PM) represents a new approach to medical practice that focuses on an individualized treatment approach based on each patient's genotype, phenotype, and environment. According to PK, PM uses enhanced machine learning to project PK values and tailor drug therapies for patients with specific diseases, thereby improving the effectiveness of treatments. Personalized PK Predictions use relevant information on the patient to develop drug therapies that suit the specific PK values of the patient. Some of the aspects of drugs that are taken into consideration include genetic makeup and biomarker data, as well as clinical statistics, so as to be in a position to determine how the drug will perform in the patient.

For example, ML techniques in oncology can integrate genomic data with PK models. The model can predict the efficacy of targeted therapies in cancer patients. The above models have predicted how individual patients metabolize specific chemotherapeutic agents [6]. Validating the personalized models requires root-mean-square error (RMSE) and mean absolute error (MAE) metrics. The above metrics help quantify the accuracy of PK predictions in real-world scenarios [4]. Therefore, based on metabolism rates, drug interactions, and disease states, the application of ML has its advantage in allowing healthcare providers to determine the correct dosage and administration schedules that will improve the effect of the drugs as well as prevent any side effects.

The primary advantage of individualized PK prediction is the prospect of optimizing therapy efficacy and reducing the incidence of adverse effects. Standard dosing practices usually involve universal dosages that lack consideration for different inter-individual drug responses [3]. In using the patient's PK profile, the application of ML thus deters toxicity rates and therapeutic failure, ensuring a high-quality outcome for the patient.

In several case studies, the combination of ML with PK prediction has proven efficient in rendering PM within various therapeutic specialties such as cancer and diabetes. In oncology, using ML algorithms enables the evaluation of a patient's genetic markers and biomarkers and outlines their response to chemotherapy, immunotherapy and targeted therapy [4]. This is important in identifying treatments believed to affect a specific patient positively; this improves the patient's survival rates based on the PK predictions. Similarly, in diabetes, ML using patients' data, including glucose, insulin ratios and food intake, determines the optimal insulin dosing plan for glycemic control [6]. By defining the patient's insulin sensitivity and variability in postprandial response, the ML algorithms can enhance insulin delivery, providing a safer metabolism and lowered tendencies of hypoglycemic and hyperglycemic events.

In diabetes management, ML models integrating patient-specific data like glucose levels can dynamically adjust insulin dosing, leading to a 15% improvement in glycemic control [6]. This level of real-time adjustment is unattainable with standard population-based models, demonstrating ML's superior adaptability. In oncology, ML has been applied to tailor chemotherapy regimens to individual patients, improving treatment efficacy and reducing toxicity. [2], for example, found that ML algorithms could personalize dosing for cancer patients, leading to a 20% reduction in adverse effects compared to traditional methods.

In the future, the application of ML in PM will offer significant value in improving patients' health status. This will come about by creating personalized prognoses through advanced PK algorithms. This can improve treatment, minimize potential adverse effects, and improve outcomes in different patient populations. However, there remain challenges with data credibility, data privacy and legal concerns that must be addressed to enhance the relevance of ML in PM [5]. Therefore, the concept of an individualized approach

in connection with applying ML methodology in medicine can be considered a breakthrough in the disease treatment field, as this approach will be more effective, considering some peculiarities of the patient's organism (Figure 1).

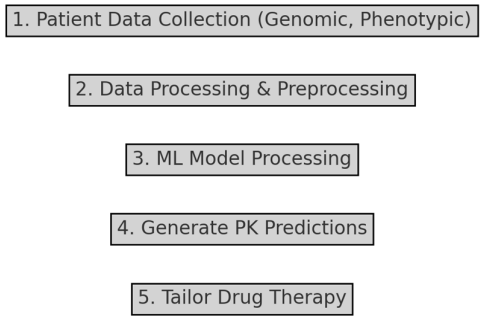

Figure 1. Personalized Medicine Workflow Using ML highlighting key stages – from data collection, to tailored drug therapy

Future Prospects

Implementing ML into PK modeling is the key to a bright future of PM and drug development. With the ongoing growth of more sophisticated ML algorithms and the expansion of big data sets, the potential for improving precision medicine and timely tailoring of effective treatments is virtually endless. Among the future implications, one of the most important is the improvement of ML algorithms to increase accuracy and the ability to work with various patients. To enhance PK prediction, researchers should rely on the deep learning approach, reinforcement learning, and ensemble modeling, as these methods would make the algorithms more reliable and interpretable, while enhancing the capture of PK dynamics [6]. These advanced algorithms will help healthcare providers develop more accurate individualized PK predictions that would assist them in making more precise and better treatment decision calls.

