

Multiscale Modeling for Drug Discovery and Precision Pharmacology: Molecular Dynamics, PBPK Modeling, and Virtual Clinical Trials



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Abstract

Multiscale modeling is increasingly shaping modern drug discovery by addressing the persistent gap between molecular mechanisms and clinical outcomes. Traditional drug discovery approaches often identify therapeutic effects without fully explaining them, contributing to limited clinical translation. In this context, multiscale modeling and systems pharmacology provide a framework for integrating molecular interactions, cellular signaling, tissue dynamics, and whole-body physiology into predictive models of drug action. This review synthesizes current advances in multiscale modeling across drug discovery, including molecular dynamics simulations, differential equation-based signaling models, agent-based simulations, and physiologically based pharmacokinetic (PBPK) modeling. These approaches enable prediction of drug efficacy, toxicity, and resistance by linking molecular-scale events to system-level responses. Emerging applications, such as virtual clinical trials and patient-specific simulations, further demonstrate the potential of multiscale modeling for precision pharmacology. Despite these advances, several challenges remain. Model accuracy depends on data availability, parameter estimation, and validation strategies, including iterative predict–learn–confirm cycles. Computational complexity and the balance between mechanistic detail and practical usability continue to limit broader implementation. Overall,

multiscale modeling is shifting drug discovery from empirical approaches toward a predictive and mechanistic science. By integrating systems pharmacology with computational modeling, these frameworks offer new opportunities to improve clinical translation and advance precision medicine.

Keywords

Multiscale modeling; Systems pharmacology; Drug discovery; PBPK modeling; Precision medicine

1. Introduction

Drug discovery, despite decades of innovation, seems to have reached a rather uneasy plateau. There is, perhaps, a growing recognition that traditional approaches—often centered on phenotypic screening without fully resolving mechanistic underpinnings—are no longer sufficient to sustain the pace of therapeutic advancement (Zhao & Iyengar, 2012). What once appeared efficient now feels incomplete, even limiting. The complexity of biological systems, long acknowledged but perhaps underappreciated in practice, continues to challenge reductionist paradigms. Cells, tissues, and organisms do not behave as linear systems; instead, they maintain functional stability through deeply interconnected, nonlinear networks spanning multiple spatial and temporal

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Significance | Bridges molecular mechanisms to clinical outcomes, enabling predictive, personalized drug development and reducing translational failure in modern pharmacology.

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scales (Hwang et al., 2013).

This complexity has historically rendered drug action somewhat opaque. Many pharmacological effects—especially adverse ones—emerge not from a single target interaction but from a cascade of unintended perturbations across biological networks. In this sense, drug mechanisms have often resembled a “black box,” where outcomes are observed but not fully explained (Hwang et al., 2013). Such opacity becomes particularly problematic when off-target interactions lead to toxicity, often only detectable in late-stage clinical trials. Unsurprisingly, this contributes to the persistent “translational dilemma,” wherein promising *in vitro* findings fail to translate into clinical success (Clancy et al., 2016).

In response to these challenges, systems pharmacology has gradually emerged—not as a replacement, but as a necessary evolution. It attempts to integrate computational modeling with experimental data to construct a more holistic understanding of drug action (Zhao & Iyengar, 2012). Yet even within this framework, a further shift is underway. There is increasing emphasis on multiscale modeling, an approach that explicitly connects molecular-level events to higher-order physiological outcomes. Drug action, after all, is inherently multiscale: a binding event at the atomic level can propagate through signaling pathways, alter cellular states, and ultimately influence organ-level function (Amaro & Mulholland, 2018).

This perspective has led to the development of multiscale biophysical models that attempt to capture both structural and functional dimensions of biological systems. These models are not merely descriptive; they aim to be predictive. By incorporating spatial organization, biochemical kinetics, and physiological context, they offer the possibility—still aspirational, but increasingly tangible—of simulating drug behavior with high fidelity (Barros et al., 2023). Such simulations hold particular promise in addressing the translational gap, as they allow researchers to test hypotheses across scales before committing to costly experimental validation (Clancy et al., 2016).

At the core of multiscale modeling lies a fundamental organizational challenge: how to coherently integrate processes that operate at vastly different resolutions. Molecular interactions occur on the scale of nanoseconds and angstroms, while physiological responses unfold over hours, days, or even longer. Bridging these scales

requires not only computational sophistication but also conceptual clarity. Typically, this is achieved through hierarchical frameworks that link distinct biological domains via mathematical formalisms (Walpole et al., 2013).

At the molecular level, techniques such as molecular mechanics (MM) and molecular dynamics (MD) simulations provide detailed insights into drug–target interactions. These approaches function, in a sense, as a “computational microscope,” revealing binding affinities, conformational changes, and free energy landscapes that are otherwise inaccessible (Amaro & Mulholland, 2018). While powerful, these models operate in isolation unless their outputs are systematically integrated into higher-level representations.

