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Sim2Real-PK framework for precision dosing: Integrating pharmacokinetic mechanisms and deep learning to decode clinical heterogeneity from sparse data

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Abstract

Precision dosing is a cornerstone of individualized therapeutics, yet its implementation is frequently hindered by clinical pharmacokinetic data that are characteristically sparse, irregularly sampled, and highly heterogeneous. Traditional mechanistic models provide structural interpretability but often lack the flexibility to capture complex patient-specific deviations, whereas purely data-driven deep learning models are prone to pharmacological inconsistency and poor generalization in low-data regimes. Here we present Sim2Real-PK, a hybrid neural-mechanistic framework that reconceptualizes pharmacokinetic forecasting as a time-aware latent state-space trajectory inference task. Sim2Real-PK first pretrains a neural dynamics core on massive synthetic datasets derived from mechanistic ordinary differential equation systems to internalize universal kinetic laws, then adapts to real-world clinical heterogeneity through a constrained residual correction pathway. Validated on individual participant data from the YODA Project for two drugs representing distinct pharmacological regimes—ibrutinib and daratumumab—Sim2Real-PK significantly outperformed conventional population-level baselines. The framework improved the F50 for ibrutinib from 32.1% to 39.9% and the F20 for daratumumab from 38.8% to 51.1%, while faithfully recovering expected linear and nonlinear pharmacological behaviors. Crucially, the model successfully resolved latent pharmacokinetic heterogeneity within patient cohorts that remained obscured under traditional analytical frameworks. These results demonstrate that mechanistically-anchored neural adaptation can bridge the gap between biological rigor and predictive agility, providing a robust foundation for next-generation model-informed precision dosing.

Main text

Precision dosing represents a central pillar of modern therapeutics, necessitating the precise alignment of pharmacological interventions with the inherent biological heterogeneity of individual patients¹. This objective is increasingly addressed through Model-Informed Drug Development (MIDD), a paradigm where Pharmacokinetic-Pharmacodynamic (PK-PD) modeling serves as the analytical engine for decoding the complex relationship between drug exposure and therapeutic response^{2,3}. Within this landscape, the methodological rigor of Pharmacokinetics (PK) has historically been anchored in the use of Ordinary Differential Equations (ODEs) to formalize drug disposition as a series of transitions across physiological compartments. These mechanistic priors provide a structurally rigorous framework for interpretability, enabling quantitative pharmacology to translate biological assumptions into the high-stakes arena of regulatory decision-making and clinical regimen optimization⁴⁻⁷.

However, a fundamental tension exists between the rigid, prescribed structures of population-level ODE systems and the high-dimensional clinical manifolds characteristic of modern patient cohorts. This challenge is not intrinsic to the ODEs themselves, but rather stems from the methodological bottleneck of inferring latent parameters from trajectories that are frequently noisy, irregularly sampled, and strongly action-conditioned by varying dosing schedules^{8,9}. While mechanistically-grounded models remain the gold standard for interpretability, their practical deployment often confronts a formidable trade-off between physiological rigor and the predictive agility required to capture complex clinical heterogeneity^{10,11}. Conversely, while deep learning offers immense representative power, its unconstrained application to sparse clinical datasets often leads to pharmacologically inconsistent predictions and poor generalization. We reasoned that these conflicting paradigms could be unified through a simulation-to-real framework, where mechanistic simulations provide a structured prior for latent dynamics, and deep learning supplies the residual flexibility needed to reconcile these priors with clinical reality¹²⁻¹⁴.

While the integration of neural networks has gained traction in pharmacometrics, purely data-driven architectures frequently lack the mechanistic inductive biases required for high-stakes clinical reliability¹⁵⁻¹⁷. Unlike the dense, high-frequency sequences typical of other machine learning domains, clinical pharmacokinetic data are characteristically sparse and irregularly sampled¹⁸. Consequently, standard architectures such as Recurrent Neural Networks and Transformers—primarily designed to capture regular temporal correlations—often struggle to resolve the underlying dynamics of drug disposition when faced with the erratic dosing and observation schedules inherent to clinical trials^{19,20}. More critically, these models remain "blind" to fundamental pharmacological laws. Although recent hybrid approaches have attempted to integrate ML with pharmacological modeling, they remain reliant on the explicit estimation of latent PK parameters, which introduces a significant inference bottleneck^{16,17,21}. Furthermore, another category of methods attempts to extrapolate the remaining concentration profile based on initial

observations^{22,23}. Yet, this sequence completion paradigm implicitly assumes a static treatment course, which may oversimplify the dynamic nature of clinical practice where dosing schedules are frequently adjusted.

The mathematical elegance of Neural Ordinary Differential Equations (Neural ODEs) [17] and Universal Differential Equations (UDEs) [24,25] represents a pioneering leap toward unifying neural architectures with the continuous-time formalism of biological dynamics. By embedding neural networks directly within the derivative functions, these approaches offer a theoretically superior landscape for modeling the fluid transitions of drug disposition. However, the unconstrained expressivity of these solvers introduces an inherent operational fragility when confronted with the stochasticity of clinical trial data. Navigating the stiff manifolds characteristic of pharmacological systems within the optimization loop frequently induces computational instability and prohibitive inference latency, complicating their integration into real-time clinical workflows. Crucially, as these models typically seek to infer high-dimensional vector fields *de novo*, they necessitate a density of longitudinal observations that is seldom available in early-phase trials or therapeutic monitoring. In the absence of a robust mechanistic anchor, such unconstrained dynamics are prone to converging on local minima or overfitting to transient noise, failing to manifest the rigorous inductive biases required to enforce non-negotiable pharmacological constraints.

Here we present Sim2Real-PK, a hybrid neural-mechanistic framework that reconceptualizes pharmacokinetic forecasting as a time-aware trajectory inference task within a latent state-space. We reasoned that while individual patient characteristics vary across clinical cohorts, the fundamental physical laws governing drug disposition provide a universal scaffold that can be effectively learned through simulation. To bridge this gap, Sim2Real-PK employs a two-stage knowledge-informed transfer strategy: a neural dynamics core is first pretrained on a massive synthetic corpus derived from mechanistic ODE systems to internalize core kinetic regularities, followed by constrained finetuning on real clinical data. This approach allows the model to leverage a mechanistically-informed prior while adapting to clinical heterogeneity through a residual correction pathway that incorporates extended clinical covariates.

We validated Sim2Real-PK using individual participant data from the YODA Project, focusing on two therapeutic agents that represent distinct pharmacokinetic regimes: ibrutinib, an orally administered small molecule, and daratumumab, a monoclonal antibody exhibiting complex target-mediated drug disposition. Our results demonstrate that Sim2Real-PK significantly outperforms conventional population-level baselines and unconstrained deep learning models, successfully reconciling structural interpretability with high predictive accuracy. Beyond retrospective forecasting, the framework serves as a differentiable engine for *in silico* regimen optimization and resolves clinically meaningful heterogeneity within patient cohorts, providing a robust foundation for next-generation model-informed precision dosing.