The blend of multiple information sources is widely considered a trend with great potential for expanding ML for PK modeling and, indirectly, for PM. As technologies for generating and aggregating variables and heterogeneous data sources progress, investigators can incorporate many kinds, such as omics data, imaging data, wearable sensor data and patient-reported outcomes [5]. These multiple data streams would be integrated with ML models and can help the understanding of the patients as individuals so as to form individually tuned treatment plans that embrace their characteristics.

One more promising future application of ML is in the fields of predictive toxicology and adverse event prediction. With the help of extensive databases on pharmacovigilance, Electronic Health Records (EHR), and preclinical toxicity data, ML algorithms can detect late-onset adverse effects and personal risks of drug-induced toxicity [2]. Such an approach towards risk evaluation will help healthcare organizations to deal effectively with safety issues regarding medications, improve treatment outcomes, and ensure better patient protection during all phases of drug development.

Furthermore, there is a possibility that by democratizing ML tools and techniques, healthcare providers and researchers will benefit globally. Increasing the availability and ease of use of platforms for healthcare specialists of different profiles and training and the assessment of pharmacokinetics and individual predictions, as well as the immediate optimization of therapy schemes, are becoming possible due to the use of ML solutions [3]. As ML techniques are made more accessible, the future of personalized medicine is poised to expand along with advancing healthcare and quality of life and pursuing fairness in its execution (Figure 2).

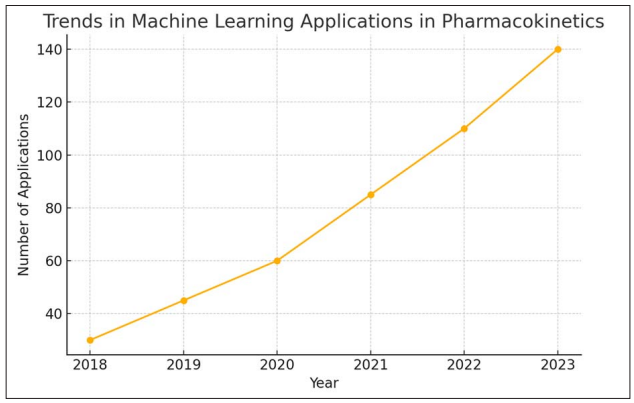

Figure 2. PK Process with ML Interventions

Challenges and considerations

Even though machine learning has a massive potential use in PK modeling and PM, certain limitations and issues need to be discussed and solved to realize the novel technology's full potential and implement it by ethical and fair principles [1]. Data Quality and Integration are critical issues in ML-driven PK modeling, as the quality of a model is directly linked to the data on which those models are built. Problems like the lack of complete datasets, biases, or inaccuracies are critical, as they contribute to model failures and subpar predictions, which are dangerous for patients and their treatment outcomes [1]. Enhancing such aspects of data quality requires proper methods of curation of the data, well-defined reporting mechanisms, and continuous efforts to validate and validate cross-sectional data.

Another potential concern is the legal and regulatory aspects of using patient data to create the ML-based PK modeling, given that health information is susceptible to legal challenge. Issues of patient data privacy, patient identity, customers' rights, and their consent to the use of data for ML are the factors that determine trust and information transparency [4]. Therefore, healthcare organizations and other regulatory authorities should establish governance measures, ethical practices, guidelines and protocols to ensure that patient rights are protected from being violated and to prevent unauthorized usage or presentation of the data.

The integration of various disciplines is crucial in tackling the complex problems that arose from the application of ML in drug PKs and PM. Realizing these goals requires the cooperation of data scientists with pharmacologists, clinicians, regulatory professionals and patients, validating predictions and consequent hypotheses, and interdisciplinary collaboration to implement the study outcomes [5]. Consequently, internal and external healthcare stakeholders may need to integrate and collaborate to acquire the know-how

required to address the various implications arising from the advent of PM.

Furthermore, it is also necessary to inculcate equity and inclusion within ML to avoid the escalation of inequality in the healthcare sector regarding PM. Thus, to prevent the generation of these suboptimal algorithms that work differently across different populations, high-quality healthcare data, computational resources, and the knowledge of ML should be available to each population [6]. Therefore, efforts should be made to remove algorithmic biases and inequalities in healthcare administrative systems to ensure health equity and reduce systematic injustice in healthcare administration. Given all these challenges and conditions, proper application of ML in PKs and PM is necessary to cope with all these problems and situations with ethical considerations in applying ML. The PK process, however, involves various stages where ML can intervene, from absorption modeling to excretion predictions (Figure 3).

