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Review

Predictive Pharmacokinetics Using Artificial Intelligence: A New Frontier in Rational Drug Discovery

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Abstract:
The integration of artificial intelligence and machine learning into pharmacokinetic prediction represents a fundamental advance in the quest to overcome the historical bottleneck of drug development. Current capabilities now extend beyond isolated property prediction, such as solubility or metabolic stability, toward sophisticated, integrated models that forecast comprehensive human PK profiles—including bioavailability, clearance, volume of distribution, and half-life—directly from molecular structure. These data-driven systems learn the complex, non-linear relationships that govern drug disposition, augmenting and often surpassing traditional metho ds like PBPK modeling, especially in early discovery where experimental data are sparse. By enabling *de novo* molecular design for optimal ADME properties and providing early, accurate human PK forecasts, AI/ML directly addresses the root cause of costly late-stage attrition, shifting the paradigm from reactive optimization to proactive, predictive design.

Keywords: Pharmacokinetics (PK), Bioavailability (BA), ADME (Absorption, Distribution, Metabolism, Excretion), Drug Development

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1. Introduction

The journey from a promising molecule to an effective medicine is a gauntlet of scientific and economic challenges, with the early stages of drug development presenting a particularly formidable bottleneck centered on the twin pillars of pharmacokinetics (PK) and bioavailability (BA)[1]. PK, the study of what the body does to a drug—encompassing its absorption, distribution, metabolism, and excretion (ADME)—and BA, the fraction of an administered dose that reaches the systemic circulation unchanged, are critical determinants of therapeutic success. A molecule may exhibit exquisite potency against a biological target in a petri dish, but this brilliance is rendered meaningless if it cannot be efficiently absorbed, if it is metabolized into inactivity before reaching its site of action, if it accumulates in toxic concentrations, or if it is expelled from the body before it can exert its effect[2]. This is the fundamental challenge of PK/BA in early development: bridging the chasm between in vitro efficacy and in vivo functionality[3]. The physicochemical properties of a compound—its solubility, permeability, and metabolic stability—become the arbiters of its fate. Poor aqueous solubility limits absorption, while excessive metabolism by enzymes like cytochrome P450 can destroy the drug molecule prematurely. Furthermore, the complex interplay of these processes within a living organism, influenced by genetics, diet, and disease state, creates a multidimensional puzzle that is extraordinarily difficult to solve using traditional, reductionist experimental approaches alone[4][5]. Historically,

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this puzzle has been addressed through iterative cycles of synthesis and testing—designing new analogues, profiling them in increasingly complex biological systems (from artificial membranes to animal models), and hoping to inch closer to an optimal ADME profile. This process is not only slow and resource-intensive but is also plagued by high failure rates, as predictive models based on simple rules or animal data often fail to translate accurately to humans. The consequences of failing to adequately address PK/BA challenges early are not merely a setback in timelines; they represent a catastrophic financial drain, manifesting most acutely in late-stage attrition[6][7]. The high cost of late-stage PK/BA failure is a dominant factor in the soaring economics of drug development. When a compound progresses through Phase I and II clinical trials based on promising therapeutic activity, only to reveal inadequate exposure, unpredictable pharmacokinetics, severe drug-drug interactions, or variable bioavailability in larger human populations during Phase III, the loss is monumental. By this stage, hundreds of millions, often exceeding a billion dollars, have been invested in synthesis, preclinical studies, and clinical trials[8][9]. The late-stage failure of a drug candidate due to suboptimal PK properties—a problem fundamentally rooted in its molecular design—represents the worst possible return on investment: all the cost with none of the revenue. Moreover, this attrition carries a profound opportunity cost. The capital, scientific talent, and clinical trial infrastructure consumed by a failing candidate are diverted from other potential therapies[10]. This economic reality creates a powerful disincentive for risk-taking and stifles innovation, as developers become increasingly conservative, favoring chemical scaffolds with known, if suboptimal, PK profiles over novel structures that might offer superior efficacy but carry greater ADME uncertainty. The industry's historical struggle with this issue has led to the infamous "90% failure rate" paradigm, where pharmacokinetics and toxicity remain leading causes of candidate mortality. Thus, the inability to accurately predict and optimize human PK/BA early is not just a technical problem; it is the central economic vulnerability of the pharmaceutical research and development model, driving up costs for healthcare systems and delaying the arrival of new medicines to patients[11].