A sim-to-real framework for pharmacokinetic prediction

Sim2Real-PK treats pharmacokinetic forecasting as a time-aware latent state-space problem, designed to bridge the gap between idealized mechanistic simulations and noisy clinical reality. The framework is structured into four interacting components: a covariate encoder, a dosing-action encoder, a time-aware latent dynamics core, and an observation decoder, supplemented by a residual correction module for clinical adaptation (Fig. 1). A central tenet of our architecture is the formal partitioning of patient information into identified covariates—those explicitly represented in mechanistic ODE systems—and extended covariates, which comprise additional clinical biomarkers available in real-world trials. Specifically, for each virtual subject within the pretraining stage, ground-truth state trajectories are integrated using these mechanistic ODEs to generate a diverse training corpus (Fig. 1A). This process allows the framework to internalize universal physical laws governing drug disposition—including mass balance, superposition, and exponential elimination—across a vast landscape of physiological conditions before encountering real patient data.

For each patient i , the model represents their physiological status as a latent state h_t , which evolves through a transition function $h_t = \mathcal{F}_\theta(h_{t-1}, \phi_{cov}(x^{(i)}), \phi_{act}(a_t), \phi_{time}(\Delta t_t))$. This time-aware update explicitly handles irregular observation intervals Δt_t , bypassing the fixed-step limitations of standard sequence models. To ensure the model respects pharmacological constraints while remaining flexible, we adopt a two-stage learning strategy. First, the latent dynamics are pretrained on massive synthetic cohorts to internalize universal kinetic regularities such as dose-exposure scaling and accumulation (Fig. 1B). Subsequently, clinical transfer is achieved through a residual pathway, defined as $\hat{\mathbf{y}}_t = \hat{\mathbf{y}}_{base,t} + \Delta \mathbf{y}_{res,t}$, where the pretrained backbone provides a mechanistic baseline ($\hat{\mathbf{y}}_{base,t}$) and the residual branch ($\Delta \mathbf{y}_{res,t}$) leverages extended covariates to correct patient-specific deviations (Fig. 1C). This constrained adaptation ensures that the model preserves its mechanistic integrity even when supervised by sparse clinical data.

Validation of Knowledge-Informed Pretraining

To initialize the latent dynamics on a pharmacologically meaningful manifold, we implemented a two-stage adaptive training strategy that transitions from teacher forcing to autoregressive rollout (Fig. 2A). During Stage I, the autoregressive probability $P_{autoreg}$ increases linearly from 0 to 0.8, allowing the model to establish stable dependency structures. In Stage II, $P_{autoreg}$ is further increased to 1.0 alongside adaptive penalty weights to enforce long-horizon physiological consistency (Fig. 2A). This adaptive curriculum yielded markedly more stable training trajectories for both compounds compared to standard scheduled sampling. Specifically, for ibrutinib, the adaptive protocol achieved a terminal validation loss of approximately 0.1, whereas the standard schedule exhibited significant divergence, resulting in a final loss of 1.8 (Fig. 2B). Similarly, for Daratumumab, the adaptive strategy converged to a loss of 0.07, representing a marked improvement over the standard approach, which plateaued at 0.5 (Fig. 2C).

Notably, ibrutinib exhibited significantly greater instability under the scheduled sampling strategy compared to Daratumumab. As the ratio of free rollout increased during later epochs, the ibrutinib model suffered from an abnormal surge in training loss (Fig. 2B), whereas daratumumab primarily experienced suboptimal convergence (Fig. 2C). This disparity can be attributed to the distinct observation-to-action ratios inherent in the two pharmacological profiles. The oral small molecule dataset of ibrutinib is characterized by a high sampling density (typically 6–10 observations per dose) required to capture rapid absorption and distribution phases, thereby imposing a long autoregressive horizon between dosing events. In contrast, the monoclonal antibody data of daratumumab is relatively sparse, primarily capturing peak and trough levels. Consequently, the standard schedule struggles to maintain stability over the extended prediction windows required for small molecules, while the two-stage-adaptive curriculum effectively mitigates error accumulation in these high-resolution sequences.

Beyond numerical stability, the pretrained model successfully internalized the distinct pharmacokinetic characteristics inherent to each therapeutic class. For the small molecule ibrutinib, the predicted Area Under the Curve (AUC) exhibited a strictly linear correlation with the administered dose ($R^2 \approx 0.992$), consistent with linear first-order elimination kinetics (Fig. 2D). Conversely, for the monoclonal antibody Daratumumab, the model captured the characteristic TMDD, where exposure increased exponentially ($Power \approx 2.01, R^2 \approx 0.997$) rather than linearly with dosage, reflecting the saturation of clearance pathways (Fig. 2E). Furthermore, the model demonstrated precise sensitivity to physiological covariates: the ibrutinib module accurately stratified concentration peaks based on categorical factors such as food effects and CYP3A inhibition status (Fig. 2F), while the daratumumab module reflected continuous variations in elimination half-life driven by serum albumin levels and other covariates (Fig. 2G, Supplementary Fig. S1). At the individual level, randomly selected subject trajectories confirm that the architecture tightly synchronizes predicted concentrations with irregular dosing impulses, effectively handling diverse accumulation and washout dynamics across both linear and non-linear regimes (Fig. 2H-K).

Clinical Data Adaptation and Predictive Performance

The predictive capability of the Sim2Real-PK framework was rigorously evaluated in comparison with PopPK models using clinical trial data. For the small molecule ibrutinib, while an initial alignment was indicated by the pretrained model, a stratified prediction pattern with limited intra-group variability was exhibited (Fig. 3A), reflecting the reliance on identified population features. These limitations were subsequently rectified by the finetuning process, by which predicted concentrations were tightly aligned around the line of unity. Consequently, the F50 metric was increased from 32.1% in the conventional PopPK baseline to 39.9%. A consistent reduction in RMSE and an improvement in F50 were revealed by pairwise comparison across all validation folds, with particularly notable gains observed in the capture of steady-state dynamics, such as AUC_{ss} and $C_{min,ss}$ (Fig. 3B).

The similar trend was observed for the monoclonal antibody daratumumab. It was demonstrated that while the PopPK baseline (F20: 38.8%) was surpassed by the pretrained model (F20: 46.6%)—which notably still retained some rigid structural bias—the alignment was further optimized to 51.1% during the finetuning phase, effectively correcting systematic deviations in high-concentration regions (Fig. 3C). Lower RMSE and higher F20 scores were consistently achieved compared to PopPK model. As highlighted by the steep pairwise slopes in Fig. 3D, substantial improvements were realized in the prediction of trough concentrations ($C_{min,ss}$ and $C_{min,Last}$), which are critical parameters for ensuring therapeutic efficacy. Additionally, the model's predictive stability across the entire concentration range was substantiated by CWRES analysis (Supplementary Fig. S2). Visual inspection revealed that the validation residuals were tightly clustered around the zero line ($y = 0$), with a significantly higher proportion of data points falling strictly within the ± 2 reference interval compared to the PopPK model. Finally, results of representative individual trajectories demonstrated that patient-specific fluctuations and irregular kinetic phases were effectively captured by the finetuned model. The model maintained high concordance with the observed concentrations throughout the treatment course, including complex profiles following multiple dosing events, exhibiting comparable or improved predictive alignment relative to conventional population approaches (Supplementary Fig. S3).