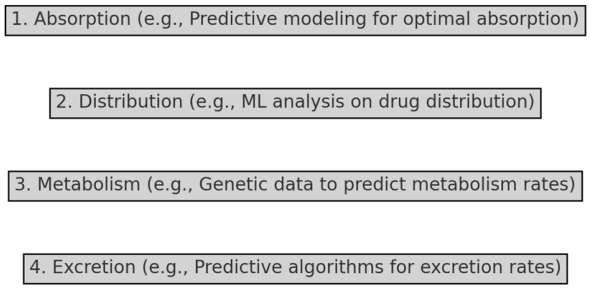

Figure 3. Trends in Machine Learning Applications in Pharmacokinetics

Expanding on Ethical and Regulatory Challenges

The application of ML in PKs presents significant challenges concerning patient data privacy and protection. Collaborating with regulatory bodies to ensure data protection compliance and adherence to ethical standards is essential for maintaining trust and transparency in research [9]. Some key issues in this domain include:

Data Privacy and Security

Patient Data Sensitivity: The use of large datasets, particularly those involving patient health records (EHR), genetic information and other sensitive data, raises significant concerns about patient privacy. ML models often require extensive data to be effective, which can conflict with patients' rights to confidentiality. Therefore, stringent data protection measures, such as encryption, anonymization and restricted access protocols, are necessary to safeguard patient information.

Compliance with Data Protection Regulations: Regulations like the General Data Protection Regulation (GDPR) in the European Union and the Health Insurance Portability and Accountability Act (HIPAA) in the United States impose strict rules on the collection, storage and processing of personal health data. Ensuring that ML applications in PK are compliant with these regulations is essential. Noncompliance could lead to legal consequences, such as hefty fines and damage to reputation, which could hinder the adoption of ML technologies in healthcare.

Ensuring compliance with data protection regulations like GDPR and HIPAA is essential for maintaining patient privacy in ML-driven PK modeling. Sherer [10] discuss effective strategies for aligning ML models with these standards, including the use of data anonymization techniques and robust encryption protocols to secure patient data.

Algorithmic Bias and Fairness

Risk of Bias in ML Models: ML models can inadvertently incorporate biases present in the training data, leading to skewed predictions that may affect certain demographic groups disproportionately. In the context of PK, this can result in suboptimal drug dosing recommendations for underrepresented groups, potentially exacerbating health disparities.

Addressing Algorithmic Fairness: To mitigate these risks, it is crucial to evaluate ML models for bias and to ensure that they are tested on diverse datasets that represent the target population. Incorporating fairness constraints into model training and regularly auditing ML systems can help ensure that personalized medicine is equitable and inclusive.

Algorithmic fairness is a crucial concern in ML-based PK modeling, as biases present in training data can lead to skewed predictions that disproportionately affect certain populations. For example, Bies [11] highlighted how data biases could result in suboptimal dosing recommendations for minority groups, underlining the importance of using diverse and representative datasets to improve algorithmic fairness in personalized medicine.

Transparency and Explainability

Challenges of Black-Box Models: Many ML models, particularly deep learning models, operate as black boxes, making it difficult for clinicians and regulators to understand how specific predictions are made. This lack of transparency can be problematic in healthcare, where understanding the rationale behind a decision is critical for patient trust and clinical decision-making.

Regulatory Expectations for Explainability: To comply with regulations and ensure the ethical use of ML in healthcare, there is a growing need for models that are interpretable. Techniques such as model simplification, the use of explainable algorithms (like decision trees), and post-hoc interpretability methods (e.g., SHAP, LIME) can help to elucidate how models arrive at specific predictions. This transparency is necessary for gaining regulatory approval and for fostering trust among healthcare providers and patients.

Clinical Validation and Accountability

Ensuring Model Validity and Reliability: ML models used in PK must undergo rigorous clinical validation to confirm that they produce reliable and accurate predictions. Unlike traditional statistical methods, ML models require ongoing validation due to potential shifts in data patterns and the inherent variability in patient populations.

Assigning Accountability: Determining who is accountable for ML-generated recommendations is a key challenge, particularly in healthcare settings where decisions can have serious implications for patient outcomes. Healthcare institutions must establish clear guidelines on the responsibilities

of model developers, data scientists, clinicians and other stakeholders. This accountability is essential to navigate legal and ethical issues surrounding liability in cases of adverse outcomes resulting from ML-driven decisions.

Informed Consent and Patient Autonomy

Ethical Implications of Data Use: Obtaining informed consent for the use of patient data in ML models is crucial. Patients should be fully aware of how their data will be used, the potential risks and their rights to withdraw consent. Transparent communication about data usage builds trust and aligns with ethical principles of patient autonomy.

Opt-in *vs*. Opt-out Models: Some patients may prefer to opt-in for data sharing, while others may wish to opt-out. Regulatory frameworks need to accommodate these preferences, ensuring that patients have control over their personal information and that their choices are respected without compromising access to high-quality care.

By addressing these ethical and regulatory challenges, the integration of ML into PK and PM can proceed in a manner that respects patient rights, promotes fairness, and complies with legal standards. Ethical and transparent use of ML in healthcare not only ensures patient safety but also builds the foundation for public trust, which is essential for the widespread adoption of these technologies in personalized medicine.