Moving upward in scale, intracellular processes are often modeled using systems of ordinary differential equations (ODEs), which describe the kinetics of biochemical reactions and signaling pathways. Pathways such as MAPK and NF- κ B, for instance, can be represented as dynamic networks where perturbations—such as drug exposure—propagate through cascades of molecular interactions (Walpole et al., 2013; Zhao & Iyengar, 2012). These models allow researchers to explore how variations in drug concentration, dosing schedules, or cellular context influence downstream signaling outcomes.

Yet, even this level of modeling captures only part of the picture. Biological function emerges not just from intracellular dynamics but from interactions between cells and their microenvironment. To address this, agent-based models (ABMs) and cellular Potts models are frequently employed. In these frameworks, individual cells are treated as autonomous agents, each with its own internal state and behavioral rules (Oduola & Li, 2018; Walpole et al., 2013). This approach allows for the simulation of complex phenomena such as tumor growth, immune responses, and tissue remodeling, where spatial heterogeneity and cell–cell interactions play critical roles (Su et al., 2014; Clancy et al., 2016).

At the highest level of organization, physiologically based pharmacokinetic (PBPK) models provide a systemic view of drug distribution and metabolism. These models represent the body as a network of compartments corresponding to organs and tissues, each characterized by specific physiological parameters (Eissing et al., 2011). By integrating data from lower-scale models, PBPK

frameworks enable the tracking of drug absorption, distribution, metabolism, and excretion in a manner that is both mechanistic and predictive (Thiel et al., 2017). When coupled with pharmacodynamic (PD) models, they offer a powerful tool for linking drug exposure to biological response.

However, the true value of multiscale modeling lies not merely in its construction but in its validation and application. Predictive accuracy must be rigorously assessed through iterative cycles of simulation and experimentation—the so-called “predict–learn–confirm” paradigm (Eissing et al., 2011; Goldring et al., 2024). In some cases, multiscale models have demonstrated remarkable predictive capabilities. For example, simulations of cardiac electrophysiology have successfully identified drug-induced arrhythmias that were not apparent at the cellular level but emerged in tissue-scale models (Costabal et al., 2018; Walpole et al., 2013).

Beyond prediction, these models also open the door to personalization. By incorporating patient-specific data—such as genetic polymorphisms, enzyme expression levels, or physiological parameters—multiscale frameworks can simulate individual responses to therapy (Clancy et al., 2016). This is particularly relevant in pharmacogenomics, where variations in enzymes like CYP2D6 can significantly alter drug metabolism and efficacy (Eissing et al., 2011). Virtual clinical trials, though still evolving, represent a compelling application of this concept.

Similarly, in the context of drug safety, multiscale models have been used to predict complex toxicological outcomes. Frameworks such as DILIsym integrate subcellular mechanisms, including oxidative stress and mitochondrial dysfunction, with systemic biomarkers to forecast drug-induced liver injury (Bhattacharya et al., 2012; Bai et al., 2014). These approaches provide actionable insights that can inform dosing strategies, identify at-risk populations, and potentially prevent adverse events before they occur.

Still, challenges remain. Multiscale models are inherently complex, often requiring extensive computational resources and high-quality data for parameterization. There is also the question—perhaps unavoidable—of how much complexity is necessary. Striking a balance between biological realism and computational tractability continues to be an area of active discussion. Nevertheless, the

trajectory is clear. As data integration improves and computational methods advance, multiscale modeling is poised to play an increasingly central role in drug development.

In many ways, this shift reflects a broader transition in biomedical science—from isolated observations toward integrated understanding. It is not merely about adding more data, but about connecting it meaningfully across scales. And while the path forward is not without uncertainty, the potential benefits—more effective therapies, reduced attrition rates, and truly personalized medicine—suggest that this is a direction worth pursuing.

2. Methodology

2.1 Search Strategy and Conceptual Scope

This narrative review was developed through a structured yet flexible synthesis of literature focusing on multiscale modeling in pharmacology and drug development. Rather than restricting inclusion to a predefined protocol, the approach was intentionally iterative, reflecting the evolving nature of the field. Core themes—such as molecular simulation, intracellular signaling, agent-based modeling, and PBPK frameworks—were identified early and refined as the literature was explored. Foundational and contemporary studies were prioritized to ensure both conceptual depth and methodological relevance.

2.2 Literature Selection and Thematic Integration

Studies were selected based on their contribution to understanding how drug responses can be modeled across biological scales. Emphasis was placed on works that explicitly linked multiple scales—for instance, connecting molecular binding events to tissue-level outcomes or integrating cellular signaling with systemic pharmacokinetics. Rather than treating each modeling technique in isolation, the review aimed to position them within a unified framework.

The integration process involved grouping studies into thematic domains: (i) molecular-scale simulations, (ii) intracellular network modeling, (iii) cellular and tissue-level modeling, and (iv) whole-body pharmacokinetic and pharmacodynamic frameworks. This structure allowed for a progressive narrative, moving from mechanistic detail toward clinical application.

2.3 Analytical Framework and Synthesis Approach

The analytical strategy centered on identifying how

different modeling approaches contribute to predictive capability. Particular attention was given to the interplay between scales—how outputs from one level inform models at another. Case studies, including toxicity prediction and resistance modeling, were examined to illustrate translational relevance.