Feature Contribution and Training Robustness with Ablation

To determine the drivers of predictive performance and validate the necessity of the proposed architecture, a comprehensive component ablation was conducted on the daratumumab dataset. As illustrated in Fig. 4A, it was observed that the model trained solely on identified covariates yielded a significantly higher RMSE compared to the PopPK models (indicated by the dashed line), suggesting that a naive neural network restricted to low-dimensional mechanistic inputs is insufficient to capture complex clinical dynamics. However, predictive accuracy was substantially recovered and enhanced by the sequential integration of the residual network and extended covariates. The inclusion of the full feature set resulted in the lowest RMSE and highest F20 scores, demonstrating that the residual learning framework effectively leverages extended clinical data to bridge the performance gap left by mechanistic constraints.

The specific contribution of clinical feature groups was further quantified via a group backward analysis (grouping details in Supplementary Table 1). It was found that the exclusion of Lab Tests (e.g., liver and kidney function markers) and Immunoglobulins resulted in the most substantial performance degradation (Fig. 4A). This empirical evidence underscores their pivotal role in capturing the inter-individual variability of antibody clearance. Moderate performance drops were also noted when free light chains and M proteins were removed, identifying them as non-negligible covariates for TMDD kinetics (Fig. 4A). Extensive collinearity was observed among these extended high-dimensional covariates, such as the intrinsic correlations between renal function markers and M protein levels (Supplementary Fig. S4). Consequently, the superior predictive accuracy achieved

by the complete feature set suggests that the neural architecture effectively synthesizes information from these entangled clinical networks, rather than relying on isolated predictors.

Finally, the critical necessity of the proposed "Freeze-Thaw" finetuning strategy was rigorously validated. The Sim2Real-PK framework was compared with alternative strategies where the dynamics core or all parameters were fully thawed. It was demonstrated that, regardless of the training sample size (ranging from 100% to 60%), the fully thawed models consistently failed to retain predictive capability, exhibiting drastic increases in RMSE and near-zero F20 scores due to severe overfitting and the loss of physical constraints (Fig. 4B). In contrast, stable performance was maintained by the proposed strategy, which preserves the pretrained mechanistic priors while adapting only the residual path, thereby ensuring robust generalization even in data-scarce scenarios.

Downstream Clinical Applications: Regimen Optimization and Subtype Discovery

To exemplify the capability for personalized regimen optimization, the iterative process of action refinement was demonstrated. The clinical objective was to determine the optimal frequency tapering schedule (transitioning from weekly to bi-weekly and tri-weekly administration). The target constraints were derived from established PK-PD relationships to ensure clinical safety and efficacy, specifically maintaining $C_{min,ss} > 236$ and peak concentrations $C_{max,ss} < 907$ mg/L²⁴. Through this simulation, a dosing configuration was identified that balanced induction saturation with maintenance safety, ensuring that therapeutic exposure was maintained within efficacy boundaries throughout the treatment course, thereby preventing both sub-therapeutic dosing and toxicity accumulation (Fig. 5A).

Parallel to action optimization, a pair of Virtual Twin Simulation was conducted to overcome the information bottleneck in conventional models, which collapse diverse disease subtypes (e.g., IgA vs. Light Chain MM) into a single category. The finetuned framework successfully disentangled the underlying kinetic divergence. The distinct accumulation profile with lower trough concentrations was revealed for the IgA-dominant cohort (Fig. 5B), whereas the Light Chain-dominant cohort exhibited a slow clearance profile (Fig. 5C). When evaluated by the pretrained model (proxy for standard PopPK logic), identical trajectories were predicted for both groups due to the reliance on identified covariates (Fig. 5D). The discrimination capability of finetuned model was further quantified by the separation in the maximum pre-dose trough distributions, demonstrating the model's capacity to recover granular pharmacokinetic variability obscured by rigid categorical classifications (Fig. 5E).

Discussion

This study presents Sim2Real-PK as a practical framework for integrating mechanistic pharmacological knowledge with deep learning-based adaptation under sparse clinical supervision. The central philosophy is that mechanistic pharmacology and deep learning need not be treated as competing paradigms; instead, they can be reconciled through a staged, sim-to-real training strategy. By leveraging large-scale mechanistic simulations as a source of pretraining signals and adapting through a constrained residual pathway, our framework retains the structural rigor of ODEs while gaining the flexibility to capture clinically observed heterogeneity that fixed compartmental models frequently leave unexplained.

Several methodological aspects of Sim2Real-PK warrant emphasis. First, rather than simply appending a neural network to a standard pharmacokinetic model, we reformulate prediction as time-aware latent state evolution. This architecture is fundamentally better suited to the irregular observation intervals and non-stationary dosing schedules characteristic of clinical practice than fixed-step sequence models. Second, our approach treats the mechanistic simulator as a foundational prior. By exposing the network to synthetic trajectories across a vast physiological landscape, the latent dynamics begin from a pharmacologically meaningful manifold, significantly reducing the learning burden on sparse and noisy clinical data. Third, clinical adaptation occurs through residual correction rather than unrestricted end-to-end retraining, which we show to be critical for preserving the pretrained mechanistic backbone and preventing overfitting in low-data regimes.

These findings also clarify the position of Sim2Real-PK relative to other continuous-time machine learning approaches, such as Neural ODEs [31,32]. While Neural ODEs offer an elegant formalism for continuous dynamics, their reliance on inferring high-dimensional vector fields *de novo* can be fragile when observations are limited to a few time points per treatment cycle. In contrast, the combination of mechanistic pretraining and constrained residual transfer in Sim2Real-PK offers a more robust balance between expressiveness and operational stability. This suggests that for sparse, action-conditioned biomedical time series, anchoring deep learning within a mechanistically informed initialization is essential for achieving both predictive accuracy and physiological consistency.

This robust alignment between mechanistic constraints and neural expressivity provides a stable platform for resolving the biological heterogeneity that is often obscured in conventional population-level analyses. A particularly significant finding of this study is that extended clinical covariates contribute meaningfully to predictive accuracy, especially for complex biologics like daratumumab. While traditional pharmacokinetic workflows often condense heterogeneous disease states into a small number of categorical labels, Sim2Real-PK instead learns from an intricate network of correlated clinical measurements—including immunoglobulins, free light chains, and laboratory markers. Our results underscore that these high-dimensional biomarkers carry critical information regarding the patient's internal physiological state, which our framework can effectively leverage to refine patient-specific trajectories.

The utility of this approach is most evident in its ability to resolve latent pharmacokinetic phenotypes. Within the daratumumab cohort, the finetuned model successfully differentiated between IgA-dominant and light-chain-dominant groups—subclasses that were indistinguishable under the pretrained mechanistic baseline alone. By uncovering the distinct clearance and accumulation profiles associated with these markers, the model moves beyond retrospective forecasting toward a tool for biological discovery. While these findings require cautious interpretation, they demonstrate that clinically meaningful heterogeneity can be recovered even when it is not explicitly encoded in the underlying mechanistic structure, provided the model is equipped with a sufficiently flexible adaptation pathway.

