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Review Article

Physics-Informed Machine Learning Meets Systems Pharmacology: Hybrid-Time Precision Dosing and Clinical Translation

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ABSTRACT

The convergence of physics-informed machine learning (PIML) and systems pharmacology represents a paradigm shift in the design and implementation of precision dosing strategies. Traditional pharmacokinetic–pharmacodynamic (PK–PD) models, while mechanistically rigorous, often struggle to capture the complexity of patient-specific variability and dynamic clinical environments. Conversely, purely data-driven machine learning approaches, though powerful, frequently lack interpretability and biological grounding. By embedding mechanistic pharmacological principles into machine learning architectures, PIML offers a hybrid framework that unites the strengths of both domains. This hybrid-time modeling approach enables the continuous refinement of dose predictions by integrating prior knowledge, real-time patient data, and adaptive learning algorithms. Systems pharmacology provides the biological scaffolding linking molecular mechanisms, drug–target interactions, and physiological pathways while machine learning accelerates model calibration, prediction accuracy, and clinical scalability. Together, these approaches facilitate robust simulation of dose–response trajectories, identification of optimal therapeutic windows, and proactive adjustment of regimens in diverse patient populations. Importantly, the hybrid-time paradigm enhances clinical translation by offering interpretable outputs that can be directly integrated into decision-support systems, thereby bridging the gap between computational innovation and bedside application. This article further discusses the implications for regulatory science, clinical trial design, and personalized medicine, emphasizing how hybrid-time dosing frameworks can reduce adverse drug reactions, improve therapeutic efficacy, and accelerate the adoption of precision pharmacotherapy

INTRODUCTION

Precision medicine has emerged as a cornerstone of modern healthcare, aiming to tailor therapeutic interventions to the unique biological and clinical characteristics of individual patients. Within pharmacotherapy, achieving precision dosing

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remains a persistent challenge due to the interplay of complex pharmacokinetic–pharmacodynamics (PK–PD) processes, interpatient variability, and dynamic treatment environments. Conventional mechanistic models provide valuable insights into drug disposition and action, yet they often lack the flexibility to adapt to real-time clinical data. In contrast, machine learning approaches excel at pattern recognition and predictive analytics but are frequently criticized for their limited interpretability and detachment from biological mechanisms. 1

Physics-informed machine learning (PIML) offers a novel solution by embedding mechanistic pharmacological principles into adaptive learning frameworks. When integrated with systems pharmacology, which situates drug–target interactions within broader biological networks, this hybrid-time approach enables interpretable, scalable, and clinically actionable dosing strategies. Such integration not only enhances predictive accuracy but also supports dynamic adjustment of therapeutic regimens, thereby bridging the gap between computational innovation and bedside application. 4

This article examines the methodological foundations and translational potential of PIML–systems pharmacology integration, highlighting its role in advancing hybrid-time precision dosing and positioning it as a critical enabler of next-generation personalized medicine. 2

Integrating Systems Pharmacology with Hybrid-Time Modeling

Systems pharmacology establishes the mechanistic framework for drug research by connecting molecular interactions, signaling cascades, and physiological responses into integrated models. It draws upon multi-scale biological information ranging from genomic and proteomic datasets to organ-level dynamics to construct a holistic picture of therapeutic action. This systems-level perspective enables the simulation of drug–target relationships, the anticipation of off-target effects, and the exploration of variability across diverse patient populations. Hybrid-time modeling extends this foundation by embedding pharmacological knowledge within adaptive machine learning architectures. Unlike conventional PK–PD models that remain static, hybrid-time approaches continuously update dose predictions by combining prior mechanistic insights with real-time patient data streams. 5

This dynamic integration supports proactive adjustments to treatment regimens, ensuring that dosing strategies remain responsive to evolving clinical conditions. By merging the biological rigor of systems pharmacology with the computational flexibility of machine learning, hybrid-time modeling enhances predictive accuracy, scalability, and interpretability. 6

The synergy between these two approaches creates a powerful framework for precision dosing. Systems pharmacology secures biological relevance and mechanistic depth, while hybrid-time modeling introduces adaptability and responsiveness. Together, they enable robust simulations of dose–response trajectories, identification of optimal therapeutic windows, and reduction of adverse drug reactions. This convergence positions hybrid-time precision dosing not merely as a methodological innovation but as a pivotal step toward next-generation personalized medicine. 4

Table-1: Integration of Systems Pharmacology and Hybrid-Time Modeling in Precision Dosing

