REVIEW PAPER

Artificial Intelligence in Pharmacokinetics and Biopharmaceutics: Current Applications, Challenges, and Future Perspectives

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Abstract

Artificial intelligence (AI) is transforming pharmacokinetics and biopharmaceutics by enabling data-driven approaches that enhance drug development, pharmacokinetic prediction, and precision therapeutics. This review provides a comprehensive overview of current AI applications, methodological advances, clinical integration, challenges, and future directions in pharmacokinetic and biopharmaceutical sciences. A structured literature search was conducted using PubMed, Scopus, and Web of Science databases, covering publications from January 2018 to December 2023, with emphasis on studies involving pharmacokinetic modeling, ADME prediction, drug-drug interaction assessment, bioavailability prediction, and AI-assisted clinical dosing. Machine learning algorithms, including random forests, support vector machines, gradient boosting methods, graph neural networks, and deep learning architectures, have demonstrated substantial potential in predicting pharmacokinetic parameters, optimizing absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles, and improving drug formulation strategies. AI-driven frameworks also facilitate the identification of complex drug-drug interactions and enhance bioavailability and dissolution modeling through advanced neural network approaches. Clinically, AI-enabled therapeutic drug monitoring, model-informed precision dosing, reinforcement learning, and adaptive decision-support systems have shown promise in personalizing treatment regimens and improving therapeutic outcomes. However, widespread implementation remains constrained by data heterogeneity, limited external validation, interoperability challenges, regulatory uncertainties, computational demands, and concerns regarding model interpretability. Emerging technologies, including multimodal foundation models, explainable AI, digital twins, federated learning, and large language models, offer opportunities to bridge the gap between predictive performance and clinical applicability. Overall, AI has the potential to revolutionize pharmacokinetic and biopharmaceutical research by supporting more accurate predictions, individualized therapies, and real-time clinical decision-making, provided that robust validation frameworks, transparent methodologies, and interdisciplinary collaboration are established to ensure safe, ethical, and effective implementation.

Keywords: Artificial Intelligence in Pharmacokinetics, Biopharmaceutics and Machine Learning, ADME and ADMET Prediction, Model-Informed Precision Dosing, AI-Driven Drug Development and Personalized Medicine

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Introduction and Background

The integration of artificial intelligence into pharmaceutical research may represent a paradigm shift, transitioning from traditional trial-and-error methodologies to data-driven, predictive models that accelerate the drug development pipeline [1]. This transformation is underpinned by a spectrum of computational techniques most notably machine learning and deep learning that facilitate the analysis of complex datasets to optimize lead compound selection, predict pharmacokinetic properties, and refine experimental design [2,3]. Beyond mere data processing, these technologies now address the critical need for explainability in modeling complex biological systems, thereby ensuring that predictive insights remain actionable within regulatory and clinical frameworks [4,5]. This review provides a comprehensive synthesis of how computational frameworks, such as machine learning and natural language processing, are currently reshaping pharmacokinetic and biopharmaceutical workflows, including drug formulation and real-time dose optimization [6].

Literature Search Strategy

To ensure a rigorous and transparent synthesis of current literature, a systematic search was conducted across databases including PubMed, Scopus, and Web of Science, covering publications from January 2018 to December 2023. Search queries integrated combinations of terms such as "artificial intelligence," "machine learning," "pharmacokinetics," and "biopharmaceutics" to capture the breadth of both mechanistic and data-driven methodologies. Studies were included based on their focus on predictive ADME modeling, integration of pharmacokinetic-pharmacodynamic frameworks, and the application of AI to optimize drug delivery or clinical dosing [7],[8]. Conversely, articles were typically excluded if they appeared to lack reproducible validation metrics or a demonstrable connection to quantitative pharmacological outcomes. This rigorous filtration suggests that the selected studies prioritise clinical

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translational value and robust validation against experimental benchmarks. By prioritising evidence from both peer-reviewed methodologies and validated computational models, this review suggests a potential role for AI in addressing the data-heavy limitations inherent in traditional allometric scaling and mechanistic simulations [9],[10].