Furthermore, the time-aware architecture allows for the detection of longitudinal deviations that may challenge stationary pharmacological assumptions. A notable phenomenon observed in the ibrutinib case study was the progressive decline in drug exposure following repeated administration, a deviation from the steady-state accumulation typically predicted by linear PopPK models (Supplementary Fig. 3). Interestingly, this trajectory mirrors empirical findings from clinical trials, where a reduction in systemic exposure (C_{max} or AUC) has been documented after multiple dosing cycles^{25,26}. We postulate that this paradoxical trend may be attributed to a biologically adaptive feedback loop involving extrahepatic metabolism. Ibrutinib is known to undergo conjugation with glutathione (GSH) or cysteine via covalent binding²⁷. Given that Glutathione S-transferases (GSTs) and related detoxification enzymes are highly inducible in response to electrophilic load or oxidative stress²⁸, repeated administration could plausibly trigger an auto-induction mechanism, thereby accelerating clearance over time. The Sim2Real-PK framework's ability to implicitly capture such non-stationary dynamics from longitudinal data—without explicit prior knowledge of enzyme induction—underscores its potential to identify physiological adaptations that are often overlooked in conventional steady-state modeling.

The architectural capacity of Sim2Real-PK extends beyond retrospective forecasting; the framework functions as a differentiable simulation engine that streamlines the pathway toward individualized clinical decision-making. As demonstrated in the personalized regimen optimization task, the model's time-aware latent dynamics enable an efficient search over complex dosing spaces to identify strategies that satisfy stringent therapeutic constraints. Crucially, this differentiable nature provides a seamless interface for integration with advanced algorithmic solvers, such as reinforcement learning (RL) agents designed for the dynamic control of therapeutic interventions²⁹⁻³¹. By serving as a high-fidelity surrogate for biological responses, Sim2Real-PK could underpin next-generation closed-loop systems where dosing is continuously adjusted in response to evolving patient data.

Despite these promising applications, several limitations warrant consideration. While our evaluation spanned two pharmacologically distinct drugs, broader validation across diverse compounds and disease states is necessary to establish the framework's full generality. Second, this study relied on retrospective clinical trial data; prospective evaluation remains a critical next step

before Sim2Real-PK can be deployed for real-world bedside decision support. Third, the quality of the pretrained manifold remains intrinsically linked to the fidelity of the underlying mechanistic simulator. Finally, the latent representations within the dynamics core are not directly equivalent to identified pharmacokinetic parameters, requiring a shift in interpretability from conventional compartmental estimation to high-dimensional state-space analysis.

Looking ahead, the principle of mechanistically-anchored neural adaptation offers a robust roadmap for the next generation of model-informed precision dosing. Since our pretraining stage is simulator-agnostic, this strategy can be extended from population-level ODEs to more detailed physiologically based pharmacokinetic (PBPK) or quantitative systems pharmacology (QSP) models. We conclude that mechanistic pharmacology and deep learning are not competing paradigms, but complementary partners. When used in a staged and constrained manner, simulation-derived priors provide the necessary data efficiency, while neural adaptation recovers the clinical variability essential for true precision medicine.

Conclusion

In summary, this work establishes Sim2Real-PK as a transformative framework that bridges the disparate domains of mechanistic pharmacometrics and deep learning. By embedding the sequential logic of differential equations into a learnable state-space architecture, a hybrid modeling paradigm is constructed—one that retains the physical interpretability of established kinetic laws while harnessing the structural plasticity of neural networks to navigate complex clinical realities. Ultimately, the modularity and physics-agnostic nature of Sim2Real-PK provide a scalable foundation for the next generation of AI-empowered drug development. The framework's potential to integrate with more complex mechanistic priors offers a scalable pathway toward high-fidelity virtual patient systems and precision medicine.

Methods

1 The Sim2Real-PK Framework: Time-Aware State-Space Modeling

1.1 Problem Formulation: From ODEs to Neural Dynamics

We conceptualize the dynamic process of drug disposition within a patient as a continuous-time system observed at discrete, irregular intervals. Building upon the foundational state-space perspective traditionally described by ODEs, Sim2Real-PK reformulates this process by employing a flexible, data-driven transition function to govern the evolution of the patient's physiological state.

This approach represents a neural evolution of the classical pharmacokinetic paradigm. By internalizing the core mechanistic logic of ODEs into a learnable state-space representation, Sim2Real-PK transforms the rigid mathematical boundaries of traditional equations into a flexible computational graph. This architecture enables the framework to strictly adhere to the mechanistic consistency of PK models while providing the stochastic flexibility needed to reconcile discrepancies with clinical trial longitudinal data. By relaxing the rigid assumptions of traditional ODEs, Sim2Real-PK effectively captures complex, non-linear dynamics driven by extended high-dimensional patient covariates—ensuring the model remains both physiologically grounded and data-responsive.

Formally, a trajectory of patient i is defined as a sequence of tuples $\mathcal{T}_i = \{(x^{(i)}, a_t, y_t, \Delta t_t)\}_{t=1}^T$, where $x^{(i)}$ comprises identified covariates ($x_{ide}^{(i)}$) and Extended Features ($x_{ext}^{(i)}$). a_t represents dynamic dosing actions, Δt_t the irregular time intervals, and y_t the observed drug concentrations.

At the core of the proposed architecture lies the latent physiological state $h_t \in \mathbb{R}^H$, a high-dimensional vector that encapsulates the comprehensive pharmacokinetic status of the patient. We model the evolution of this state as a Time-Aware State-Space Process:

$$h_t = \mathcal{F}_\theta(h_{t-1}, \phi_{cov}(x^{(i)}), \phi_{act}(a_t), \phi_{time}(\Delta t_t)) \quad (1)$$

$$\hat{y}_t = \mathcal{G}_\psi(h_t) \quad (2)$$

where $\mathcal{F}_\theta$ represents the neural dynamics core (latent state transition function), and $\mathcal{G}_\psi$ denotes the observation decoder. The functions ϕ_{cov} , ϕ_{act} , and ϕ_{time} are specialized encoders designed to project heterogeneous inputs into a unified latent space.

1.2 Covariates Encoders and Action Encoder

To bridge the gap between structured pharmacology and high-dimensional clinical data, Sim2Real-PK employs specialized modules to project heterogeneous inputs into a unified latent space.

Covariate Encoder (ϕ_{cov}) features a dual-stream architecture. In pretraining, only the mechanistic stream ϕ_{ide} is active to learn physiological scaling laws, which contains the limited subset of physiological drivers typically included in established models. During finetuning, the extended stream ϕ_{ext} is introduced, ensuring that the dynamic core is initialized with a robust, noise-free understanding of basic pharmacology before adapting to the complex, data-driven associations present in extended clinical features:

$$z_{cov}^{(fine)} = [\phi_{ide}(x_{ide}^{(i)}) \oplus \phi_{ext}(x_{ext}^{(i)})] \quad (3)$$

Action Encoder (ϕ_{act}) projects a composite dosing vector $a_t = [d_t, \delta_{dose,t}, D_{cum,t}]$ (representing dose, time since last dose, and cumulative exposure) into an embedding $z_{act,t}$, capturing accumulation and steady-state dynamics.