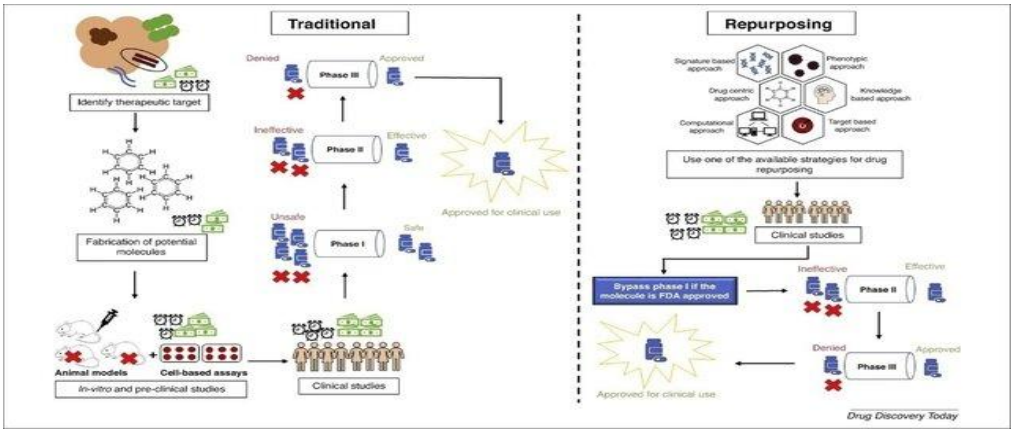

Fig: 1 A traditional drug discovery process vs drug repurposing

It is against this backdrop of persistent challenge and staggering cost that the promise of artificial intelligence (AI) and machine learning (ML) emerges as a potentially transformative force. AI/ML offers a paradigm shift from the iterative, trial-and-error methodology to a predictive, data-driven, and generative science[12][13]. The core promise lies in these systems' ability to ingest, integrate, and find complex, non-linear patterns within vast, heterogeneous datasets far beyond human cognitive capacity. This includes not only high-throughput experimental ADME data from past and present projects but also structural information from chemical libraries, quantum chemical properties, outcomes from clinical trials, and real-world evidence. Machine learning models, particularly deep neural networks, can learn the hidden relationships between a molecule's intricate

structural features—its fragments, topological descriptors, and three-dimensional conformations—and its PK/BA outcomes[14][15]. This capability enables in silico prediction of human pharmacokinetic parameters, such as clearance, volume of distribution, and oral bioavailability, with an accuracy and speed previously unattainable. Furthermore, AI moves beyond mere prediction into the realm of generative design[16]. Deep generative models and reinforcement learning algorithms can be trained on the rules of medicinal chemistry and desirable PK properties to virtually conceive and optimize novel molecular structures that are synthetically accessible and are *de novo* designed for optimal human ADME profiles from the outset[17]. This transforms the drug discovery workflow from "make and test" to "predict and generate." Instead of screening existing libraries for compounds that might have acceptable properties, AI can propose novel chemical entities engineered to meet a precise multi-parameter profile: high potency, minimal toxicity, and ideal PK. By front-loading the development process with these powerful computational insights, AI/ML holds the potential to dramatically reduce late-stage PK/BA attrition. Candidates entering the pipeline would be inherently "better behaved," having been vetted against sophisticated in silico human models. This would lead to a more efficient development process, with fewer failures and a higher probability of success, ultimately lowering costs and accelerating the delivery of new therapies. The promise, therefore, is nothing less than the re-engineering of the foundational economics of drug discovery, turning the historical challenge of PK/BA from a major vulnerability into a manageable, predictable, and optimizable component of rational therapeutic design[18].

2. Fundamentals of Pharmacokinetics and Bioavailability

The precise characterization of a drug's journey through the body hinges on quantifying a specific set of pharmacokinetic (PK) parameters, most commonly conceptualized within the ADME framework—Absorption, Distribution, Metabolism, and Excretion. Absorption, the process by which a drug moves from its site of administration into the bloodstream, is fundamentally encapsulated by the parameter of bioavailability (F), expressed as the fraction (or percentage) of an administered dose that reaches the systemic circulation unchanged and is thus available to exert a pharmacological effect[19]. For an intravenous dose, bioavailability is by definition 100%, as the drug is placed directly into the blood. For all other routes, especially the preferred oral route, F is a critical hurdle, determined by a compound's solubility in gastrointestinal fluids and its permeability across the intestinal mucosa[20]. This is formalized in the Biopharmaceutics Classification System (BCS), which categorizes drugs based on these two properties. Once absorbed, a drug's journey is governed by distribution and elimination. The apparent volume of distribution (Vd) is a theoretical parameter that relates the total amount of drug in the body to its concentration in plasma. A large Vd suggests the drug is extensively distributed into tissues beyond the blood, often due to high lipid solubility or active tissue binding, while a small Vd indicates confinement largely to the vascular space[21][22]. This parameter is crucial for determining the loading dose required to achieve a target plasma concentration rapidly. Simultaneously, the body works to eliminate the drug primarily via metabolism and excretion. Clearance (CL) is the paramount parameter describing the body's efficiency in irreversibly removing the drug from the bloodstream, typically measured as the volume of plasma cleared of drug per unit time. It is the sum of metabolic clearance (often hepatic) and renal excretion clearance. The interplay between Vd and CL determines the half-life (t½), the time required for the plasma concentration to reduce by half. Half-life dictates the dosing frequency necessary to maintain therapeutic levels without excessive fluctuation; a short half-life necessitates frequent dosing, while a long half-life allows for once-daily or even weekly regimens. Interwoven with all these processes is the phenomenon of plasma protein binding, primarily to albumin and alpha-1-acid glycoprotein[23]. Only the unbound, or free, fraction of a drug is considered pharmacologically active and available for distribution and elimination. High protein binding can act as a circulating reservoir, prolonging the drug's presence but also potentially

limiting its therapeutic activity and making it susceptible to displacement by other highly bound drugs, leading to sudden increases in free concentration and toxicity. Thus, the therapeutic profile of a drug is a dynamic equilibrium defined by its bioavailability, its partitioning between blood and tissues (Vd), the body's relentless removal mechanisms (CL), the resulting persistence (t½), and its binding to plasma proteins[24].