AI Methodologies in Pharmaceuticals

The computational foundation of these methodologies relies on a diverse hierarchy of paradigms, ranging from classical machine learning algorithms like random forests and support vector machines, which are used in Absorption, Distribution, Metabolism, and Excretion (ADME) prediction to deep neural networks capable of capturing complex, non-linear relationships in pharmacokinetic data[11] Specifically, tree-based ensemble methods such as XGBoost and random forests are well-suited for managing smaller datasets and avoiding overfitting during the prediction of physiological parameters [12]. In contrast, deep learning architectures, such as graph convolutional networks and recurrent neural networks, are used to learn molecular representations directly from chemical structures, facilitating a more nuanced analysis of drug-target interactions[13],[14] Furthermore, integrating these deep learning (fig 1) architectures with mechanistic compartmental models allows for the implicit incorporation of physiological constraints, which may significantly mitigate estimation errors prevalent in conventional curve-fitting techniques[15].

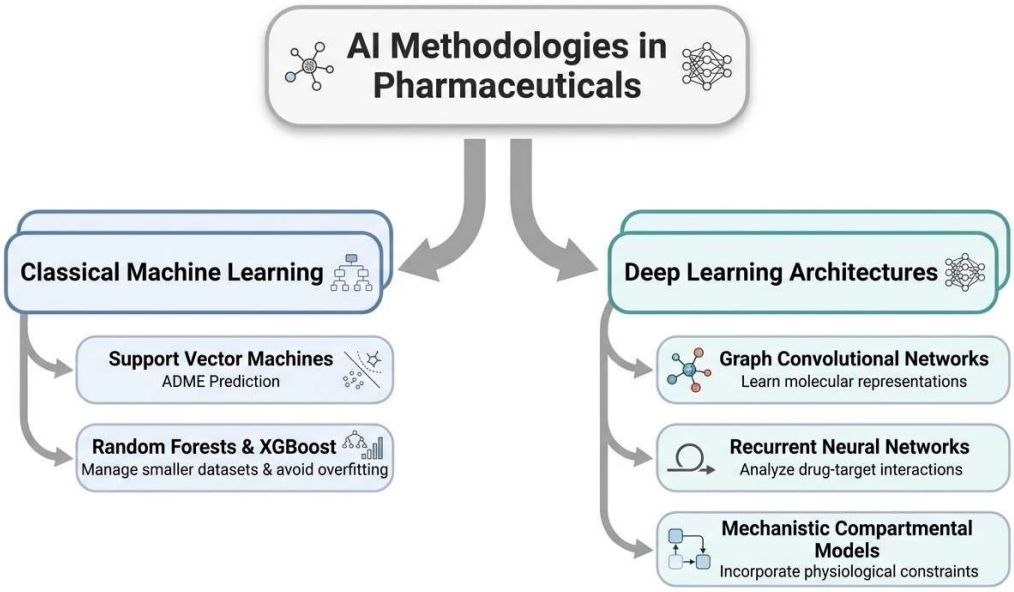

Fig 1: Hierarchy of AI Methodologies in Pharmaceuticals

AI in Pharmacokinetic Modeling

The implementation of modern pharmacokinetic modeling is increasingly leveraging machine learning to enhance dose prediction by processing vast longitudinal datasets that surpass the capacity of classical non-compartmental or compartmental analyses [16]. For instance, advanced algorithms, including gradient boosting and convolutional neural networks, facilitate the refinement of clearance predictions and the identification of vital covariate effects that traditional stepwise methods may overlook [17]. These machine-learning platforms, often complemented by graph neural networks, may facilitate the rapid and accurate assessment of absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles, shifting the predictive focus from simple curve fitting toward comprehensive safety modeling [18]. While traditional quantitative structure–activity relationship models have long been utilized to estimate physicochemical parameters like log P, they may manifest significant limitations when predicting intricate biological responses, frequently arising from restricted training sets and a reliance on potentially erroneous experimental data [19]. In contrast, modern deep learning approaches mitigate these limitations by implicitly integrating molecular structure with physiological constraints, thereby suggesting potential enhancements in the accuracy of forecasting complex plasma concentration-time profiles [20]. Moreover, hybrid models now synthesize deep learning with mechanistic compartmental systems to approximate complex biological processes like metabolic transitions, thereby potentially circumventing the computational demands associated with traditional methods [21]. Additionally, the deployment of phenotype-based deep learning and transformer-based architectures has emerged as a robust alternative, enabling the decoding of non-linear patterns directly from compound activity profiles with greater computational efficiency than static rule-based systems [22].