Stage	Core Components	Key Functions	Outcome / Contribution
Biological & Clinical Data	Genomic, proteomic, and patient-specific clinical data	Provides foundational information for modeling; captures inter-patient variability	Enables personalized input for pharmacological modeling
Systems Pharmacology	Drug–target interactions, signaling pathways, physiological responses	Builds mechanistic models linking molecular and systemic processes	Ensures biological relevance and mechanistic understanding
Hybrid-Time Modeling	Adaptive machine learning algorithms, real-time data integration	Continuously refines dose predictions using prior knowledge and live data	Improves prediction accuracy and responsiveness to clinical changes
Clinical Decision Support	Decision-support tools, interpretability frameworks	Translates model outputs into actionable clinical insights	Optimizes dosing regimens and enhances therapeutic outcomes

Pharmacokinetics–Pharmacodynamics (PK–PD)

Pharmacokinetics (PK) and pharmacodynamics (PD) together form the cornerstone of quantitative pharmacology. PK describes the time course of drug absorption, distribution, metabolism, and elimination, while PD characterizes the relationship between drug concentration and its biological effect. Traditional PK–PD models provide mechanistic insights into dose–response relationships and have long guided therapeutic decision-making. However, these models often assume homogeneity across patient populations and may not fully capture the variability introduced by genetic factors, comorbidities, or dynamic clinical environments. 6

In precision dosing, PK–PD modeling remains indispensable because it links drug exposure to therapeutic outcomes. Yet, its limitations highlight the need for integration with advanced computational approaches. Physics-informed machine learning (PIML) offers a way to embed PK–PD principles into adaptive frameworks, allowing continuous refinement of predictions as new patient data become available. This hybridization ensures that mechanistic rigor is preserved while enhancing flexibility and scalability. 7

Flow Chart: PK–PD, Systems Pharmacology, and Hybrid-Time Modeling in Precision Dosing

Biological & Clinical Data

↓

Systems Pharmacology

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Hybrid-Time Modeling

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Clinical Decision Support

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Optimized Precision Dosing

Explanation of stages:

- **Biological & Clinical Data** → Genomics, proteomics, patient vitals
- **Systems Pharmacology** → Mechanistic models of drug–target interactions and physiological pathways
- **Hybrid-Time Modeling** → Real-time data integration with adaptive machine learning

- **Clinical Decision Support** → Interpretable outputs for clinicians

- **Optimized Precision Dosing** → Personalized therapy, reduced adverse reactions, improved efficacy

Clinical Translation of Hybrid-Time Precision Dosing

The integration of physics-informed machine learning (PIML) with systems pharmacology offers substantial potential for clinical translation, particularly in advancing precision dosing. Conventional PK–PD models, although mechanistically sound, often remain limited to research contexts because they lack adaptability in dynamic clinical environments. By embedding pharmacological principles into adaptive machine learning frameworks, hybrid-time modeling produces outputs that are both mechanistically rigorous and clinically actionable. 6

A key translational advantage lies in the ability to incorporate real-time patient information—such as laboratory results, vital signs, and biomarker profiles—into continuously updated dosing algorithms. This dynamic refinement ensures that therapeutic regimens remain responsive to changing clinical conditions, thereby minimizing adverse drug reactions and enhancing treatment efficacy. Furthermore, the interpretability of PIML-based predictions facilitates seamless integration into electronic health records and decision-support platforms, enabling clinicians to make informed adjustments directly at the point of care. From a regulatory standpoint, hybrid-time precision dosing frameworks align with the growing emphasis on model-informed drug development and individualized therapy. Their transparent, mechanistically grounded predictions can be validated against clinical trial data, supporting regulatory approval and accelerating adoption in practice. Ultimately, this approach bridges computational innovation with patient care, positioning hybrid-time dosing as a pivotal enabler of next-generation pharmacotherapy. 7

Table-2: Clinical Translation Pathway of Hybrid-Time Precision Dosing

Stage	Input / Basis	Process / Integration	Clinical Impact
Mechanistic PK–PD Models	Drug absorption, distribution, metabolism, elimination; dose–response relationships	Provides foundational mechanistic understanding of pharmacology	Establishes baseline for dosing strategies
Systems Pharmacology	Molecular interactions, signaling pathways, physiological networks	Builds multi-scale mechanistic models linking drug action to systemic responses	Ensures biological relevance and mechanistic rigor
Physics-Informed Machine Learning (PIML)	PK–PD principles embedded in ML frameworks	Preserves mechanistic knowledge while enabling computational adaptability	Enhances interpretability and scalability
Hybrid-Time Modeling	Real-time patient data (labs, vitals, biomarkers)	Continuously refines dose predictions with adaptive algorithms	Maintains responsiveness to evolving clinical conditions
Clinical Decision Support	Electronic health records, bedside tools	Translates model outputs into actionable dosing recommendations	Enables informed, patient-specific adjustments