Rather than quantitatively aggregating findings, the review adopts a qualitative synthesis approach. This allows for the exploration of methodological nuances, limitations, and emerging trends that may not be readily captured through statistical aggregation. The emphasis, therefore, is on conceptual coherence rather than numerical comparison.

2.4 Validation and Translational Considerations

An important component of the methodology involved assessing how multiscale models are validated and applied in real-world contexts. Studies employing iterative validation cycles, virtual populations, and *in silico* clinical trials were examined to understand how predictive models are refined and translated into practice.

2.5 Limitations of the Methodological Approach

As a narrative review, this study does not follow strict systematic protocols such as PRISMA. While this allows for flexibility and depth, it may introduce selection bias and limits reproducibility. Nevertheless, efforts were made to ensure that the included literature represents a balanced and comprehensive overview of the field.

3. Multiscale Modeling of Cellular Responses to Drugs: Bridging Mechanism and Translation

3.1 Reframing Drug Discovery Through Multiscale Thinking

The path from molecular discovery to clinical application has rarely been straightforward. In fact, if one looks closely, it often appears fragmented—guided by observable outcomes rather than a coherent mechanistic understanding. Historically, drug discovery has leaned heavily on phenotypic observations, where therapeutic success or failure is judged by measurable outcomes without necessarily deciphering the cascade of biological events that produced them (Hwang et al., 2013; Zhao & Iyengar, 2012). This approach, while pragmatic, has left a persistent gap—a kind of conceptual discontinuity—between molecular action and organism-level response.

It is within this gap that the so-called “translational

dilemma” emerges. Promising compounds, validated in controlled laboratory conditions, frequently falter when exposed to the complexity of human physiology (Clancy et al., 2016). The reasons are not entirely surprising. Biological systems are not merely complicated; they are deeply interconnected, adaptive, and context-dependent. A perturbation at one scale—say, a ligand binding event—can ripple across networks in ways that are difficult to anticipate without a framework capable of integrating across scales.

Multiscale modeling, then, is less a methodological innovation and more a conceptual necessity. It invites us to reconsider the human body not as a collection of isolated systems, but as a dynamic hierarchy—from atoms to cells, tissues, organs, and ultimately populations—where interactions at each level shape the whole (Amaro & Mulholland, 2018; Walpole et al., 2013). This shift, subtle yet profound, reorients drug discovery toward mechanism-based prediction rather than empirical approximation.

3.2 Architectural Foundations of Multiscale Frameworks

At its core, multiscale modeling is an exercise in integration. It attempts to answer a deceptively simple question: how does a molecular interaction translate into a clinical outcome? Addressing this requires a structured framework in which distinct biological domains are not only modeled independently but also meaningfully connected (Hwang et al., 2013; Zhao & Iyengar, 2012).

3.2.1 Molecular Scale: Capturing Atomic-Level Interactions

The foundation of this hierarchy lies at the molecular scale, where drug–target interactions are governed by physicochemical principles. Molecular mechanics (MM) and molecular dynamics (MD) simulations provide a window—perhaps the closest approximation we have to a “computational microscope”—into these interactions (Amaro & Mulholland, 2018). Through these approaches, researchers can observe binding events, estimate free energy landscapes, and evaluate conformational flexibility, all of which inform drug potency and selectivity.

These simulations have proven particularly valuable in anticipating adverse effects. For instance, modeling interactions with cardiac ion channels, such as the hERG channel, has allowed researchers to identify compounds that may induce arrhythmogenic risk long before clinical

Table 1. Hierarchical Structure of Multiscale Modeling Frameworks and Formalisms. This table presents the hierarchical organization of multiscale modeling frameworks, linking biological processes from molecular interactions to population-level outcomes. Each scale is associated with specific modeling formalisms and predictive outputs, illustrating how drug effects propagate across biological systems. The framework emphasizes the integration of spatial and temporal resolutions for mechanistic prediction.

Scale	Biological Domain	Spatial Resolution	Temporal Resolution	Modeling Formalism	Key Biological Process	Primary Predictive Output	Supporting Reference
Molecular	Atomic / Protein	Å	fs–ns	Molecular Dynamics (MD)	Drug–target binding	Binding free energy	Amaro & Mulholland (2018)
Intracellular	Signaling Networks	nm	sec–hrs	ODEs / Boolean logic	Phosphorylation cascades	Pathway activation levels	Zhao & Iyengar (2012)
Metabolic	Cellular Metabolism	nm	sec–min	Flux Balance Analysis	Biochemical reactions	Metabolic flux	Amaro & Mulholland (2018)
Cellular	Individual Cell	m	min–hrs	Agent-Based Model (ABM)	Phenotypic switching	Cell state transitions	Walpole et al. (2013)
Multicellular	Cell Clusters	m	hrs–days	Cellular Potts Model	Cell–cell adhesion	Tumor morphology	Frieboes et al. (2009)
Tissue	Local Environment	mm	days–weeks	Finite Element Model (FEM)	Angiogenesis / strain	Tissue reorganization	Walpole et al. (2013)
Organ	Specific Viscera	cm	min–hrs	Spatiotemporal PDEs	Blood flow / oxygenation	Organ drug uptake	Bhattacharya et al. (2012)
Whole Body	Organ Systems	m	min–months	PBPK Modeling	Systemic distribution	Plasma concentration	Eissing et al. (2011)
Population	Patient Cohorts	—	yrs–decades	Stochastic Simulation	Inter-individual variability	Virtual clinical outcomes	Eissing et al. (2011)
Pathological	Disease Niche	Variable	Variable	Rule-based Modeling	Chronic inflammation	Disease progression	Hwang et al. (2013)