ADME Prediction

Current computational strategies for absorption, distribution, metabolism, and excretion assessment utilize diverse machine learning architectures to map molecular features to pharmacokinetic endpoints with increasing fidelity. Graph neural networks, in particular, allow for the rapid prediction of ADMET profiles, thereby streamlining the selection of lead candidates during early discovery [23]. These deep learning models may exhibit consistent superiority over traditional random forest approaches, particularly when applied to high-throughput screening data for endpoints such as hepatic microsomal stability and plasma protein binding [24]. By facilitating the analysis of large libraries of compounds, these predictive platforms offer a scalable alternative to resource-intensive in vitro metabolic assays [23]. Furthermore, these artificial intelligence (AI)-driven frameworks may address critical gaps in coverage by providing pharmacokinetic and toxicity predictions for diverse chemical scaffolds that often remain opaque to conventional, target-specific computational models [25]. Recent advancements, such as the implementation of DeepCt, appear to facilitate the direct prediction of concentration-time curves, effectively bridging the gap between molecular structural features and dynamic compartmental modeling [26]. Similarly, unified neural frameworks incorporating neural ordinary differential equations have shown promise in modeling dynamic concentration trajectories while maintaining mechanistic grounding, which enhances generalizability beyond the constraints of traditional compartmental analysis [27].

Drug-Drug Interactions

Advanced computational frameworks for identifying drug-drug interactions have transitioned toward sophisticated graph embedding methods that model interactions as link prediction problems within expansive knowledge graphs [28]. Specifically, graph neural networks and hypergraph architectures appear to excel at capturing high-order relationships between drugs and side effects by modeling sparse connectivity patterns that characterize multi-type interaction scenarios [29]. By leveraging these topological features, researchers may be able to forecast complex drug-enzyme interactions and metabolic interference that traditional screening methods often fail to detect [30]. Furthermore, architectures such as the 'AttentionDDI' model appear to have enhanced clinical utility by employing attention mechanisms to provide interpretability regarding specific molecular substructures responsible for adverse pharmacological interference [11]. These predictive models may increasingly support clinical decision-making by identifying latent risk profiles in polypharmacy, allowing practitioners to anticipate potential adverse events before they manifest in patient populations [31]. Despite these advancements, practitioners must remain cognizant of significant bottlenecks, such as data sparsity, source heterogeneity, and the presence of unreliable negative samples, which continue to challenge the robust clinical validation of these predictive frameworks [32]. To further mitigate these limitations, emerging approaches incorporate natural language processing to extract structured information from chemical sequences alongside hierarchical representation learning to integrate complex biological similarity networks [33]. For example, models like SumGNN leverage these knowledge graphs to extract relevant subgraphs and generate reasoning paths, which appears to improve the precision of multi-typed interaction predictions [34].

AI in Biopharmaceutics

Machine learning algorithms are increasingly utilised to predict intestinal drug absorption by integrating physicochemical properties with physiological parameters, which may enhance the precision of oral bioavailability estimations[35]. These models concurrently classify compounds within the Biopharmaceutics Classification System by analysing the interplay between aqueous solubility and membrane permeability[36]. These predictive frameworks further optimize dissolution modelling by identifying key dissolution parameters through physics-informed and deep neural networks[37]. Furthermore, the integration of attention-based mechanisms has appeared to bolster model interpretability by highlighting the specific molecular descriptors that dictate dissolution rates, thereby providing insights for formulation design[38]. Beyond solubility-permeability mapping, advanced generative models are now being deployed to predict the impact of formulation-specific excipients on drug dissolution profiles, potentially providing a digital foundation for evaluating the bioequivalence of complex drug delivery systems[39].

Bioavailability Prediction

Sophisticated neural network architectures may be utilized to estimate oral bioavailability by integrating diverse datasets, including physiological transit kinetics and complex drug-delivery matrix interactions. New research indicates that deep learning models are being developed to potentially facilitate the prediction of oral drug absorption and bioavailability from in vitro data by integrating complex physiological and drug interaction parameters. These architectures leverage graph-based transformers to map molecular topologies directly onto systemic clearance pathways, potentially enabling more precise predictions for non-oral administration routes such as transdermal or parenteral delivery. Moreover, these models facilitate robust in vitro-in vivo correlation by utilizing neural networks to interpret the non-linear relationship between dissolution data and plasma concentration trajectories, potentially mitigating the temporal and economic burden of traditional kinetic evaluations. Specifically, physics-informed neural networks have been integrated, which may combine with deep learning architectures to extract fundamental dissolution rate constants and saturation parameters from experimental data, overcoming previous

limitations in predicting dissolution profiles [37]. Furthermore, the hybridization of machine learning with physiologically based pharmacokinetic modeling may permit the prediction of complex parameters such as the fraction unbound in plasma and total clearance, providing a powerful methodology to overcome the physiological complexities often inaccessible to standard in vitro assays [40].

