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Review Article

Patient-Specific Digital Twins in Drug Development: A Multi-Scale Modelling Approach Integrating Genomics, Pharmacokinetics, and Real-World Evidence

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ABSTRACT

The advent of precision medicine has exposed profound limitations in the one-size-fits-all paradigm that has historically governed drug development. Conventional pharmacological pipelines rely on population-averaged pharmacokinetic and pharmacodynamic (PK/PD) models that systematically obscure the biological heterogeneity driving differential drug responses across patients. Patient-specific digital twins (PSDTs) represent a transformative computational paradigm that mirrors an individual's physiology, genomics, disease state, and environmental exposures within a dynamic, continuously updated virtual model. This paper advances the conceptual and technical architecture of PSDTs by proposing a multi-scale integration framework spanning the sub-cellular genomic layer through organ-level physiology and extending into real-world evidence (RWE) streams. We developed a hierarchical modelling architecture comprising: (i) a genomic-pharmacogenomic layer encoding CYP450 polymorphisms, transporter variants, and pharmacodynamic receptor genotypes; (ii) a whole-body physiologically based pharmacokinetic (PBPK) compartmental model calibrated with individual patient covariates; (iii) a systems pharmacology disease module integrating target engagement, downstream signalling cascades, and biomarker trajectories; and (iv) a real-world evidence assimilation engine ingesting electronic health record (EHR) data,

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wearable biosensor streams, and population registries. Uncertainty quantification was achieved through Bayesian hierarchical inference with Markov chain Monte Carlo (MCMC) sampling, while federated learning protocols were employed to enable privacy-preserving multi-site model refinement. Simulation studies using synthetic patient cohorts derived from published pharmacogenomic databases demonstrated that multi-scale PSDTs reduced predicted AUC variability by 38-52% compared with population-average PBPK models and improved time-to-therapeutic-response predictions with a mean absolute error reduction of 41% in oncology and 29% in cardiology virtual patients. RWE integration through federated learning reduced model calibration time by 67% without compromising individual data privacy. Patient-specific digital twins, when constructed through rigorous multi-scale integration of genomic, PBPK, systems pharmacology, and real-world evidence layers, offer a scientifically grounded pathway toward virtual clinical trials, personalised dosing, and accelerated drug approval. Regulatory co-development, standardised ontologies, and federated infrastructure are prerequisites for clinical translation

INTRODUCTION

Drug development is among the most capital-intensive and failure-prone undertakings in modern science. The average fully-capitalised cost of bringing a new molecular entity (NME) to market now exceeds USD 2.6 billion, and roughly 90% of compounds entering Phase I trials never achieve regulatory approval [1]. The dominant reasons for late-stage attrition remain inadequate efficacy and unforeseen toxicity—failures that are not random but rather predictable consequences of using population-average preclinical and clinical data to make decisions about profoundly heterogeneous individuals [2]. Inter-individual variability in drug absorption, distribution, metabolism, and excretion (ADME) arises from genetic polymorphisms in drug-metabolising enzymes and transporters, co-morbidity burden, microbiome composition, age-related physiological shifts, and co-medication interactions, none of which are adequately captured by standard clinical trial designs [3].

The concept of the digital twin—a dynamic virtual replica of a physical system that is continuously synchronised with real-world data—originated in aerospace engineering and industrial process monitoring [4]. Its migration to biomedicine has accelerated since Lim and colleagues first articulated a mathematical framework for patient-specific physiological models in 2012 [5]. By 2020, the United States Food and Drug Administration (FDA) had formally acknowledged digital twins and model-informed drug development (MIDD) as tools capable of augmenting or, in specific contexts, partially replacing conventional clinical evidence [6]. The European Medicines Agency (EMA)'s 2021 framework on in silico trials further recognised multi-scale mechanistic models as an emerging evidentiary pillar [7].

What distinguishes a patient-specific digital twin (PSDT) from a conventional computational model is its individuation: the PSDT is calibrated against a particular patient's genomic profile, longitudinal biomarker trajectories, imaging data, and real-world activity patterns, and it is iteratively updated as new information accrues [8]. This stands in contrast to virtual average patients or simulation cohorts, which encode population-level statistics but cannot predict the response of a specific individual with adequate fidelity for clinical decision-making [9]. The PSDT is not merely a forward simulation tool; it supports inverse problems—inferring patient-specific parameters from sparse clinical observations—and scenario analysis, enabling clinicians and developers to test hypothetical dosing regimens before administering them to a real patient [10].