1.3 The Time-Aware Dynamics Core

The core engine of Sim2Real-PK is the dynamics function $\mathcal{F}_\theta$, which propagates the system state forward in time. A critical limitation of standard Recurrent Neural Networks (RNNs) in clinical settings is the implicit assumption of fixed time steps, rendering them unsuitable for irregular clinical data. To address this, we introduce a dedicated Time Encoder (ϕ_{time}) and integrate it within a Gated Recurrent Unit (GRU) architecture. The Time Encoder explicitly maps the scalar time interval Δt_t into a high-dimensional vector representation:

$$z_{time,t} = \phi_{time}(\Delta t_t) = \text{Linear}(\text{ReLU}(\text{Linear}(\Delta t_t))) \quad (4)$$

Simultaneously, the dosing action $\mathbf{a}_t$ is encoded into an action embedding $\mathbf{z}_{act,t} = \phi_{act}(\mathbf{a}_t)$. These embeddings are concatenated with the population embedding $\mathbf{z}_{cov}^{(i)}$ and the previous state-derived input to form the comprehensive input vector for the GRU:

$$\text{Input}_t = [\mathbf{z}_{obs,t-1} \oplus \mathbf{z}_{act,t} \oplus \mathbf{z}_{cov} \oplus \mathbf{z}_{time,t}] \quad (5)$$

$$h_t = \text{GRU}(\text{Input}_t, h_{t-1}) \quad (6)$$

By explicitly conditioning the state update on $\mathbf{z}_{time,t}$, the model learns to adjust the magnitude of state decay or accumulation according to the exact time elapsed, enabling accurate prediction of drug disposition over arbitrary intervals.

2 Phase I: Knowledge-Informed Pretraining

To initialize the Sim2Real-PK framework with a rigorous understanding of pharmacokinetic principles, we first expose the model to a massive-scale synthetic dataset generated from mechanistic ODE systems, parameterized by typical values derived from non-linear mixed-effects modeling.

For each virtual subject and random dosing strategy, the ground-truth state trajectories $\mathbf{y}_{GT}$ are integrated using standard ODEs (Fig. 1A). This process generates a diverse training corpus that encodes the fundamental physical laws governing drug disposition—such as mass balance, superposition, and exponential elimination—across a wide range of physiological conditions.

Pretraining is formulated as a supervised task minimizing the discrepancy between predicted $\hat{\mathbf{y}}_t$ and ODE-derived $\mathbf{y}_{GT,t}$ (Supplementary Algorithm 1). To better align the dense, continuous simulations with the sparse, irregular nature of clinical data, we implement an adaptive sampling strategy during data extraction. This algorithm prioritizes high-flux regions (e.g., absorption phases) over stable elimination phases, forcing the time-aware dynamics core to prioritize non-linear kinetic transitions and establish a physically consistent initialization before exposure to noisy clinical trial data (Fig. 1B).

3 Phase II: Sim-to-Real Transfer via Residual Finetuning

Clinical data differs from simulations due to unmapped extended covariates ($\mathbf{x}_{ext}$) and systematic kinetic deviations (Supplementary Algorithm 2). We bridge this gap via a residual correction framework:

$$\hat{\mathbf{y}}_t = \hat{\mathbf{y}}_{base,t} + \Delta \mathbf{y}_{res,t} \quad (7)$$

Here, $\hat{\mathbf{y}}_{base,t}$ is generated by the pretrained core using identified covariates. The correction term $\Delta \mathbf{y}_{res,t}$ is generated by a Residual Decoder ($\mathcal{G}_{res}$), which conditions on the current state, temporal context, and the full covariate embedding to compensate for "Sim-to-Real" discrepancies:

$$\Delta \mathbf{y}_{res,t} = \mathcal{G}_{res} (h_t \oplus \mathbf{z}_{cov}^{(fine)} \oplus \mathbf{z}_{time,t}) \quad (8)$$

To train this composite architecture on sparse clinical data, we employ a strict optimization protocol designed to prevent overfitting, implemented as a ‘freeze-thaw’ strategy. We begin with Physics Freezing, where the parameters of the pretrained dynamics core and action encoder are fixed to maintain the ODE-validated backbone. To ensure the model initially relies solely on this physical prior, we apply Residual Zero-Initialization to the residual decoder, guaranteeing that $\Delta \mathbf{y}_{res,t} = 0$ at the onset of finetuning. Subsequently, we enable Covariate Adaptation by thawing the covariate encoder; specifically, the identified covariates stream (ϕ_{ide}) is finetuned for recalibration, while the extended covariates stream (ϕ_{ext}) is trained from scratch to integrate complex associations from extended high-dimensional clinical features (Fig. 1C).

4 Optimization Strategy: Segment Rollout & Adaptive Loss

To mitigate exposure bias, training sequences are split into a warm-up phase (teacher forcing) and a free-run phase (Autoregression) (Fig. 2A). The standard training process of recurrent sequence typically relies on teacher forcing, where ground-truth inputs are provided at each time step. While stable, this approach suffers from exposure bias³², creating a discrepancy between training and inference that leads to compounding errors in long-term predictions.

A common mitigation is scheduled sampling³³, which linearly decays the teacher forcing ratio over rigid epoch schedules. However, we argue that fixed schedules are suboptimal for complex pharmacokinetic dynamics, as they may force the model into autonomous generation before it has learned stable transitions.

Instead, we introduce a two-stage adaptive strategy. Unlike the rigid decay in standard scheduled sampling, our strategy employs a two-stage adaptive curriculum to manage the transition: Phase I linearly increases the autoregressive probability ($P_{autoreg}$) from 0 to 0.8 to encourage dependency learning; Phase II increases $P_{autoreg}$ to 1.0 while activating adaptive weights (w_{adapt}) to penalize long-term physiological inconsistencies.

To guarantee that the predicted trajectories are not only numerically close to the data but also pharmacologically plausible, we minimize a compound loss function that explicitly penalizes violations of key PK metrics:

$$\mathcal{L}_{total} = \mathcal{L}_{MSE} + w_{adapt} \cdot (\lambda_1 \mathcal{L}_{rollout} + \lambda_2 \mathcal{L}_{AUC} + \lambda_3 \mathcal{L}_{peak} + \lambda_4 \mathcal{L}_{trough}) \quad (9)$$

This includes standard fidelity ($\mathcal{L}_{MSE}$), trajectory stability ($\mathcal{L}_{rollout}$), systemic exposure accuracy ($\mathcal{L}_{AUC}$), and penalties for deviations in peak ($\mathcal{L}_{peak}$) and trough ($\mathcal{L}_{trough}$) concentrations.

5 Experimental Design and Validation Protocols

To comprehensively evaluate the Sim2Real-PK framework, a multi-stage validation protocol was established, spanning mechanistic verification, clinical data benchmarking, and downstream clinical application. We utilized individual participant data obtained from the YODA Project (Yale Open Data Access). The study focuses on two distinct therapeutic agents representing the spectrum of pharmacokinetic complexity: ibrutinib (NCT02195869), a small molecule inhibitor administered orally with rapid absorption characteristics, and daratumumab (NCT01998971), a monoclonal antibody administered intravenously exhibiting complex target-mediated drug disposition (TMDD).