To estimate these critical in vivo parameters early in development, scientists rely on a battery of in vitro and in vivo assays designed to simulate biological barriers and processes. The assessment begins with fundamental physicochemical properties like solubility and lipophilicity (log P/D). For absorption, assays such as the Caco-2 monolayer model, which uses human colon carcinoma cells to mimic the intestinal epithelium, provide a measure of permeability and potential for active transport[25][26]. Parallel Artificial Membrane Permeability Assays (PAMPA) offer a simpler, non-cellular high-throughput screen for passive transcellular permeability. Metabolism is preliminarily evaluated using liver microsomes or hepatocytes (from various species, including human) to measure metabolic stability, identify major metabolites, and assess the involvement and potential inhibition or induction of specific cytochrome P450 enzymes, which are pivotal for drug-drug interaction predictions. Plasma protein binding is typically quantified using techniques like equilibrium dialysis or ultrafiltration[27]. For distribution and excretion, more complex systems are required, often progressing to in vivo studies in preclinical species. Animals (rodents, dogs, non-human primates) are dosed, and serial blood samples are taken to construct concentration-time profiles[28]. These curves are then analyzed using non-compartmental analysis or compartmental modeling to derive the key PK parameters: AUC (area under the curve, related to exposure and bioavailability), Cmax (maximum concentration), CL, Vd, and t½. Tissue distribution studies can further quantify where a drug accumulates. While these in vivo animal studies are indispensable, their significant limitation is the frequent poor extrapolation to humans due to interspecies differences in physiology, enzyme expression, and transporter activity. Thus, the in vitro assays, especially those using human-derived tissues and cells, serve as the essential bridge between chemical structure and predicted human outcome, feeding data into more sophisticated predictive models[29].

The traditional approach to translating this cascade of experimental data into a human PK prediction relies on two primary, and complementary, modeling strategies: In Vitro-In Vivo Correlation (IVIVC) and Physiologically-Based Pharmacokinetic (PBPK) modeling. IVIVC is a mathematical model that establishes a quantitative relationship between an in vitro property (typically the rate or extent of drug dissolution) and a relevant in vivo response (such as the fraction absorbed or the plasma concentration profile)[30][31]. The highest level of correlation, a point-to-point relationship, allows the in vitro dissolution profile to serve as a surrogate for in vivo bioavailability, which can be incredibly powerful for justifying biowaivers for formulation changes during development without requiring new clinical studies. However, IVIVC is often most successful for drugs whose absorption is primarily limited by dissolution rate and is less universally applicable to all compounds. In contrast, PBPK modeling represents a more holistic and mechanistic framework. A PBPK model is a mathematical simulation that incorporates a wealth of prior physiological knowledge—organ sizes, blood flow rates, tissue compositions, and the expression levels of enzymes and transporters—and integrates specific drug data (e.g., lipophilicity, pKa, in vitro metabolic clearance, plasma protein binding) into a species-specific "virtual organism[32].

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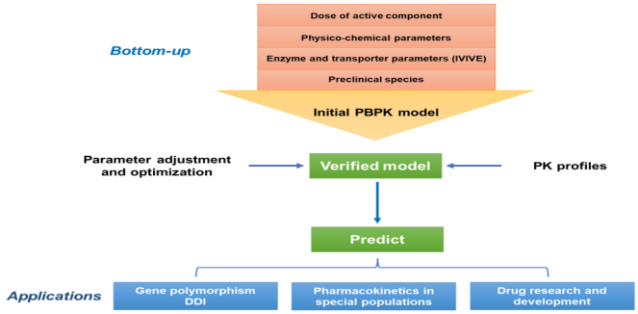

Fig: 2 Strategies for studying the pharmacokinetics of natural medicine using the PBPK model.

The model essentially simulates the journey of the drug through this physiological representation, predicting its concentration not just in plasma but in various tissues over time. Its greatest strength is its ability to scale parameters from in vitro systems and preclinical species to humans by replacing the species-specific physiological parameters with human ones, while retaining the drug-specific data[33]. This allows for the prediction of human PK profiles prior to First-In-Human studies. Furthermore, PBPK models are exceptionally valuable for exploring "what-if" scenarios: predicting the impact of organ dysfunction (e.g., hepatic or renal impairment), drug-drug interactions, age, or genetic polymorphisms (e.g., poor metabolizer phenotypes) on PK[34]. They enable a more tailored and de-risked clinical development plan. However, both IVIVC and traditional PBPK modeling have their constraints. Their predictive accuracy is fundamentally dependent on the quality and relevance of the input data. An IVIVC may not exist for many drugs, and building a robust PBPK model requires extensive, high-quality compound data that may not be available in early discovery. Furthermore, traditional PBPK models can struggle with the extreme complexity of biological systems, particularly where non-linear processes or poorly understood transporter effects dominate. They often rely on simplifying assumptions and may not fully capture the intricate, non-linear relationships between molecular structure and complex PK outcomes. This gap between the promise of mechanistic prediction and the limitations of traditional models sets the stage for a new generation of data-driven approaches that seek to learn these relationships directly from historical data, augmenting and enhancing these established methodologies[35][36].