Clinical Applications

In clinical settings, artificial intelligence-driven pharmacokinetic tools appear to be increasingly deployed to automate therapeutic drug monitoring, enabling real-time adjustments of dosage regimens for narrow therapeutic index medications. These systems leverage patient-specific physiological data to optimize dosing in electronic health records, thereby reducing the incidence of toxic exposure during routine hospital care[41]. However, the clinical validation of these tools remains heavily dependent on rigorous prospective trials that demonstrate improved patient outcomes beyond mere pharmacokinetic precision [42]. Evidence currently suggests the necessity of robust multi-center study protocols, as such external validation appears essential for ensuring consistent performance across heterogeneous patient populations[43]. To address these challenges, clinical practitioners are transitioning toward adaptive learning systems that continuously update model parameters based on real-world evidence, thereby improving decision-support accuracy within diverse healthcare ecosystems. This transition toward "artificial intelligence enabled clinical pharmacologists" signifies a critical shift from static modeling to dynamic, data-driven stewardship of patient therapy. Such advancements may facilitate the conceptual integration between modern deep learning paradigms and traditional pharmacokinetic and pharmacodynamic methodologies, ensuring that models remain both pharmacologically meaningful and actionable in real-time care settings [44]. For instance, the application of machine learning in combination with population pharmacokinetics has demonstrated clinical utility in refining individualized clearance estimations for agents like tacrolimus in pediatric populations [45]. Such deployments may highlight the transition from theoretical predictive potential to functional technologies that may demonstrably influence clinical decision-making and patient management [46]. Despite these advancements, widespread clinical integration faces hurdles as prospective, large-scale trials remain necessary to confirm the real-world impact of AI-predicted pharmacogenes and dosage optimizations on therapeutic target attainment[47]. For example, the prospective validation of the CURATE.AI platform has already demonstrated that dynamically adjusting chemotherapy dosages based on real-time tumor marker feedback can improve patient response rates while simultaneously lowering the risk of adverse events [41]. Moreover, ensuring the clinical reliability of these autonomous systems necessitates stringent external validation protocols that utilize datasets distinct from initial training cohorts to mitigate performance biases [48]. Furthermore, the implementation of "human-in-the-loop" agentic workflows ensures that clinicians maintain oversight of autonomous recommendations, balancing computational efficiency with essential regulatory and safety standards [49]. To further advance clinical adoption, integrating Model-Informed Precision Dosing within population health informatics is essential for transforming AI-driven insights into scalable, bedside decision-support tools [50]. Integrating these ensemble-based models into hospital information systems can substantially reduce computational overhead during covariate screening, thereby facilitating more agile adjustments to personalized dosing regimens [51]. Furthermore, the utilization of biosensors in conjunction with these systems allows for continuous, real-time monitoring of drug concentrations, enabling a proactive approach to maintaining therapeutic targets rather than reactive dose modifications[52].