5.1 Pretraining Validation on Synthetic Cohorts

First, to ensure the physical consistency of the initialization, synthetic cohorts were constructed based on established PopPK model derived from literature^{34,35} (Supplementary Method 3.1). Comparative experiments were conducted to assess the stability of the proposed two-stage adaptive curriculum against scheduled sampling strategies, monitoring the convergence of rollout loss across ibrutinib and daratumumab (Supplementary Method 3.2). Furthermore, the model's sensitivity to pharmacological laws was verified by simulating single-dose trajectories under varying dosage levels and identified covariates (e.g., body weight, albumin), confirming the internalization of dose-exposure linearity and covariate-dependent clearance scaling (Supplementary Method 3.3).

5.2 Finetuning Validation on Clinical Cohorts

For clinical adaptation, the pretrained models were finetuned on clinical trial individual participant data (IPD) from the YODA project. A rigorous 5-fold cross-validation scheme was employed, where patients were stratified by ID to prevent data leakage. Goodness-of-Fit (GOF) analysis was utilized to visualize the progressive adaptation on validation dataset. The performance was benchmarked against standard PopPK models using strictly disjoint test sets, evaluated via RMSE, F-scores (F20/F50), and Conditional Weighted Residuals (CWRES) (Supplementary Method 3.4). Besides the overall concentration or in steady-state, the compared key exposure metrics were extracted, including peak concentration (C_{max}), trough concentration (C_{min}), and area under the curve (AUC) across both initial or last dosing and steady-state phases.

5.3 Ablation experiments of model architecture

To quantify the specific contribution of the proposed architecture and the high-dimensional clinical features, a comprehensive ablation study was performed. This involved the systematic removal of model components (e.g., residual network) and specific feature groups (e.g., Immunoglobulins, lab tests) to assess their impact on predictive accuracy (Supplementary Method 3.5). Furthermore, to validate the necessity of the 'Freeze-Thaw' optimization strategy, we evaluated alternative parameter adaptation protocols. Specifically, we benchmarked the proposed method against scenarios where the pretrained dynamics core, the observation decoder, or the entire network were fully thawed, thereby assessing the stability of mechanistic priors under unconstrained finetuning.

5.4 Downstream Clinical Applications

Finally, to demonstrate the translational utility of the framework, simulations were performed under two representative application settings, encompassing both dose-level and patient-level scenarios.

Personalized dosing frequencies were optimized by navigating a discrete strategy space $(n_{QW}, n_{Q2W}, n_{Q3W})$ under therapeutic window constraints using a representative subject (Supplementary Method 3.6). Additionally, a virtual twin simulation was conducted to explore cryptic pharmacokinetic subtypes. By generating virtual patients via a multi-covariate sampling strategy to preserve the correlation of features, the impact of extended covariates (e.g., IgA vs. Light Chain subtypes) was isolated while controlling for identified physiological parameters (Supplementary Method 3.7).

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Figure

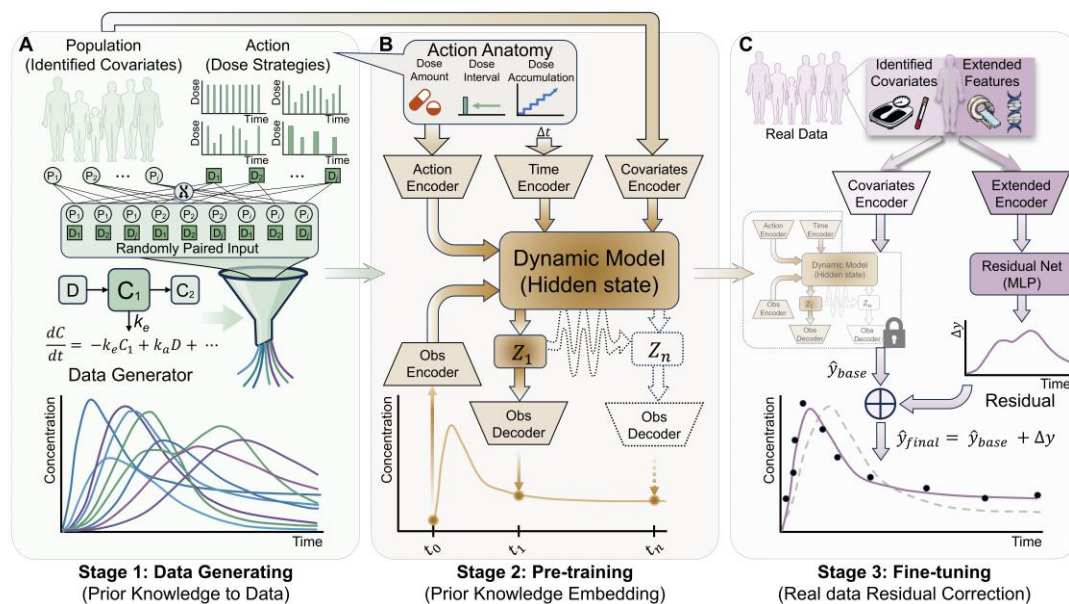


Figure 1. The schematic framework of the Sim2Real framework for PK prediction. (A) Data Generating: Leveraging prior pharmacological knowledge to simulate large-scale synthetic datasets, which bridges population-level identified covariates with diverse dosing strategies to generate extensive concentration-time profiles. **(B) Pretraining:** Embedding prior knowledge into the neural network architecture. An encoder-decoder framework, featuring a dynamic model (hidden state), is pretrained on synthetic data to capture the underlying temporal dynamics of drug disposition. **(C) Finetuning:** Real data residual correction. The pretrained model provides a baseline prediction ($\hat{y}_{base}$), while a residual network extracts features from extended data to predict the discrepancy (Δy). The final prediction ($\hat{y}_{final}$) is the ensemble of the knowledge-based baseline and the data-driven residual, achieving high-fidelity alignment with real clinical observations.