Clinical Translation Outcome	Integration of mechanistic and adaptive models	Regulatory alignment, validated predictions, bedside application	Optimized precision dosing, improved safety and efficacy

Patient-Specific Variability in Precision Dosing

A major challenge in precision dosing is the need to address patient-specific variability. Pharmacokinetics (PK) and pharmacodynamics (PD) are influenced by numerous individual factors, including genetic variations, age, sex, body weight, organ function, coexisting diseases, and concurrent medications. These determinants can significantly affect drug absorption, distribution, metabolism, and elimination, as well as receptor sensitivity and downstream biological responses. 9

Conventional PK–PD models often rely on average population parameters, which may not adequately reflect the diversity encountered in clinical practice. As a result, dosing strategies based solely on population data can lead to suboptimal therapeutic outcomes, heightened risk of adverse drug reactions, or reduced efficacy in certain patient groups. 8

The integration of systems pharmacology with Physics Informed machine learning (PIML) offers a solution to this limitation. Hybrid-time modeling frameworks can incorporate patient-specific information such as genomic and proteomic profiles, biomarker data, and real-time clinical measurements into adaptive algorithms. This continuous refinement enables dosing regimens to remain aligned with the unique physiological and pathological characteristics of each patient. 15

By systematically addressing variability, precision dosing evolves from generalized, population-based approaches into individualized therapeutic strategies. This transformation enhances safety, improves efficacy, and ultimately supports better clinical outcomes. 8

Table-3: Patient-Specific Factors Influencing PK–PD Variability

Factor	Impact on PK–PD	Clinical Implications	Factor
Genetic Polymorphisms (e.g., CYP450, transporters, receptors)	Alters drug metabolism, transport, and receptor sensitivity	Variable drug response; need for pharmacogenomic dosing	Genetic Polymorphisms (e.g., CYP450, transporters, receptors)
Age (pediatric, elderly)	Differences in enzyme activity, organ maturity/decline	Adjusted dosing in neonates, children, and elderly patients	Age (pediatric, elderly)
Sex	Hormonal influences on metabolism and distribution	Sex-specific differences in efficacy and adverse effects	Sex
Body Weight / BMI	Affects volume of distribution and clearance	Dose adjustments in obese or underweight patients	Body Weight / BMI
Organ Function (renal, hepatic)	Reduced clearance and altered metabolism	Risk of toxicity; requires renal/hepatic dose modification	Organ Function (renal, hepatic)
Comorbidities	Interactions with disease states (e.g., diabetes, cardiovascular disease)	Altered PK–PD; need for individualized therapy	Comorbidities

Concomitant Medications	Drug–drug interactions affecting metabolism and transport	Increased risk of adverse drug reactions or reduced efficacy	Concomitant Medications
Biomarker Profiles	Reflect dynamic physiological states	Enables adaptive, real-time dosing strategies	Biomarker Profiles

CONCLUSION

This review underscores the transformative potential of integrating pharmacokinetics–pharmacodynamics (PK–PD) with systems pharmacology and Physics Informed machine learning (PIML) to advance precision dosing. Traditional PK–PD models, while foundational, often fail to capture the complexity of patient-specific variability in real-world clinical practice. By embedding mechanistic principles into adaptive hybrid-time frameworks, dosing strategies can be continuously refined using real-time patient data, thereby enhancing safety, efficacy, and therapeutic outcomes. The review highlights how patient heterogeneity driven by genetic, physiological, and clinical factors necessitates individualized approaches that go beyond population-based regimens. Hybrid-time modeling and PIML bridge this gap by offering interpretable, dynamic, and clinically actionable predictions. Importantly, these innovations align with regulatory priorities for model-informed drug development, accelerating translation from computational models to bedside application. In review , the integration of PK–PD, systems pharmacology, and machine learning represents a paradigm shift in pharmacotherapy. By addressing patient-specific variability and enabling adaptive precision dosing, this approach lays the foundation for next-generation personalized medicine and positions itself as a cornerstone of future clinical practice.

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