Table 2. Representative Case Studies in Multiscale Drug Response and Toxicity. This table summarizes key case studies demonstrating how multiscale modeling predicts drug efficacy, toxicity, and resistance mechanisms. It highlights the integration of molecular targets with cellular responses and clinical outcomes. These examples illustrate the translational potential of multiscale approaches in pharmacology.

Drug / Agent	Target Organ	Model Type	Molecular Node	Intracellular Pathway	Cellular Response	Clinical Insight	Supporting Reference
Acetaminophen	Liver	PICD / PBPK	NAPQI adducts	Oxidative stress	Hepatocyte necrosis	Dose-dependent DILI	Thiel et al. (2017)
Dofetilide	Heart	Multiscale Electrophysiology	hERG channel	IKr block	APD prolongation	Arrhythmic risk	Obiol-Pardo et al. (2011)
Bortezomib	Bone marrow	Agent-based	MIC signaling	NF-B / apoptosis	Myeloma cell death	Niche resistance	Su et al. (2014)
Sitagliptin	Pancreas	Rule-based	DPP-4 enzyme	Insulin signaling	Glucose regulation	T2D efficacy	Hwang et al. (2013)
Trastuzumab	Breast tissue	Systems pharmacology	HER2 receptor	G1/S transition	Growth arrest	Resistance prediction	Ait-Oudhia et al. (2017)
Bevacizumab	Tumor	Hybrid model	VEGF	Angiogenesis	Vascular normalization	Drug delivery	Vavourakis et al. (2017)
Caffeine	Liver	PBPK-PD	CYP1A2	Bioactivation modulation	Competitive inhibition	APAP interaction	Thiel et al. (2017)
Wnt / BMP2	Bone	ODE-Tissue	-catenin	Smad signaling	Stem differentiation	Cytokine timing	Sun et al. (2012)
Anthrax factor	Tumor niche	Agent-based	MEK protein	MAPK pathway	Growth inhibition	Tumor suppression	Bhattacharya et al. (2012)
Lapatinib	Lung cancer	Stochastic hybrid	EGFR/HER2	ERK survival	Phenotypic switching	Dose-response	Oduola & Li (2018)

exposure (Obiol-Pardo et al., 2011; Walpole et al., 2013). Yet, while detailed, these models remain inherently reductionist unless their outputs are propagated into higher-order systems.

3.2.2 Intracellular Networks: Modeling Dynamic Decision Systems

Once a drug engages its target, the resulting signal does not remain localized. Instead, it propagates through intricate intracellular networks that regulate cellular fate. These networks—often conceptualized as signaling cascades—are typically modeled using systems of ordinary differential equations (ODEs), which describe the kinetics of biochemical reactions over time (Walpole et al., 2013; Zhao & Iyengar, 2012).

Pathways such as MAPK/ERK and NF- κ B exemplify this complexity. They do not simply transmit signals; they integrate, amplify, and sometimes dampen them, depending on context. By simulating these pathways, researchers can explore how variations in drug dosing, timing, or cellular state influence outcomes such as proliferation, apoptosis, or differentiation (Oduola & Li, 2018; Zhao & Iyengar, 2012).

Interestingly, not all modeling at this level is strictly quantitative. Rule-based approaches have gained traction as a way to manage combinatorial complexity. By encoding biological interactions into logical rules, these models allow for scalable simulations of signaling behavior without requiring exhaustive parameterization (Hwang et al., 2013). While less mechanistically explicit, they offer a pragmatic compromise between detail and tractability.

3.2.3 Cellular and Tissue Scales: Emergence and Spatial Context

Biological behavior, however, cannot be fully understood at the intracellular level alone. Cells exist within environments—structured, heterogeneous, and often dynamic. It is here that emergent phenomena arise, driven by interactions among cells and between cells and their surroundings.

Agent-based models (ABMs) have become a preferred tool for capturing these dynamics. In these frameworks, each cell is represented as an individual “agent” with its own internal state and behavioral rules (Su et al., 2014; Walpole et al., 2013). This allows for the simulation of spatial phenomena such as tumor growth, immune infiltration, and tissue remodeling.

In multiple myeloma, for example, ABMs have been used to model the bone marrow microenvironment, revealing how physical properties—such as extracellular matrix stiffness—can influence drug resistance (Su et al., 2014). These insights are difficult, if not impossible, to obtain from traditional *in vitro* systems, where spatial heterogeneity is largely absent (Clancy et al., 2016).