CONCLUSION

In conclusion, integrating ML in PK modeling significantly advances drug metabolism and individualization [12]. In this way, applying powerful algorithms and cooperation with various disciplines assist in improving the forecast of drug behavior, patient treatment plans, and outcomes by solving various comprehensive problems with the help of big data and ML approaches. For instance, in drug discovery, using ML techniques, the PK properties of newly synthesized molecules can be predicted, dose schedules during clinical trials can be established, and patient-specific drug treatments based on the patient's genetic profile can be administered. The attributes of ML versus traditional PK techniques are summarized in Table 3.

Table 3. Comparison of the attributes of traditional PK and ML Techniques

Aspect	Traditional PK	Machine Learning (ML)
Data Sources	Limited to small-scale clinical trials and empirical models	Utilizes big data from EHR, molecular data, and clinical trials
Modeling Approach	Based on compartmental models	Incorporates flexible algorithms like neural networks and random forests
Accuracy	Subject to high inter-individual variability	High accuracy in predicting complex nonlinear relationships
Flexibility	Less adaptable to complex datasets	Highly adaptable to large and varied datasets
Applications	Mainly used for population-wide analysis	Suited for both individual and population-wide predictions

However, several obstacles must be considered to achieve this potential, such as data quality, privacy, ethical questions and health equity. With growing research and more robust interaction between researchers and healthcare providers, the future of ML technology in understanding PKs and developing PM looks promising. There is tremendous potential in the progressive enhancement of customized therapy, better treatment plans, and quality healthcare for patients worldwide. Through the adoption of ML-based solutions and ensuring that ethical objectives are the guiding policies on the use of ML, the intended benefits of this approach could be realized to transform healthcare systems and potentially enhance patient care for various generations to come [13].

ORCID iDs

Łukasz Dudarski https://orcid.org/0009-0008-5511-3578

REFERENCES

1. Chou WC, Lin Z. Machine learning and artificial intelligence in physiologically based pharmacokinetic modeling. Toxicol Sci. 2022;191(1):1-14.
2. Janssen A, Bennis FC, Mathôt RAA. Adoption of machine learning in pharmacometrics: An overview of recent implementations and their considerations. Pharmaceutics. 2022;14(9):1814.
3. McComb M, Bies R, Ramanathan M. Machine learning in pharmacometrics: Opportunities and challenges. Br J Clin Pharmacol. 2021.
4. Terranova N, Venkatakrishnan K, Benincosa LJ. Application of machine learning in translational medicine: Current status and future opportunities. AAPS J. 2021;23:4.
5. Pawar V, Patil A, Tamboli F, Gaikwad D, Mali D, Shinde A. Harnessing the power of AI in Pharmacokinetics and Pharmacodynamics: A comprehensive review. Int J Pharm Qual Assur. 2023;14(2):426-39.
6. Sahu M, Gupta R, Ambasta RK, Kumar P. Artificial intelligence and machine learning in precision medicine: A paradigm shift in big data analysis. In: D. B. Teplow (ed). Science Direct Academic Press; 2022.
7. McCoubrey LE, Elbadawi M, Orlu M, Gaisford S, Basit AW. Harnessing machine learning for the development of microbiome therapeutics. Gut Microbes. 2021;13(1):1-20.
8. Koch G, Pfister M, Daunhawer I, Wilbaux M, Wellmann S, Vogt JE. Pharmacometrics and machine learning partner to advance clinical data analysis. Clin Pharmacol Ther. 2020;107:926-33.
9. Vora LK, Gholap AD, Jetha K, Thakur RRS, Solanki HK, Chavda VP. Artificial intelligence in pharmaceutical technology and drug delivery design. Pharmaceutics. 2023;15(7):1916.
10. Sherer EA, Sale ME, Pollock BG, Belani C, Egorin MJ, Ivy PS, et al. Application of a single-objective, hybrid genetic algorithm approach to pharmacokinetic model building. J Pharmacokinet Pharmacodyn. 2012;39:393-414.
11. Bies RR, Muldoon MF, Pollock BG, Manuck S, Smith G, Sale ME. A Genetic algorithm-based, hybrid machine learning approach to model selection. J Pharmacokinet.Pharmacodyn. 2006;33:195-221.
12. Simonsson USH, You H, Farnoud A, Nyberg J, Wicha SG, Maher-Edwards G, et al. Machine learning and pharmacometrics for prediction of pharmacokinetic data: Differences, similarities and challenges illustrated with rifampicin. Pharmaceutics. 2022;14(8):1530.
13. Janssen A, Leebeek F, Cnossen H, Mathôt R. The neural mixed effects algorithm: leveraging machine learning for pharmacokinetic modelling. [https://www.page-meeting.org/?abstract=9826] (accessed: 10 Jul 2024).