Empirical Evaluations and Clinical Integration of Artificial Intelligence

Recent clinical investigations have begun to integrate machine learning with physiologically based pharmacokinetic models to optimize dosing regimens for infectious diseases, specifically targeting the impact of enzyme and transporter variants on drug exposure [53]. Furthermore, these studies emphasize the transition from traditional therapeutic drug monitoring to Model-Informed Precision Dosing, which rigorously integrates mathematical predictions with patient-specific covariates to enhance outcomes in fields such as oncology and transplant medicine [54]. For example, reinforcement learning methods are being increasingly utilized to automate dose individualization in oncology, enabling model-free predictions that maximize therapeutic efficacy while minimizing systemic toxicity [55]. Similarly, Bayesian sequential hierarchical modeling has been successfully applied to optimize neutrophil-guided paclitaxel dosing, demonstrating the capability of continuous learning frameworks to adapt to individual patient trajectories over time[56]. Additionally, continuous learning approaches have been validated in pediatric vancomycin dosing, where population models were successfully refined to reflect local clinical environments and improve predictive accuracy [56]. Furthermore, research has established the feasibility of utilizing automated dosing software to assist intensive care unit personnel in managing antibiotic administration, while the exploration of novel Neural Ordinal Differential Equations may facilitate the capture of hidden, time-varying physiological effects, such as fluctuating renal clearance, [57]. Additionally, recent efforts have demonstrated that combining population pharmacokinetic models with machine learning strategies improves the prediction of individual clearance rates for renally eliminated drugs in neonates [58]. In parallel, the development of the "MeroDose" clinical decision support system suggests that the

integration of machine learning with patient-specific Continuous Renal Replacement Therapy (CRRT) parameters and clinical variables may substantially enhance the precision of individualized meropenem dosing compared to traditional models[59]. Similarly, robust random forest algorithms appear to exhibit superior accuracy in the prediction of steady-state trough concentrations for vancomycin; these models offer a potentially scalable alternative to conventional Bayesian frameworks for bedside therapeutic optimization[60]. Furthermore, emerging evidence suggests that machine learning models can serve as robust alternatives to traditional population pharmacokinetic approaches for guiding initial antibiotic therapy, particularly in scenarios where complex dosing regimens are required [61]. In parallel, the application of Extreme Gradient Boosting (XGBoost) algorithms to voriconazole therapy may prove effective in the identification of critical predictors—such as serum albumin and bile acid levels thereby achieving a 78.8% accuracy rate in the forecasting of toxic plasma trough concentrations [62]. Additionally, hybrid population pharmacokinetic–machine learning frameworks have enabled continuous learning from clinical data, providing a scalable mechanism to improve the predictive performance of Bayesian estimation for biologics like infliximab[63]. Beyond these applications, researchers have successfully utilized machine learning classifiers to select optimal pharmacokinetic models for individual patients, which significantly stabilizes therapeutic drug monitoring performance compared to static models [64]. Similarly, studies utilizing Gradient Boosting Machines to analyze rifampicin pharmacokinetics have demonstrated that machine learning can effectively predict entire plasma concentration-time series, providing a high-throughput alternative to computationally intensive mechanistic modeling [65]. Building on this progress, clinical trials involving remifentanil have further validated the utility of random forest models in forecasting concentration-time profiles using real-world data, confirming their adaptability to diverse dosing schedules [66]. These implementation efforts suggest that the transition from pilot-scale validation to widespread clinical integration necessitates rigorous prospective trial evidence to confirm long-term improvements in patient mortality and pharmacokinetic target attainment [59,60].

Translation to Practice

The successful translation of these predictive frameworks into routine bedside care remains hindered by significant interoperability challenges between electronic prescribing systems and complex decision-support algorithms[67]. Furthermore, the lack of standardized regulatory pathways for updating model parameters in real-time may present a critical barrier, as current hospital information systems are often ill-equipped to handle the dynamic nature of machine-learning-driven pharmacokinetic updates[68]. Moreover, clinicians often express skepticism regarding the "black box" nature of these algorithms, necessitating the development of interpretable Artificial Intelligence (AI) frameworks that provide transparent, evidence-based rationales for each recommended dose adjustment[69]. To overcome these hurdles, prioritization of the integration of these tools into Electronic Health Records (EHRs) may be essential to facilitate the automatic extraction of patient data and support continuous model refinement through automated pipelines that harmonize pharmacological parameters with real-time electronic health data[50]. Addressing the requirements for broader clinical adoption may also necessitate multicenter external validation studies, as current models frequently rely on single-center datasets that could limit their generalizability to diverse patient populations [70]. Ultimately, the achievement of clinical maturation necessitates a formalization of the transition from retrospective model performance metrics to prospective, controlled implementation trials, which ought to evaluate real-world clinical endpoints rather than statistical precision alone [71],[72]. Crucially, the successful implementation of model-informed precision dosing may necessitate robust clinical studies with sufficient statistical power to unequivocally demonstrate patient benefits and, subsequently, justify the associated costs of integration [72].