Multi-scale modelling is the scientific backbone of PSDTs. Biological complexity spans many orders of magnitude in space and time: genetic variants alter protein structure and function at the

molecular scale; altered enzymatic kinetics reshape systemic drug exposure at the whole-body scale; systemic drug exposure drives receptor occupancy and downstream signalling cascades at the tissue and cellular scale; and clinical outcomes emerge from the integration of all these layers over days, months, and years [11]. No single modelling formalism can simultaneously represent all these scales with the necessary resolution. A practical PSDT therefore requires a hierarchical, modular architecture in which sub-models representing different scales are coupled through rigorously defined interfaces [12].

Real-world evidence (RWE) is the third pillar alongside genomics and pharmacokinetics. Clinical trials, by design, enrol restricted populations under tightly controlled conditions that rarely reflect the diversity of patients who will ultimately receive a drug [13]. Electronic health records, claims databases, disease registries, patient-reported outcome platforms, and wearable biosensor streams collectively contain orders of magnitude more information about drug use and outcome in heterogeneous real-world populations than any single trial can generate [14]. Integrating RWE into digital twin models offers a mechanism for continuously refining model parameters, detecting emergent safety signals, and validating predictions prospectively in the very population the drug will serve [15].

The present paper makes four principal contributions. First, we articulate a conceptual and mathematical architecture for multi-scale PSDTs that spans the genomic, PBPK, systems pharmacology, and RWE layers with explicit interface definitions. Second, we develop Bayesian uncertainty quantification methods suited to the sparse, noisy, and partially observed data typical of clinical settings. Third, we describe a federated learning framework that enables multi-site model refinement without exposing identifiable patient data. Fourth, we discuss the regulatory, ethical, and infrastructural prerequisites for clinical translation, situating PSDTs within current FDA and EMA guidance frameworks. The remainder of the paper is organised as follows: Section 2 reviews the relevant theoretical background; Sections 3-6 develop the four model layers; Section 7 addresses uncertainty and validation; Section 8 presents simulation results; Section 9 discusses regulatory and ethical considerations; and Section 10 concludes with a translational roadmap.

THEORETICAL BACKGROUND

Digital Twins: Origins and Biomedical Adaptation

The digital twin concept was formalised by Grieves and Vickers in the context of NASA's product lifecycle management in 2003, describing a virtual counterpart to a physical asset that shares data bidirectionally and exists in parallel throughout the asset's lifecycle [4]. Three elements define a digital twin in all domains: the physical entity, the virtual model, and the data connection that synchronises them. In biomedicine, these translate to the patient, the computational model, and the clinical data pipeline respectively [16].

Early biomedical adaptations focused on organ-level models—cardiac digital twins derived from patient-specific MRI geometry and electrophysiological recordings were among the first to demonstrate clinical utility, enabling pre-procedural simulation of ablation therapy in atrial fibrillation [17]. More recently, oncology has seen digital twin applications for optimising chemotherapy scheduling in colorectal cancer, where tumour growth models personalised to imaging and circulating tumour DNA (ctDNA) trajectories were used to forecast response prior to

treatment initiation [18]. Diabetes management has produced perhaps the most commercially mature example: the UVA/Padova type 1 diabetes metabolic simulator, which received FDA clearance as a replacement for preclinical animal testing of insulin dosing algorithms [19].

Critically, these domain-specific twins have remained largely siloed. Cardiac twins do not communicate with metabolic twins; oncology growth models rarely incorporate pharmacokinetic layers. The vision advanced in this paper is of an integrated, whole-body PSDT that couples multiple organ and process models within a coherent computational framework, capable of addressing the multi-system nature of drug effects [20].

Multi-Scale Modelling Theory

Multi-scale modelling addresses phenomena that operate on disparate spatial and temporal scales by constructing coupled models at each scale with formally defined upscaling and downscaling operators [21]. In pharmacology, the relevant scales span: (i) molecular—protein structure, binding affinity, enzymatic catalysis; (ii) cellular—transporter flux, intracellular signalling, gene expression regulation; (iii) tissue and organ—perfusion, absorption, distribution; (iv) whole-body—systemic PK/PD; and (v) population—inter-individual variability and RWE [11].

Three broad strategies exist for coupling models across scales: sequential (passing outputs of fine-scale models as parameters to coarse-scale models, a form of metamodelling), concurrent (running models at multiple scales simultaneously with iterative exchange), and adaptive (dynamically selecting the appropriate scale based on the local state of the system) [22]. For PSDTs in drug development, a hierarchical sequential strategy is most computationally tractable, with the molecular-level outputs (e.g., intrinsic clearance estimates from structure-activity relationships or in vitro data) being fed into PBPK compartmental models, whose outputs drive disease-progression models [23].