Similarly, in oncology, multiscale models of tumor growth and angiogenesis have provided valuable predictions about drug penetration and efficacy within complex tissue architectures (Frieboes et al., 2009; Vavourakis et al., 2017). Such models underscore an important point: therapeutic response is not solely determined by molecular potency but also by spatial accessibility and microenvironmental constraints.

3.3 From Simulation to Clinical Relevance: Validation and Translation

While the construction of multiscale models is intellectually compelling, their true value lies in their ability to inform real-world decisions. This necessitates rigorous validation and thoughtful translation into clinically actionable insights (Clancy et al., 2016; Eissing et al., 2011).

3.4 Bridging In Vitro and In Vivo: The PICD Paradigm

One of the most promising translational strategies is the integration of *in vitro* data into physiologically based pharmacokinetic (PBPK) models—a process often referred to as PBPK-based *in vivo* contextualization of *in vitro* data (PICD) (Thiel et al., 2017). This approach effectively “maps” cellular-level responses onto whole-body systems, allowing researchers to predict how laboratory findings might manifest in clinical settings.

A notable example involves the interaction between caffeine and acetaminophen. Through multiscale modeling, it was shown that caffeine can exert both inhibitory and stimulatory effects on pathways associated with liver toxicity, depending on dose and timing (Thiel et al., 2017). Such findings highlight the importance of context—something that purely experimental approaches may overlook.

3.5 Virtual Populations and Personalized Medicine

Another powerful application of multiscale modeling lies in the simulation of virtual populations. Biological variability, driven by genetic and environmental factors, means that drug responses are rarely uniform across individuals

(Hwang et al., 2013; Zhao & Iyengar, 2012). By incorporating parameters such as enzyme polymorphisms, models can predict differential responses among patient subgroups.

For instance, variations in CYP2D6 activity can significantly alter drug metabolism, affecting both efficacy and toxicity (Eissing et al., 2011). By simulating these variations, multiscale models can identify high-risk populations and inform personalized dosing strategies.

In hepatotoxicity research, frameworks such as DILIsym have demonstrated how integrating subcellular mechanisms with systemic biomarkers can yield predictive insights into drug-induced liver injury (Bhattacharya et al., 2012; Bai et al., 2014). These models, validated against clinical data, offer a compelling alternative to traditional animal testing while providing mechanistic clarity (Diaz Ochoa et al., 2013).

3.6 Optimizing Combination Therapies Through Systems Insight

The treatment of complex diseases often requires combination therapies, where multiple drugs target different components of a biological network. Multiscale models are uniquely suited to explore such strategies, as they can simulate interactions across pathways and scales simultaneously (Hwang et al., 2013; Su et al., 2014).

In tissue engineering, for example, models have been used to predict how combinations of cytokines—such as Wnt and BMP2—can be timed to optimize bone regeneration (Sun et al., 2012; Clancy et al., 2016). These findings illustrate how computational approaches can reduce the need for exhaustive experimental screening, guiding more efficient therapeutic design.

3.7 Challenges, Trade-offs, and Future Directions

Despite their promise, multiscale models are not without limitations. One of the most significant challenges is data availability. Accurate parameterization requires detailed, high-resolution data across multiple scales—data that are often scarce or difficult to obtain (Clancy et al., 2016; Walpole et al., 2013).

Computational demands also remain substantial. High-fidelity simulations, particularly those involving spatial and temporal complexity, can require extensive resources, limiting their accessibility (Amaro & Mulholland, 2018). As a result, modelers are often forced to make trade-offs

between realism and feasibility.

This leads to an ongoing debate between “black box” and “grey box” modeling approaches. While mechanistic models offer interpretability, they can become unwieldy at larger scales. Conversely, phenomenological models are computationally efficient but may sacrifice biological fidelity (Walpole et al., 2013). Navigating this balance is, perhaps, one of the central challenges of the field.

3.8 Concluding Perspective

Multiscale modeling represents a significant, perhaps even transformative, shift in how we approach drug discovery and development. By linking molecular interactions to systemic outcomes, it provides a framework for understanding—not just observing—drug action (Amaro & Mulholland, 2018; Clancy et al., 2016; Zhao & Iyengar, 2012).

There is still uncertainty, of course. The models are imperfect, the data incomplete, and the systems themselves endlessly complex. Yet, the direction is unmistakable. As computational tools advance and data integration improves, these models are likely to move from theoretical constructs to indispensable components of clinical decision-making (Eissing et al., 2011; Walpole et al., 2013).

In that sense, multiscale modeling does not merely refine existing paradigms—it challenges them. It suggests that the future of pharmacology may lie not in isolated observations, but in connected understanding. And perhaps, in that shift, the long-standing gap between discovery and application may finally begin to close.

4. Translating Multiscale Modeling into Mechanistic and Clinical Insight

4.1 Reconstructing Drug Action Across Scales

The integration of multiscale modeling into drug development has, gradually but unmistakably, begun to reshape how pharmacological knowledge is constructed. What was once largely an empirical process—guided by observable phenotypes and iterative experimentation—now appears to be evolving into a more structured, predictive discipline. By linking molecular interactions with cellular responses and, ultimately, organism-level outcomes, multiscale frameworks enable a reconstruction of drug action that is both mechanistically grounded and clinically meaningful (Walpole et al., 2013;

Zhao & Iyengar, 2012).