3. Machine Learning Primer for Pharmaceutical Sciences

The precise characterization of a drug's journey through the body hinges on quantifying a specific set of pharmacokinetic (PK) parameters, most commonly conceptualized within the ADME framework—Absorption, Distribution, Metabolism, and Excretion. Absorption, the process by which a drug moves from its site of administration into the bloodstream, is fundamentally encapsulated by the parameter of bioavailability (F), expressed as the fraction (or percentage) of an administered dose that reaches the systemic circulation unchanged and is thus available to exert a pharmacological effect. For an intravenous dose, bioavailability is by definition 100%, as the drug is placed directly into the blood[37][38]. For all other routes, especially the preferred oral route, F is a critical hurdle, determined by a compound's solubility in gastrointestinal fluids and its permeability across the intestinal mucosa. This is formalized in the Biopharmaceutics Classification System (BCS), which categorizes drugs based on these two properties. Once absorbed, a drug's journey is governed by distribution and elimination. The apparent volume of distribution (Vd) is a theoretical parameter that relates the total amount of drug in the body to its concentration in plasma. A large Vd suggests the drug is extensively distributed into tissues beyond the blood, often due to high lipid solubility or active tissue binding, while a small Vd indicates confinement largely to the vascular space. This parameter is crucial for determining the loading dose required to achieve a target plasma concentration rapidly. Simultaneously, the body works to eliminate the drug primarily via

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ML Applications for Predicting Specific PK Properties

The application of artificial intelligence and machine learning is revolutionizing the prediction of every fundamental pharmacokinetic parameter, offering a paradigm shift from sequential, assay-dependent estimation to simultaneous, structure-informed forecasting. In the critical realm of absorption and bioavailability, models now directly predict human oral bioavailability (%F) from chemical structure by learning from historical clinical data, capturing complex non-linear relationships that elude simple rules. Concurrently, deep learning algorithms analyze molecular fingerprints and three-dimensional conformations to accurately classify permeability, predicting both passive transcellular movement (as in Caco-2 assays) and active efflux by transporters like P-glycoprotein (P-gp), which can severely limit intestinal absorption and brain penetration[51][52]. For the foundational challenge of solubility, quantum mechanical calculations and graph neural networks predict thermodynamic solubility and dissolution rates, essential for anticipating formulation hurdles and guiding salt or polymorph selection early in development[53].

For distribution, ML models trained on large datasets of clinically derived parameters can predict the volume of distribution (Vd) by implicitly learning the complex interplay between a molecule's physicochemical properties—its lipophilicity, polarity, and ionization—and its tendency to bind to tissues versus remain in plasma[54]. Plasma protein binding (PPB), a key determinant of free drug concentration, is predicted with high accuracy using models that recognize structural motifs prone to binding with albumin or alpha-1-acid glycoprotein. Perhaps one of the most consequential applications is in predicting blood-brain barrier (BBB) penetration. Here, sophisticated models integrate data on passive permeability, transporter substrate likelihood (especially for P-gp efflux), and specific molecular descriptors to classify central nervous system (CNS) penetrability, de-risking programs for both CNS and non-CNS targets by ensuring molecules are designed with the appropriate distribution profile from the outset[55][56].

In metabolism and clearance, AI demonstrates profound utility. Models predict susceptibility to metabolism by specific Cytochrome P450 (CYP) isoforms, flagging potential for high clearance or polymorphic variability. Crucially, they also predict the likelihood of a compound acting as a CYP inhibitor or inducer, a major source of costly late-stage drug-drug interaction failures. Beyond enzyme interaction, ML algorithms estimate intrinsic clearance (CLint) directly from in vitro hepatocyte or microsomal stability data with improved human translatability. More innovatively, generative models and metabolite predictors are now used to anticipate the structures of major metabolites, allowing chemists to preemptively block labile metabolic soft spots or assess metabolite safety virtually, steering synthesis toward metabolically stable candidates[57][58].

Ultimately, the most powerful application of AI lies in synthesizing these discrete predictions into a holistic pharmacokinetic profile. Machine learning models are being trained to predict total clearance (CL) and half-life (t½) directly from chemical structure or by integrating predictions of its individual determinants (CL, Vd). The frontier, however, is the development of integrated end-to-end PK prediction models[59]. These systems, often leveraging deep neural networks or hybrid approaches that combine ML with elements of PBPK theory, take a molecular structure as input and output a comprehensive set of human PK parameters simultaneously—including %F, Vd, CL, t½, and Cmax—simulating a virtual human concentration-time curve. This represents a move from piecemeal analysis to a systems-level, generative prediction of drug behavior, enabling true in silico candidate triage and optimization before a single molecule is synthesized, thereby compressing timelines and dramatically reducing the likelihood of PK-related attrition in clinical development[60].