The mathematical substrate for most scales involves either ordinary differential equations (ODEs) for well-mixed compartments, partial differential equations (PDEs) for spatially distributed systems, or agent-based models (ABMs) for discrete cellular populations [24]. Whole-body PBPK models typically consist of systems of coupled ODEs with state variables representing drug mass in each physiological compartment, while tumour growth or immune interaction models may require hybrid ODE/ABM formulations [25].

Physiologically Based Pharmacokinetics: Theoretical Foundations

Physiologically based pharmacokinetic (PBPK) models describe drug disposition mechanistically using anatomically realistic compartments corresponding to organs and tissues, connected by blood flow [26]. Unlike classical compartmental models, which are purely descriptive, PBPK models encode physiological parameters—tissue volumes, blood flow rates, organ permeability-surface area products, and tissue-plasma partition coefficients—that can be estimated a priori from in vitro experiments and allometric scaling, permitting extrapolation across species, populations, and formulations [27].

The governing equation for drug mass (A_i) in tissue compartment i is:

$$dA\mathrm{i}/\mathrm{dt} = \mathrm{Qi} \times (\mathrm{Ca} - \mathrm{Cv,i}) - \mathrm{CLint,i} \times \mathrm{Cu,i}$$

where Q_i is organ blood flow, C_a is arterial drug concentration, C_v,i is venous concentration leaving the organ, CL_int,i is the intrinsic metabolic or transport clearance in that organ, and C_u,i is the unbound drug concentration in tissue [28]. Tissue-plasma partition coefficients (K_p) are estimated from physicochemical drug properties—lipophilicity, ionisation, protein binding—using validated in silico methods [29].

For patient-specific PBPK, the model parameters must be individualised. Organ volumes and blood flows are scaled from standard physiological references using patient-specific covariates including age, weight, height, sex, and measures of hepatic and renal function [30]. Genetic variants in drug-metabolising enzymes modify intrinsic clearance terms, while co-medication data informs competitive inhibition or induction kinetics [31]. This individualisation transforms a population PBPK model into the pharmacokinetic layer of a PSDT.

Pharmacogenomics and Precision Medicine

Pharmacogenomics (PGx) is the study of how genetic variation influences drug response. Two categories of genetic determinants are pharmacokinetically and pharmacodynamically relevant: variants affecting drug-metabolising enzymes and transporters (PKrelated), and variants affecting drug targets, disease pathways, or immune responses (PD-related) [32]. The cytochrome P450 (CYP) enzyme family—particularly CYP2D6, CYP2C19, CYP2C9, and CYP3A4/5—metabolises the majority of clinically used drugs, and polymorphisms in these genes produce discrete phenotypic categories: poor metabolisers (PM), intermediate metabolisers (IM), normal metabolisers (NM), and ultra-rapid metabolisers (UM) [33].

The population frequency of metaboliser phenotypes varies dramatically across ancestries. The PM phenotype for CYP2D6 occurs in approximately 6-10% of Europeans but only 1-2% of East Asians, while the UM phenotype arising from gene duplication shows prevalence of up to 29% in Ethiopians and 3-5% in Europeans [34]. These differences generate pharmacoethnic disparities in drug safety and efficacy that conventional clinical trials, dominated by European participants, systematically underestimate [35]. A PSDT that encodes individual CYP genotype provides a mechanism for correcting these disparities prospectively.

Beyond monogenic CYP polymorphisms, polygenic scores (PGS) aggregating the modest effects of many common variants are emerging as predictors of complex drug responses including antidepressant efficacy, statin-induced myopathy risk, and warfarin dosing requirements [36]. The integration of PGS into PSDT models requires careful handling of linkage disequilibrium and population stratification, and remains an area of active methodological development [37].

Real-World Evidence in Drug Development

Real-world evidence encompasses data derived from routine clinical practice outside randomised controlled trials, including electronic health records (EHRs), administrative claims, disease registries, mobile health applications, wearable device outputs, and patient-reported outcomes [38]. The 21st Century Cures Act (2016) in the United States and parallel EMA initiatives have mandated expanded use of RWE in regulatory submissions, recognising that it complements the internal validity of RCTs with ecological validity and generalisability [13].

Methodologically, leveraging RWE for causal inference requires sophisticated techniques to

address confounding by indication, time-varying treatment and covariate relationships, selection bias from incomplete follow-up, and informative censoring [39]. Target trial emulation—wherein an RWE analysis is designed to mimic a specific hypothetical randomised trial—has emerged as a principled framework for drawing causal conclusions from observational data [40]. When embedded within a PSDT framework, RWE serves a different but complementary function: rather than replacing causal inference, it provides high-dimensional covariate information for model personalisation and longitudinal outcome data for prospective model validation [41].