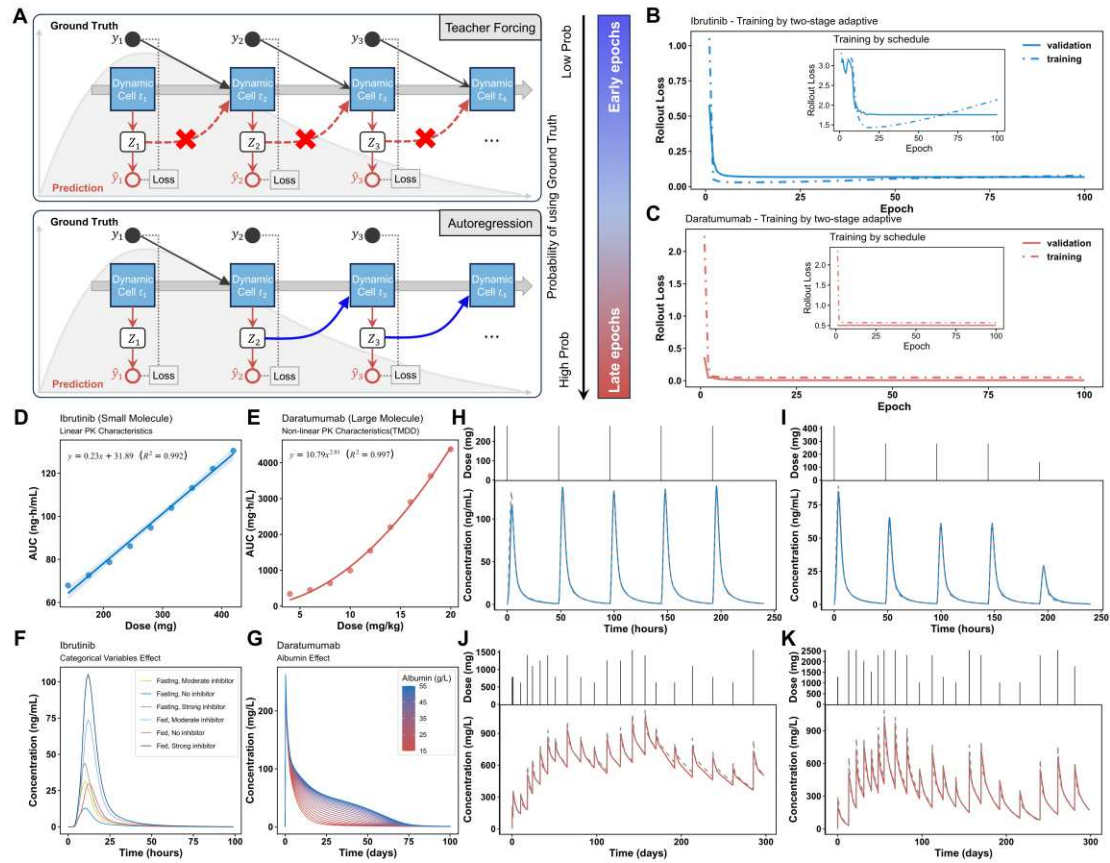


Figure 2. Validation of the physics-informed pretraining and pharmacological consistency. (A) **Schematic of the two-stage adaptive training strategy:** The model transitions from Teacher Forcing in early epochs to Autoregression in later epochs to mitigate long-term error accumulation. Training stability comparison. **Training stability comparison:** Rollout loss curves for ibrutinib (B) and daratumumab (C) comparing the proposed two-stage adaptive method (solid lines) against a standard schedule-based approach (dashed lines in insets). **Dose-proportionality analysis:** Correlation between administered dose and predicted Area Under the Curve (AUC) from pretrained model for small-molecule ibrutinib (D), showing linear PK characteristics, and monoclonal antibody daratumumab (E), capturing non-linear TMDD characteristics. **Covariate sensitivity and stratification:** (F) Predicted concentration-time profiles for ibrutinib stratified by categorical factors (food effects and CYP3A inhibitor status). (G) Impact of continuous serum albumin levels on daratumumab elimination dynamics. **Individual-level trajectory synchronization:** Representative examples of predicted versus simulated concentration profiles under complex, irregular dosing regimens for ibrutinib (H-I) and daratumumab (J-K).

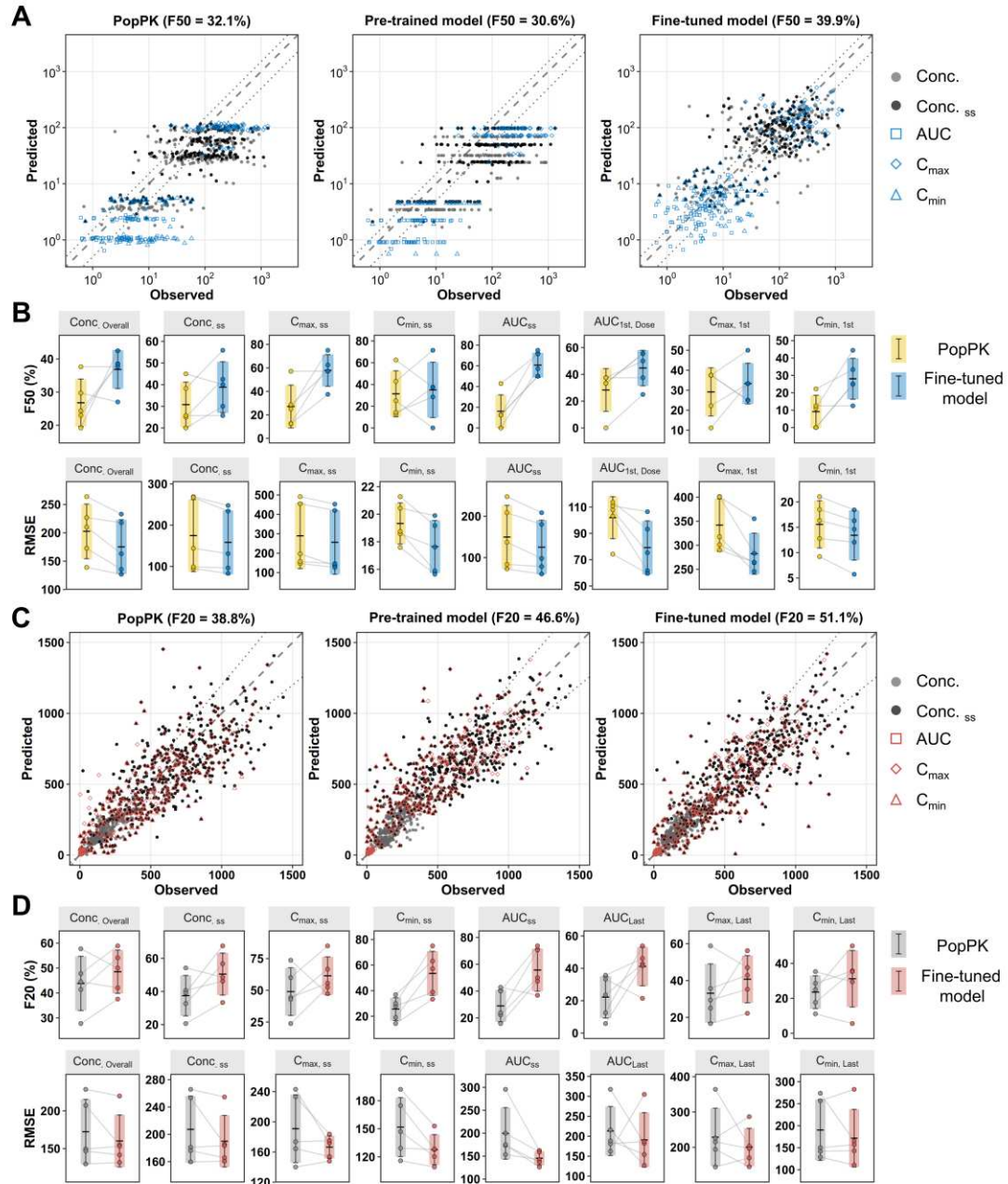


Figure 3. Comparative evaluation of predictive performance on clinical datasets via 5-fold cross-validation. (A) Goodness-of-Fit (GOF) analysis for Ibrutinib: Scatter plots displaying predicted versus observed concentrations and pharmacokinetic (PK) parameters (AUC , C_{max} , C_{min}) across three model stages: the Population Pharmacokinetic (PopPK) baseline, the pretrained model, and the finetuned model. The dashed lines represent the line of identity and the twofold error (F50) boundaries. **(B) Quantitative benchmarking for Ibrutinib:** Pairwise comparisons of F50 (%) and Root Mean Square Error (RMSE) between the PopPK baseline and the finetuned model. **(C) Goodness-of-Fit (GOF) analysis for Daratumumab:** Observed versus predicted plots for the PopPK, pretrained, and finetuned models. The F20 metric (percentage of predictions within a 20% error margin) is indicated for each stage, with red markers representing specific PK parameters (AUC , C_{max} , C_{min}). **(D) Quantitative benchmarking for Daratumumab:** Pairwise comparison of F20 (%) and RMSE across validation folds. Evaluation includes overall and steady-state concentrations, trough concentrations.