Conclusion

This technological shift is concurrently catalyzing the evolution of the computational scientist's role within drug development teams. No longer confined to providing retrospective analysis or operating in siloed support functions, the computational scientist is becoming a central architect of the molecular design process. Their expertise in curating high-quality datasets, selecting and validating appropriate algorithms, and interpreting ML-generated insights is critical for translating computational predictions into tangible chemical matter. This role demands a hybrid skill set, combining deep pharmacological knowledge with data science proficiency, to act as a crucial translator between the domains of chemistry, biology, and informatics, thereby guiding project teams toward better-informed, de-risked decisions from the earliest stages. The path forward toward a more predictive and efficient early-stage development pipeline lies in the continued maturation of hybrid models that marry the mechanistic foundations of physiology-based modeling with the pattern-recognition power of machine learning. Success will depend on the industry-wide aggregation and standardization of high-quality experimental and clinical PK data to fuel these models, alongside rigorous validation in prospective drug discovery campaigns. Ultimately, the promise of AI-driven PK prediction is not merely incremental improvement but the systematic re-engineering of development economics. By front-loading the discovery pipeline with molecules engineered for human pharmacokinetic success, the field can move decisively toward a future where PK/BA is a solved problem in design rather than a recurrent cause of failure, accelerating the delivery of safer, more effective medicines to patients.

References

1. Adiwidjaja, J., Boddy, A. V., & McLachlan, A. J. (2020). Physiologically-Based Pharmacokinetic Predictions of the Effect of Curcumin on Metabolism of Imatinib and Bosutinib: In Vitro and In Vivo Disconnect. *Pharmaceutical Research, 37*(8), 128. https://doi.org/10.1007/s11095-020-02846-4
2. Adiwidjaja, J., Boddy, A. V., & McLachlan, A. J. (2020). Potential for pharmacokinetic interactions between Schisandra sphenanthera and bosutinib, but not imatinib: In vitro metabolism study combined with a physiologically-based pharmacokinetic modelling

approach. *British Journal of Clinical Pharmacology, 86*(10), 2080–2094. https://doi.org/10.1111/bcp.14301

3. Adiwidjaja, J., Boddy, A. V., & McLachlan, A. J. (2022). Physiologically based pharmacokinetic model predictions of natural product-drug interactions between goldenseal, berberine, imatinib and bosutinib. *European Journal of Clinical Pharmacology, 78*(4), 597–611. https://doi.org/10.1007/s00228-021-03262-2
4. Adiwidjaja, J., McLachlan, A. J., & Boddy, A. V. (2017). Curcumin as a clinically-promising anti-cancer agent: Pharmacokinetics and drug interactions. *Expert Opinion on Drug Metabolism & Toxicology, 13*(9), 953–972. https://doi.org/10.1080/17425255.2017.1360279
5. Bayer, B., Duerkop, M., Striedner, G., & Sissolak, B. (2021). Model transferability and reduced experimental burden in cell culture process development facilitated by hybrid modeling and intensified design of experiments. *Frontiers in Bioengineering and Biotechnology, 9*, 740215. https://doi.org/10.3389/fbioe.2021.740215
6. Bertolino, G. M., Maumus, M., Jorgensen, C., & Noël, D. (2022). Recent advances in extracellular vesicle-based therapies using induced pluripotent stem cell-derived mesenchymal stromal cells. *Biomedicines, 10*(9), 2281. https://doi.org/10.3390/biomedicines10092281
7. Bhat, B., Karve, S., & Anderson, D. G. (2021). mRNA therapeutics: Beyond vaccine applications. *Trends in Molecular Medicine, 27*(9), 923–924. https://doi.org/10.1016/j.molmed.2021.05.004
8. Bonvin, D., Georgakis, C., Pantelides, C. C., Barolo, M., Grover, M. A., Rodrigues, D., Schneider, R., & Dochain, D. (2016). Linking models and experiments. *Industrial & Engineering Chemistry Research, 55*(25), 6891–6903. https://doi.org/10.1021/acs.iecr.5b04801
9. Brantley, S. J., Argikar, A. A., Lin, Y. S., Nagar, S., & Paine, M. F. (2014). Herb-drug interactions: Challenges and opportunities for improved predictions. *Drug Metabolism and Disposition, 42*(3), 301–317. https://doi.org/10.1124/dmd.113.055236
10. Canzani, E., & Timmer, S. W. (2021). Beyond building predictive models: TwinOps in biomanufacturing. In *Springer eBooks*. Springer.
11. Cardillo, A. G., Castellanos, M. M., Desailly, B., Dessoy, S., Mariti, M., Portela, R. M. C., Schofield, M., Souquet, J., Stonier, A., & Brocard, C. (2021). Towards in silico process modeling for vaccines. *Trends in Biotechnology, 39*(11), 1120–1130. https://doi.org/10.1016/j.tibtech.2021.02.004
12. Carvalho, M., Riesberg, J., & Budman, H. (2022). Hybrid model to predict the effect of complex media changes in mammalian cell cultures. *Biochemical Engineering Journal, 186*, 108560. https://doi.org/10.1016/j.bej.2022.108560
13. Chen, L., Bernard, O., Bastin, G., & Angelov, P. (2000). Hybrid modelling of biotechnological processes using neural networks. *Control Engineering Practice, 8*(7), 821–827. https://doi.org/10.1016/s0967-0661(00)00036-8
14. Chen, Y., Yang, O., Sampat, C., Bhalode, P., Ramachandran, R., & Ierapetritou, M. (2020). Digital twins in pharmaceutical and biopharmaceutical manufacturing: A literature review. *Processes, 8*(9), 1088. https://doi.org/10.3390/pr8091088
15. Chopra, B., & Dhingra, A. K. (2021). Natural products: A lead for drug discovery and development. *Phytotherapy Research,*