This reconstruction is not merely conceptual but operational. Hierarchical integration allows parameters derived at one biological scale to inform behaviors at higher levels. As summarized in Table 1, the multiscale framework organizes molecular, intracellular, cellular, and systemic processes into a coherent hierarchy that enables the propagation of drug effects across biological scales. Through this structure, even a single molecular binding event can be traced through signaling cascades and tissue-level interactions to produce clinically observable outcomes.

4.2 Mechanistic Insights into Toxicity and Drug Safety

One of the most significant contributions of multiscale modeling lies in its ability to elucidate drug-induced toxicity. Historically, toxicity—particularly hepatotoxicity—has been difficult to predict due to the complex interplay between metabolism and cellular stress pathways (Bhattacharya et al., 2012). Traditional models often identified toxicity only after irreversible damage had occurred, limiting their clinical utility.

Multiscale frameworks have begun to address this limitation by integrating processes across scales. Platforms such as DILIsym combine subcellular mechanisms, including mitochondrial dysfunction and oxidative stress, with organ-level biomarkers such as ALT and bilirubin (Bai et al., 2014; Bhattacharya et al., 2012). As illustrated in Table 2, case studies of multiscale toxicity modeling demonstrate how integrating intracellular stress pathways with organ-level biomarkers provides mechanistic explanations for drug-induced liver injury.

A particularly illustrative example is the multiscale analysis of acetaminophen toxicity using the PBPK-based in vivo contextualization of in vitro data (PICD) approach. This framework links cellular gene expression responses with systemic pharmacokinetics, revealing a nuanced, dose-dependent interplay (Thiel et al., 2017). The finding that caffeine can both mitigate and exacerbate acetaminophen toxicity underscores the importance of context in pharmacological prediction (Thiel et al., 2017). The quantitative parameters used to evaluate such dose-dependent toxicity relationships—particularly those describing cellular viability and systemic exposure—are detailed in Table 4, which defines the key modeling variables used across scales.

In cardiology, multiscale modeling has similarly advanced the understanding of drug-induced arrhythmias. Simulations demonstrate that QT prolongation arises not solely from ion channel blockade but from emergent interactions within heterogeneous cardiac tissue (Costabal et al., 2018; Walpole et al., 2013). These findings reinforce the idea that toxicity is rarely a single-scale phenomenon.

4.3 Overcoming Resistance and Optimizing Combination Therapy

Drug resistance, particularly in oncology, represents another domain where multiscale modeling has yielded important insights. Resistance is not simply a consequence of genetic mutations; rather, it emerges from interactions between tumor cells and their surrounding microenvironment.

Agent-based modeling (ABM) has proven particularly effective in capturing these dynamics. In multiple myeloma, simulations of the bone marrow niche have demonstrated how physical properties—such as extracellular matrix stiffness—can protect tumor cells from chemotherapeutic agents (Su et al., 2014). As summarized in Table 2, multiscale case studies highlight how incorporating microenvironmental factors into computational models enables the identification of mechanisms underlying drug resistance.

These models also provide a platform for exploring therapeutic strategies. By simulating interactions across signaling pathways and spatial environments, researchers can identify synergistic drug combinations. For example, the combination of arsenic trioxide and bortezomib has been shown to overcome niche-mediated resistance when evaluated within a multiscale framework (Su et al., 2014; Sun et al., 2012).

Beyond oncology, rule-based multiscale models have been applied to systemic diseases such as Type 2 diabetes. By encoding biological knowledge into rule sets, these models simulate the effects of multiple drugs across interconnected metabolic compartments (Hwang et al., 2013). The rule-based modeling structure and its integration across biological domains are conceptually summarized in Table 1, which outlines how qualitative and quantitative modeling approaches can be unified within a multiscale framework.

4.4 Balancing Complexity with Clinical Actionability

Despite these advances, the translation of multiscale

Table 3. Computational Platforms for Multiscale Pharmacological Modeling. This table categorizes widely used computational tools for multiscale pharmacological modeling across biological scales. It highlights their modeling approaches, integration capabilities, and regulatory relevance. These platforms collectively enable the development of predictive and personalized simulation frameworks.