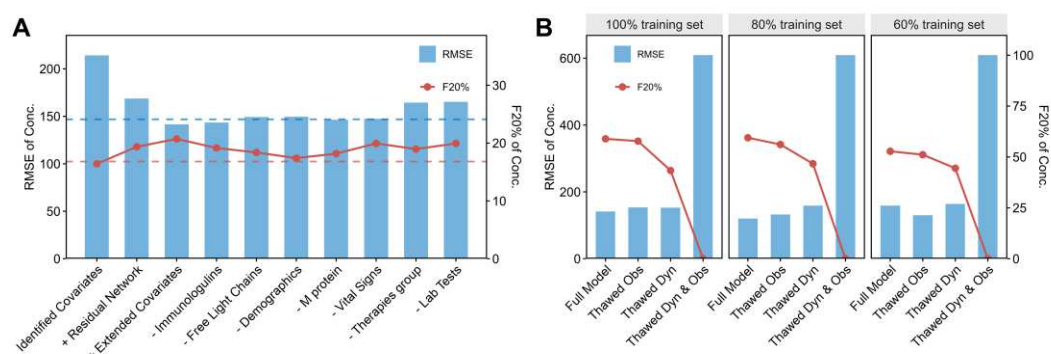


Figure 4. Ablation study on feature contributions and evaluation of finetuning strategies. (A) Impact of model components and covariate groups: The step-wise analysis quantifies the performance gain (decrease in RMSE, blue bars; increase in F20%, red line) when integrating the residual network and extended covariates compared to the baseline using only identified covariates. The horizontal dashed lines represent the benchmark performance of the conventional PopPK model, serving as the reference standard. The subsequent columns display a "leave-one-group-out" ablation analysis, assessing the sensitivity of the model to specific clinical feature categories. **(B) Robustness of freezing strategies under varying data availability:** Performance comparison of different parameter-tuning strategies across 100%, 80%, and 60% training set sizes. The "Full Model" (proposed strategy) is compared against scenarios where the Dynamic module ("Thawed Dyn") and/or Observation module ("Thawed Obs") are unfrozen. The rapid performance degradation in the "Thawed Dyn & Obs" group.

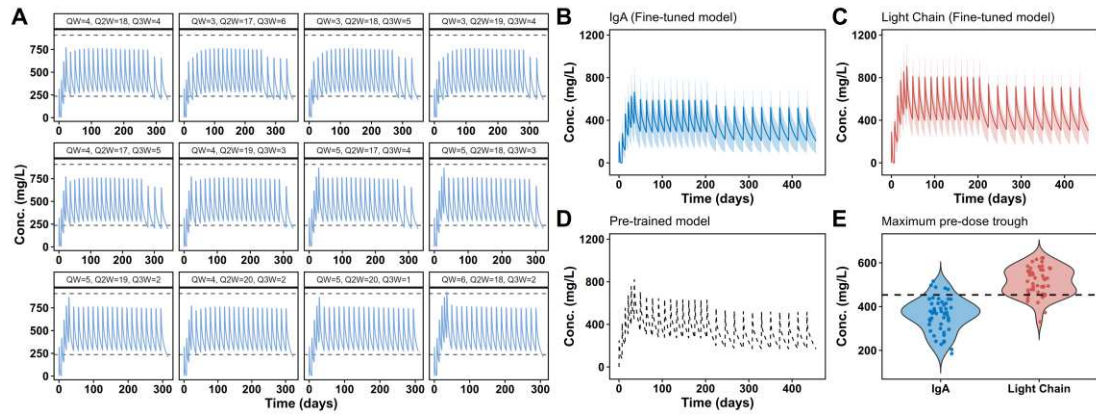


Figure 5. Downstream clinical applications: Personalized regimen optimization and disease subtype discovery. (A) Navigation of the dosing state space for regimen optimization: Representative concentration-time profiles generated during the iterative neighborhood search algorithm to identify optimal tapering schedules. The annotations (e.g., QW=4, Q2W=18, Q3W=4) indicate the duration (in weeks) of weekly, bi-weekly, and tri-weekly administration phases. The horizontal dashed lines represent the safety and efficacy constraints ($C_{min} > 236$ mg/L and $C_{max} < 907$ mg/L). (B-E) Virtual Twin simulation for cryptic subtype differentiation: Comparative simulation of pharmacokinetic profiles for IgA-dominant (B, blue) and Light Chain-dominant (C, red) cohorts using the finetuned model, contrasted with the indiscriminate prediction generated by the pretrained model (D, dashed lines). Violin plots (E) displaying the distribution of maximum pre-dose trough concentrations for the simulated IgA and Light Chain cohorts.

Author contributions

Lu-Yao Han, Xiang Chen, and Guo Yu wrote the manuscript; Lu-Yao Han, Guo Yu, Yang Yu and Haiping Hao designed the research; Xiang Chen, Meng-Han Wu, Jia-Qian Li, Jin-Yi Wang, Man-Qing Jia, Zhi-Long Zhang, Tian-Shuo Liu, Huize Wang, De-Xuan Kong and Wen-Bo Pang performed the research; Lu-Yao Han, Guo Yu, and Zi-Qi Wang applied and analyzed the data.

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Data Availability

The synthetic datasets generated for the pretraining phase and model validation in this study are publicly available in the GitHub repository at <https://github.com/hly3220090967/Sim2Real-PK>. The clinical trial datasets analyzed during the finetuning and downstream application phases were obtained from the Yale University Open Data Access (YODA) Project (Project #2023-5502), which has a data-sharing agreement with JANSSEN RESEARCH & DEVELOPMENT, L.L.C. Due to patient privacy, legal constraints, and the strict terms of the data-sharing agreement, these clinical datasets cannot be made publicly available by the authors. Qualified researchers can apply for access to these clinical data directly through the YODA Project website (<https://yoda.yale.edu/>) by submitting a formal research proposal.

Code Availability

The custom source code for the Sim2Real-PK framework is open-source and publicly available on GitHub at <https://github.com/hly3220090967/Sim2Real-PK>.

Conflicts of interest

All authors declare that no potential conflicts of interest.

Supplementary Files

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