35(9), 4660–4702. https://doi.org/10.1002/ptr.7099

16. Cruz-Bournazou, M. N., Narayanan, H., Fagnani, A., & Butté, A. (2022). Hybrid Gaussian Process Models for continuous time series in bolus fed-batch cultures. *IFAC-PapersOnLine, 55*(7), 204–209. https://doi.org/10.1016/j.ifacol.2022.07.445
17. Dong, J., Olaleye, O. E., Jiang, R., Li, J., Lu, C., Du, F., Xu, F., Yang, J., Wang, F., Jia, W., & Li, C. (2018). Glycyrrhizin has a high likelihood to be a victim of drug-drug interactions mediated by hepatic organic anion-transporting polypeptide 1B1/1B3. *British Journal of Pharmacology, 175*(17), 3486–3503. https://doi.org/10.1111/bph.14393
18. Doyle, K., Tsopanoglou, A., Fejér, A., Glennon, B., & del Val, I. J. (2023). Automated assembly of hybrid dynamic models for CHO cell culture processes. *Biochemical Engineering Journal, 191*, 108763. https://doi.org/10.1016/j.bej.2022.108763
19. Farid, S. S., Baron, M., Stamatis, C., Nie, W., & Coffman, J. (2020). Benchmarking biopharmaceutical process development and manufacturing cost contributions to R&D. *mAbs, 12*(1), 1754999. https://doi.org/10.1080/19420862.2020.1754999
20. Ferreira, A. R., Dias, J. M. L., Von Stosch, M., Clemente, J., Cunha, A. E., & Oliveira, R. (2014). Fast development of Pichia pastoris GS115 Mut+ cultures employing batch-to-batch control and hybrid semi-parametric modeling. *Bioprocess and Biosystems Engineering, 37*(4), 629–639. https://doi.org/10.1007/s00449-013-1029-9
21. Feyo de Azevedo, S., Dahm, B., & Oliveira, F. R. (1997). Hybrid modelling of biochemical processes: A comparison with the conventional approach. *Computers & Chemical Engineering, 21*, S751–S756. https://doi.org/10.1016/S0098-1354(97)87593-X
22. Fleischer, T., Chang, T. T., Chiang, J. H., Chang, C. M., Hsieh, C. Y., & Yen, H. R. (2016). Adjunctive Chinese Herbal Medicine therapy improves survival of patients with chronic myeloid leukemia: A nationwide population-based cohort study. *Cancer Medicine, 5*(4), 640–648. https://doi.org/10.1002/cam4.629
23. Galvanauskas, V., Simutis, R., & Lübbert, A. (2004). Hybrid process models for process optimisation, monitoring and control. *Bioprocess and Biosystems Engineering, 26*(6), 393–400. https://doi.org/10.1007/s00449-004-0385-x
24. Gargalo, C. L., Caño, S., Heras, D., Jones, M. N., Udugama, I., Mansouri, S. S., Krühne, U., & Gernaey, K. V. (2020). Towards the development of digital twins for the bio-manufacturing industry. *Advances in Biochemical Engineering/Biotechnology, 176*, 1–34. https://doi.org/10.1007/10_2020_142
25. George, B., Lumen, A., Nguyen, C., Wesley, B., Wang, J., Beitz, J., & Crentsil, V. (2020). Application of physiologically based pharmacokinetic modeling for sertraline dosing recommendations in pregnancy. *NPJ Systems Biology and Applications, 6*(1), 36. https://doi.org/10.1038/s41540-020-00152-8
26. Gilbert, C., & Ellis, T. (2019). Biological engineered living materials: Growing functional materials with genetically programmable properties. *ACS Synthetic Biology, 8*(1), 1–15. https://doi.org/10.1021/acssynbio.8b00423
27. Gong, Z., Lin, Z., & Han, L. (2021). Analysis of research status based on projects in pharmacokinetics of traditional Chinese medicine funded by National Natural Science Foundation of

China. *China Journal of Chinese Materia Medica, 46*(5), 1010–1016. (In Chinese) [Analysis of research status based on projects in pharmacokinetics of traditional Chinese medicine funded by National Natural Science Foundation of China.]