Tool	Primary Scale	Approach	Language	Scope	Data Integration	Regulatory Use	Reference
PK-Sim	Whole body	PBPK	C++ / GUI	Systemic PK	Anatomy databases	FDA use	Eissing et al. (2011)
MoBi	Molecular	ODE/network	C++ / XML	Pathways	Pathway DB	Research/industry	Eissing et al. (2011)
DILIsym	Liver	Mechanistic	MATLAB/C++	Hepatotoxicity	Toxicogenomics	Industry	Bhattacharya et al. (2012)
PhysiCell	Multicellular	Agent-based	C++	Tissue modeling	3D imaging	Research	Ghaffarizadeh et al. (2017)
CellML	Subcellular	Mathematical	XML	Model sharing	Curated DB	Standard	Walpole et al. (2013)
COPASI	Biochemical	ODE/stochastic	C++	Kinetics	Time-course data	Academic	Cappuccio et al. (2016)
Cell Collective	Intracellular	Logic-based	Web	Networks	Qualitative data	Education	Helikar et al. (2015)
ENISI MSM	Immunology	Hybrid	Java	Immunity	Cytokine data	Research	Cappuccio et al. (2016)
CompuCell 3D	Tissue	Potts model	Python/C++	Morphogenesis	Mechanical data	Research	Swat et al. (2012)
PK-Sim R/Mat	Population	Statistical	R/MATLAB	Variability	Genomics	Clinical sim	Eissing et al. (2011)

Table 4. Key Mechanistic Parameters and Biological Inputs in Multiscale Models. This table defines key mechanistic parameters used to link biological processes across scales in multiscale models. These variables capture molecular potency, cellular dynamics, and tissue-level transport phenomena. Together, they provide the quantitative backbone required for model calibration and predictive accuracy.

Parameter	Context	Typical Value	Units	Role	Data Source	Scale Linkage	Reference
IC50	Drug–target	Variable	nM/M	Binding potency	Patch clamp	Molecular Intracellular	Obiol-Pardo et al. (2011)
Vth	Cell vitality	0.5	—	Apoptosis trigger	Flow cytometry	Intracellular Cellular	Nikmaneshi et al. (2020a)
a1/a2	Nuclear signal	—	—	Translocation rate	Imaging	Signal Gene expression	Umegaki et al. (2024)
k	Microvasculature	—	m/(mmHg·s)	Leakage rate	MRI	Organ Tissue	Cai et al. (2016)
Tcc	Cell cycle	20–24	hrs	Growth rate	In vitro	Cellular Tissue	Umegaki et al. (2024)

Tm	Membrane flux	10	—	Motility	Assays	Cellular Multicellular	Jafari Nivlouei et al. (2022)
rf	Interstitial	1.0	—	Transport barrier	Diffusion	Tissue Cellular	Baxter & Jain (1989)
L	Vessel wall	6.0	—	Permeability	Histology	Vessel Tissue	Nikmaneshi et al. (2021)
Osmotic pressure	Interstitial fluid	10–15	mmHg	Pressure gradient	Catheters	Tissue Organ	Zhao et al. (2007)
Ds	Vascular damage	0–1	—	Perfusion loss	Imaging	Cellular Organ	Schutt & Haemmerich (2008)

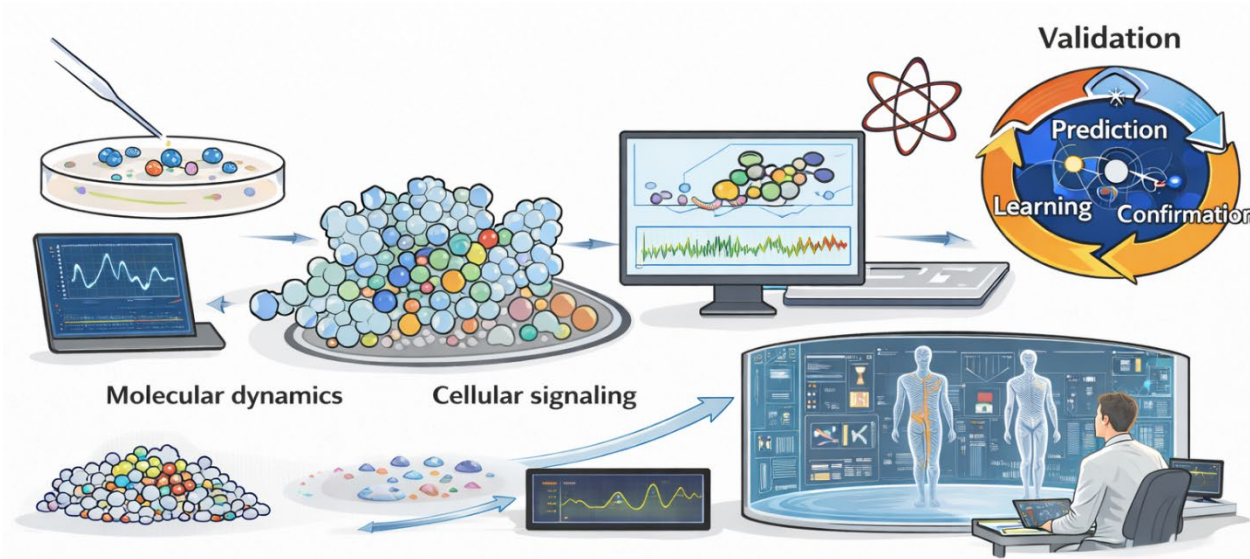


Figure 1. Multiscale modeling framework in drug discovery. This schematic illustrates how multiscale modeling integrates molecular dynamics, cellular signaling, and whole-body physiology to predict drug behavior. The framework highlights the flow of information across biological scales and emphasizes iterative validation through predict–learn–confirm cycles, enabling more accurate and mechanistically informed therapeutic development.

modeling into clinical practice remains an ongoing challenge. Biological systems demand detailed representation, yet overly complex models can become computationally burdensome and difficult to interpret (Walpole et al., 2013; Amaro & Mulholland, 2018).