Challenges and Limitations

Despite these advancements, the reliance on retrospective designs in many current studies, often utilizing single-center databases, may inherently constrain (Fig 2) the capacity to establish definitive causality and generalizability [73]. Furthermore, existing decision-support systems frequently suffer from "alert fatigue," where the overwhelming volume of non-specific notifications leads clinicians to ignore critical dosing recommendations entirely [74]. Additionally, methodological rigor is frequently compromised by small sample sizes and the reliance on biased clinician responses, which undermine the trust necessary for the adoption of these tools in clinical workflows [69]. Beyond these data-centric issues, the persistent "black-box" nature of deep learning architectures may complicate the assignment of legal liability for adverse events, thereby creating significant regulatory uncertainty for healthcare institutions [75]. Moreover, the lack of external validation across diverse clinical settings may precipitate model overfitting, potentially resulting in overestimation and diminished performance when applied to external patient populations [76]. Furthermore, the challenges in accessing highly longitudinal samples may complicate the development of robust, model-based predictive approaches [77]. Furthermore, the computational overhead required for real-time model calibration and parameter estimation remains a technical bottleneck, as current pipelines often struggle to maintain timely updates when faced with complex, multi-dimensional pharmacokinetic datasets

[78]. Additionally, the reliance on incomplete covariate data often necessitates the imputation of missing values, which poses a significant challenge in maintaining data quality [79]. Moreover, the significant disparity between the highly controlled conditions of clinical research and the erratic nature of real-world oncology environments may often result in an inability to account for complex tumor heterogeneity and the microenvironmental diversity that fundamentally alters drug distribution [80].

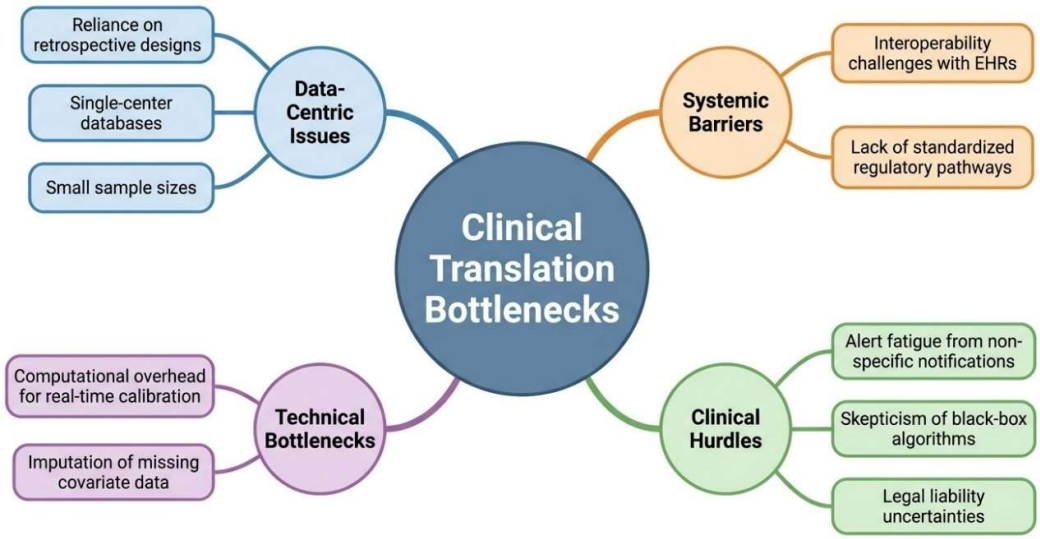

Fig 2: Bottlenecks in Clinical Translation

Future Perspectives

Future innovation may prioritize the development of explainable Artificial Intelligence architectures that bridge the gap between predictive accuracy and mechanistic transparency, thereby fostering clinician trust through interpretable decision rationales [5]. Moreover, leveraging reasoning-oriented large language models and continuous feedback loops between clinicians and automated systems may prove essential to ensure that recommendations remain grounded in real-world clinical outcomes and evidence-based pharmacotherapy [81]. Furthermore, the integration of multimodal foundation models may offer a transformative path forward, enabling the synthesis of heterogeneous patient data from genomic profiles to real-world pharmacokinetic signatures to refine precision dosing in real-time[82]. Simultaneously, establishing a strategic roadmap may necessitate the implementation of standardized regulatory frameworks that address data security, accountability for outcomes, and the validation of algorithmic diversity to ensure equitable patient care[83] This roadmap might also mandate the creation of collaborative workflows that incorporate functional drug response data alongside molecular profiling to establish a foundation for refining individualized treatment strategies and identifying novel predictive biomarkers [84].