28. Grimstein, M., Yang, Y., Zhang, X., Grillo, J., Huang, S. M., Zineh, I., & Wang, Y. (2019). Physiologically Based Pharmacokinetic Modeling in Regulatory Science: An Update From the U.S. Food and Drug Administration's Office of Clinical Pharmacology. *Journal of Pharmaceutical Sciences, 108*(1), 21–25. https://doi.org/10.1016/j.xphs.2018.10.033
29. Gufford, B. T., Barr, J. T., González-Pérez, V., Layton, M. E., White, J. R., Jr., Oberlies, N. H., & Paine, M. F. (2015). Quantitative prediction and clinical evaluation of an unexplored herb-drug interaction mechanism in healthy volunteers. *CPT: Pharmacometrics & Systems Pharmacology, 4*(12), 701–710. https://doi.org/10.1002/psp4.12042
30. Guo, S., Wang, Q., Lin, S., Que, H., & Yang, J. (2012). Pharmacokinetics of triptolide as active metabolite of iso-tripthiocyanatolide in SD rats. *Chinese Journal of Clinical Pharmacology, 28*(5), 355–357. (In Chinese) [Pharmacokinetics of triptolide as active metabolite of iso-tripthiocyanatolide in SD rats.]
31. Hastie, T., Tibshirani, R., & Friedman, J. H. (2017). *The elements of statistical learning: Data mining, inference, and prediction* (12th printing). Springer.
32. Hutter, C., von Stosch, M., Cruz Bournazou, M. N., & Butté, A. (2021). Knowledge transfer across cell lines using hybrid Gaussian process models with entity embedding vectors. *Biotechnology and Bioengineering, 118*(11), 4389–4401. https://doi.org/10.1002/bit.27907
33. Hutter, S., Villiger, T. K., Brühlmann, D., Stettler, M., Broly, H., Soos, M., Morbidelli, M., & Butté, A. (2017). Glycosylation flux analysis reveals dynamic changes of intracellular glycosylation flux distribution in Chinese hamster ovary fed-batch cultures. *Metabolic Engineering, 43*(Pt B), 9–20. https://doi.org/10.1016/j.ymben.2017.07.005
34. Jamei, M. (2016). Recent Advances in Development and Application of Physiologically-Based Pharmacokinetic (PBPK) Models: A Transition from Academic Curiosity to Regulatory Acceptance. *Current Pharmacology Reports, 2*(3), 161–169. https://doi.org/10.1007/s40495-016-0059-9
35. Jiang, X. L., Samant, S., Lewis, J. P., Horenstein, R. B., Shuldiner, A. R., Yerges-Armstrong, L. M., Peletier, L. A., Lesko, L. J., & Schmidt, S. (2016). Development of a physiology-directed population pharmacokinetic and pharmacodynamic model for characterizing the impact of genetic and demographic factors on clopidogrel response in healthy adults. *European Journal of Pharmaceutical Sciences, 82*, 64–78. https://doi.org/10.1016/j.ejps.2015.11.010
36. Jin, Z., He, Q., Zhu, X., Zhu, M., Wang, Y., Wu, X. A., Lv, Q., & Xiang, X. (2022). Application of physiologically based pharmacokinetic modelling for the prediction of drug-drug interactions involving anlotinib as a perpetrator of cytochrome P450 enzymes. *Basic & Clinical Pharmacology & Toxicology, 130*(5), 592–605. https://doi.org/10.1111/bcpt.13720
37. Jones, H. M., Chen, Y., Gibson, C., Heimbach, T., Parrott, N., Peters, S. A., Snoeys, J., Upreti, V. V., Zheng, M., & Hall, S. D. (2015). Physiologically based pharmacokinetic modeling in drug discovery and development: A pharmaceutical industry perspective. *Clinical Pharmacology &*

Therapeutics, 97(3), 247–262. https://doi.org/10.1002/cpt.37

38. Klyachko, N. L., Arzt, C. J., Li, S. M., Gololobova, O. A., & Batrakova, E. V. (2020). Extracellular vesicle-based therapeutics: Preclinical and clinical investigations. *Pharmaceutics, 12*(12), 1171. https://doi.org/10.3390/pharmaceutics12121171
39. Kotidis, P., Pappas, I., Avraamidou, S., Pistikopoulos, E. N., Kontoravdi, C., & Papathanasiou, M. M. (2021). DigiGlyc: A hybrid tool for reactive scheduling in cell culture systems. *Computers & Chemical Engineering, 154*, 107460. https://doi.org/10.1016/j.compchemeng.2021.107460
40. Le Foll, B., & Tyndale, R. F. (2015). Cannabinoids: Friend or foe? *Clinical Pharmacology & Therapeutics, 97*(6), 528–531. https://doi.org/10.1002/cpt.122
41. Lesko, L. J. (2021). Perspective on model-informed drug development. *CPT: Pharmacometrics & Systems Pharmacology, 10*(10), 1127–1129. https://doi.org/10.1002/psp4.12722
42. Li, Y., Wang, Y., Luo, H., Huang, C., & Zhu, J. (2014). Determination of Serum Concentration of Triptolide in Patients with Rheumatoid Arthritis and its Pharmacokinetics Study. *Chinese Journal of Information on Traditional Chinese Medicine, 21*(12), 85–87. (In Chinese) [Determination of Serum Concentration of Triptolide in Patients with Rheumatoid Arthritis and its Pharmacokinetics Study.]
43. Ling, X., Chen, Y., Wang, P., Li, C., & Li, X. (2021). Effects of flavonoids from Chinese traditional Medicine on other drugs mediated by metabolic enzymes and transporters. *China Pharmacy, 32*(18), 2287–2293. (In Chinese) [Effects of flavonoids from Chinese traditional Medicine on other drugs mediated by metabolic enzymes and transporters.]
44. Liu, C. (2005). Difficulty and hot-points on pharmacokinetics studies of traditional Chinese medicine. *Acta Pharmaceutical Sinica, 40*(5), 395–401. (In Chinese) [Difficulty and hot-points on pharmacokinetics studies of traditional Chinese medicine.]
45. Liu, H., Chen, F., Xiang, X., Quan, Y., & Jin, S. (2019). Application of Physiologically Based Pharmacokinetic Modeling in Pharmaceutics. *Chinese Journal of Pharmaceuticals, 50*(4), 383–391. (In Chinese) [Application of Physiologically Based Pharmacokinetic Modeling in Pharmaceutics.]
46. Liu, L., Jia, Z., Yan, X., Zhu, M., Fang, C., Feng, M., Huang, B., Liu, J., Li, Q., & Xiao, H. (2021). Effect of Chuanxiong Rhizoma on the absorption and clearance of four coumarins in Angelicae Dahuricae Radix. *Acta Pharmaceutical Sinica, 56*(6), 1804–1810. (In Chinese) [Effect of Chuanxiong Rhizoma on the absorption and clearance of four coumarins in Angelicae Dahuricae Radix.]
47. Mazzari, A. L. D. A., & Prieto, J. M. (2014). Herbal medicines in Brazil: Pharmacokinetic profile and potential herb-drug interactions. *Frontiers in Pharmacology, 5*, 162. https://doi.org/10.3389/fphar.2014.00162
48. Mullard, A. (2023). 2022 FDA approvals. *Nature Reviews Drug Discovery, 22*(2), 83–88. https://doi.org/10.1038/d41573-023-00001-3
49. Murphy, D. E., de Jong, O. G., Brouwer, M., Wood, M. J., Lavieu, G., Schiffelers, R. M., & Vader, P. (2019). Extracellular vesicle-based therapeutics: Natural versus engineered targeting and trafficking. *Experimental & Molecular Medicine, 51*(3), 32. https://doi.org/10.1038/s12276-019-0223-5
50. Narayanan, H., Behle, L., Luna, M. F., Sokolov, M., Guillén-Gosálbez, G., Morbidelli, M., & Butté, A. (2020). Hybrid-