This tension is particularly evident in efforts to bridge simulation outputs with clinical decision-making. While models can reproduce experimental observations with high fidelity, their utility ultimately depends on interpretability and applicability (Clancy et al., 2016). The diversity of modeling tools and platforms used to manage this complexity—ranging from PBPK simulators to hybrid multiscale frameworks—is summarized in Table 3, which categorizes software platforms based on their functional capabilities and integration levels.

4.5 Data Limitations and the Imperative of Validation

A recurring limitation in multiscale modeling is the scarcity of high-quality, time-resolved data required for parameterization. Without such data, models risk becoming mathematically consistent yet biologically uncertain (Clancy et al., 2016).

To address this, researchers increasingly rely on iterative validation strategies. The “predict–learn–confirm” paradigm involves continuous refinement of models through comparison with experimental and clinical data (Eissing et al., 2011; Zhao & Iyengar, 2012). The parameters and validation variables used in these iterative processes—such as dose-response relationships, signaling outputs, and physiological endpoints—are systematically defined in Table 4, providing a standardized basis for model calibration and evaluation.

4.6 Toward Digital Twins and Personalized Pharmacology

The emergence of specialized computational platforms has significantly expanded the accessibility of multiscale modeling. Tools such as PK-Sim and MoBi enable the integration of physiological, biochemical, and genetic data into unified simulation environments (Eissing et al., 2011).

These developments point toward the concept of the “digital twin”—a virtual representation of an individual patient that can be used to simulate therapeutic interventions. By incorporating genetic polymorphisms, such as CYP2D6 variability, these models can predict patient-specific responses to drugs (Zhao & Iyengar, 2012). As outlined in Table 3, modern multiscale software platforms provide the computational infrastructure

necessary to construct such individualized models, supporting the transition toward precision pharmacology.

4.7 Addressing Spatial and Temporal Heterogeneity

A critical insight emerging from multiscale modeling is the importance of spatial heterogeneity. Biological systems are inherently non-uniform, with gradients of oxygen, nutrients, and metabolic activity influencing drug distribution and efficacy (Bhattacharya et al., 2012; Frieboes et al., 2009).

Multiscale models that incorporate spatial dynamics—through partial differential equations or agent-based rules—are uniquely positioned to capture these effects (Walpole et al., 2013). In tumor modeling, for instance, drug penetration is often limited by diffusion constraints, resulting in heterogeneous exposure within tissues (Vavourakis et al., 2017). These spatial parameters and diffusion-related variables, which critically influence drug penetration and efficacy, are quantitatively represented in Table 4, emphasizing their role in multiscale simulations.

Taken together, the discussed here suggest that multiscale modeling is transitioning from a conceptual framework to a practical tool in drug development. By integrating data across biological scales, these models provide a mechanistic basis for predicting both efficacy and toxicity. While challenges remain—particularly in data availability and computational demand—the trajectory is clear.

Multiscale modeling is gradually dissolving the traditional “black box” of pharmacology, replacing it with a structured, predictive, and increasingly personalized approach. As computational capabilities expand and data integration improves, these frameworks are likely to become indispensable in shaping the future of precision medicine.

5. Limitations

Despite its integrative scope, this review is not without limitations. The narrative approach, while allowing for conceptual depth and flexibility, inherently lacks the rigor of systematic methodologies, potentially introducing selection bias. The rapidly evolving nature of multiscale modeling further complicates synthesis, as new computational techniques and datasets continue to emerge, sometimes outpacing comprehensive evaluation. Additionally, the review relies heavily on studies that successfully demonstrate multiscale integration, which

may unintentionally underrepresent negative or inconclusive findings.

Another limitation lies in the variability of modeling approaches themselves. Differences in assumptions, parameterization strategies, and validation methods make direct comparison difficult. Furthermore, the reliance on published literature means that underlying data quality and reproducibility cannot always be independently verified. Finally, while clinical relevance is discussed, real-world implementation of multiscale models remains limited, and thus some conclusions remain, to an extent, anticipatory rather than fully realized.

6. Conclusion

Multiscale modeling, while still evolving, appears to offer a meaningful shift in how drug discovery is conceptualized and executed. By connecting molecular events to systemic outcomes, it provides a framework for understanding drug action with greater depth and predictive capability (Figure 1). Yet, the transition from theoretical promise to routine clinical application remains incomplete. Challenges in data integration, computational complexity, and validation persist. Even so, the trajectory suggests that multiscale approaches will play an increasingly central role in shaping a more precise, mechanistically informed paradigm of pharmacology—one that may ultimately reduce uncertainty and improve therapeutic outcomes.

Author Contributions

S.S.K. conceptualized the study, designed the review framework, conducted literature synthesis, and drafted the original manuscript. T. contributed to data interpretation, critical analysis of the literature, and revision of the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

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