Emerging Technologies

Beyond standard machine learning, the emergence of graph neural networks holds promise for modeling complex drug-target interactions within biological networks, significantly enhancing the precision of pharmacokinetic predictions[25]. Furthermore, the application of pretrained transformers and foundation models may facilitate the integration of high-dimensional, longitudinal clinical data, enabling more robust predictions of patient-specific drug response and treatment efficacy[85],[86]. These biomedical models, such as LLaVA-Rad, appear to demonstrate an increasing capacity to interpret complex diagnostic imaging and pathological conditions, thereby enriching the feature space available for individualized biopharmaceutical modeling[87]. Additionally, the adoption of digital twin technology—dynamic, simulation-enhanced virtual models may allow for the continuous integration of multi-omic, imaging, and real-time laboratory data to provide a longitudinal representation of patient physiology [88]. By synthesizing these emerging tools, practitioners could conceivably move toward a paradigm where predictive in silico modeling proactively informs dosing regimens, ensuring treatments are tailored to the right patient at the right time. Strategic integration might warrant prioritization of the adoption of "learning-and-confirming" cycles that reconcile computational outputs with regulatory standards, fostering a robust framework for evidence-based decision-making [89]. Ultimately, this multidisciplinary synergy, supported by policy-driven ethical frameworks and robust interdisciplinary collaboration, is essential to institutionalize AI-driven precision medicine as a standard of care while safeguarding patient equity and safety in therapeutic delivery [90].

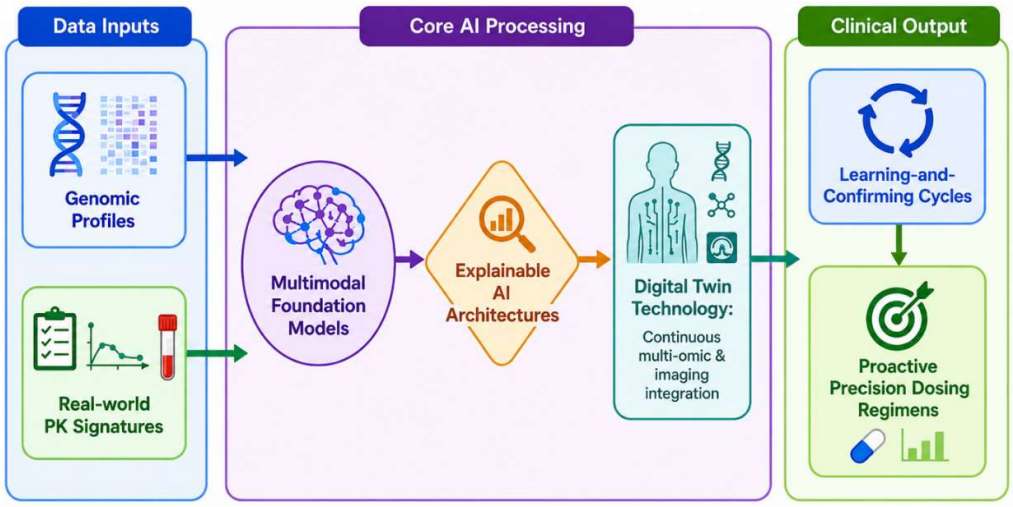

Fig 3: The Future Ecosystem of Precision Dosing

Conclusion

The integration of artificial intelligence into pharmacokinetics represents a paradigm shift toward truly personalized biopharmaceutics[1], necessitating a robust alignment between computational innovation and rigorous clinical validation. To bridge this gap, future efforts ought to prioritize the development of federated learning architectures that enable secure, privacy-preserving data sharing across institutions[91], which may enhance model robustness. Achieving this transformation may necessitate a concerted interdisciplinary approach and the fostering of continuous collaboration between clinicians, computational scientists, and regulatory experts to ensure that these sophisticated tools are both transparent and ethically sound. By committing to such collaborative workflows and prioritizing the creation of standardized, interpretable regulatory frameworks, the field could conceivably facilitate the transition of AI-driven models from promising research instruments into the foundation of a more equitable, personalized, and efficient clinical practice.

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