EKF: Hybrid model coupled with extended Kalman filter for real-time monitoring and control of mammalian cell culture. *Biotechnology and Bioengineering, 117*(9), 2703–2714. https://doi.org/10.1002/bit.27437

51. Newman, D. J., & Cragg, G. M. (2020). Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. *Journal of Natural Products, 83*(3), 770–803. https://doi.org/10.1021/acs.jnatprod.9b01285
52. Nicolussi, S., Drewe, J., Butterweck, V., & Meyer Zu Schwabedissen, H. E. (2020). Clinical relevance of St. John's wort drug interactions revisited. *British Journal of Pharmacology, 177*(6), 1212–1226. https://doi.org/10.1111/bph.14936
53. Niu, W., Li, S., Jin, S., Lin, X., Zhang, M., Cai, W., Jiao, Z., & Xiang, X. (2021). Investigating the interaction between nifedipine- and ritonavir-containing antiviral regimens: A physiologically based pharmacokinetic/pharmacodynamic analysis. *British Journal of Clinical Pharmacology, 87*(5), 2790–2806. https://doi.org/10.1111/bcp.14685
54. Offman, E., & Edginton, A. N. (2015). A PBPK workflow for first-in-human dose selection of a subcutaneously administered pegylated peptide. *Journal of Pharmacokinetics and Pharmacodynamics, 42*(2), 135–150. https://doi.org/10.1007/s10928-014-9403-z
55. Pilla Reddy, V., Jo, H., & Neuhoff, S. (2021). Food constituent- and herb-drug interactions in oncology: Influence of quantitative modelling on Drug labelling. *British Journal of Clinical Pharmacology, 87*(10), 3988–4000. https://doi.org/10.1111/bcp.14828
56. Qian, H., Zhang, M., Zou, Y., Liu, S., Wang, W., Chen, Q., Liu, G., Liu, Y., Lu, C., & Jia, J. (2021). Pharmacokinetics and Safety of Huperzine A in Chinese Elderly Subjects. *Herald of Medicine, 40*(6), 764–767. (In Chinese) [Pharmacokinetics and Safety of Huperzine A in Chinese Elderly Subjects.]
57. Rao, T., Tan, Z., Peng, J., Guo, Y., Chen, Y., Zhou, H., & Ouyang, D. (2019). The pharmacogenetics of natural products: A pharmacokinetic and pharmacodynamic perspective. *Pharmacological Research, 146*, 104283. https://doi.org/10.1016/j.phrs.2019.104283
58. Salehi, B., Stojanović-Radić, Z., Matejić, J., Sharifi-Rad, M., Anil Kumar, N. V., Martins, N., & Sharifi-Rad, J. (2019). The therapeutic potential of curcumin: A review of clinical trials. *European Journal of Medicinal Chemistry, 163*, 527–545. https://doi.org/10.1016/j.ejmech.2018.12.016
59. Soldin, O. P., & Mattison, D. R. (2009). Sex differences in pharmacokinetics and pharmacodynamics. *Clinical Pharmacokinetics, 48*(3), 143–157. https://doi.org/10.2165/00003088-200948030-00001
60. Sun, X., Wu, Q., Ma, W., Zhen, X., Lv, S., & Guo, Y. (2018). Advances in pharmacokinetics of Traditional Chinese medicine. *Journal of Hebei Traditional Chinese Medicine and Pharmacology, 33*(6), 52–55. (In Chinese) [Advances in pharmacokinetics of Traditional Chinese medicine.]

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