THE GENOMIC-PHARMACOGENOMIC LAYER

Genotype-to-Phenotype Translation

The foundational challenge in constructing the genomic layer of a PSDT is translating a patient's raw genomic data—typically from whole-genome sequencing (WGS), whole-exome sequencing (WES), or clinically targeted genotyping arrays—into quantitative functional parameters that can be incorporated into the PK/PD model [42]. This translation proceeds through two stages: variant calling and annotation, followed by functional phenotype assignment.

Variant calling from WGS data involves alignment of short reads to a reference genome, identification of single nucleotide polymorphisms (SNPs) and insertions/deletions (indels), phasing to reconstruct haplotypes, and copy number variation (CNV) detection to identify gene duplications and deletions [43]. For pharmacogenes, phasing is particularly critical because the functional consequence of two heterozygous variants depends on whether they occur on the same haplotype (cis configuration, likely compound heterozygote) or on different haplotypes (trans configuration, carrier state) [44].

The PharmVar consortium has standardised star (*) allele nomenclature for major pharmacogenes, providing a curated repository of variant-to-allele assignments [45]. Clinical Pharmacogenomics Implementation Consortium (CPIC) guidelines provide evidence-graded genotype-to-phenotype translations and prescribing recommendations for over 80 drug-gene pairs [46]. In the PSDT framework, we implement a computational phenotyper that accepts phased haplotype calls, queries the PharmVar and CPIC databases via structured APIs, and returns quantitative activity scores for each relevant enzyme and transporter [47].

Parameterising Enzyme Activity

The functional output of the genomic layer for metabolic enzymes is the activity score (AS), a quantitative metric that aggregates the functional consequences of two allelic variants, with NM homozygotes assigned AS = 2.0, each fully non-functional allele contributing 0, and intermediate function alleles contributing 0.5 [48]. Activity scores are then mapped to metaboliser phenotype categories (PM: AS = 0, IM: $0 < AS \leq 1.0$, NM: AS = 1.5-2.0, UM: $AS > 2.0$) and further translated into quantitative clearance scaling factors for the PBPK model.

For CYP2D6, the relationship between activity score and hepatic intrinsic clearance has been empirically characterised from clinical PK studies in genotyped subjects [49]. We model this relationship using a saturating Michaelis-Menten-type function to avoid unbounded clearance predictions in ultra-rapid metabolisers:

$$CL_{int} = CL_{int,ref} \times (AS \times K_{max}) / (AS + K_{50})$$

where CL_int,ref is the reference clearance in a diplotype-normal individual, K_max is the maximum fold-increase in clearance, and K_50 is the activity score at half-maximum clearance [50]. Parameter values are derived from meta-analysis of published clinical PK studies stratified by metaboliser phenotype. For transporters including SLCO1B1, ABCB1, and ABCG2, analogous scaling factors are applied to uptake and efflux clearance terms in hepatic and intestinal compartments [51].

Polygenic Pharmacodynamic Layer

Beyond monogenic enzyme polymorphisms, complex polygenic architectures govern pharmacodynamic variability in many therapeutic areas. For psychiatric pharmacology, genome-wide association studies (GWAS) have identified hundreds of common variants associated with antidepressant response, none individually predictive but collectively informative through polygenic scoring [52]. For cardiovascular pharmacology, polygenic scores for LDL-C trajectories under statin therapy, residual cardiovascular risk despite therapy, and drug-induced QT prolongation have demonstrated clinical utility in retrospective analyses [53].

In the PSDT genomic layer, polygenic scores are computed from imputed genotype data using weights derived from the largest available GWAS summary statistics for relevant outcomes. These scores are incorporated as modifiers of pharmacodynamic parameters—receptor sensitivity terms, disease progression rates, or adverse effect susceptibility parameters—within the systems pharmacology module [54]. Critically, the PSDT framework enables prospective updating of PGS-derived parameters as new GWAS data become available, ensuring that the genomic layer reflects the advancing state of pharmacogenomic knowledge [55].

THE PBPK LAYER: WHOLE-BODY PHARMACOKINETICS

Structural Architecture

The PBPK layer is the quantitative scaffold on which the drug's time-concentration profile in all relevant tissues is predicted. We implement a 15-compartment whole-body PBPK model encompassing: lung, adipose, bone, brain, gut, heart, kidney, liver, muscle, pancreas, skin, spleen, thyroid, venous blood pool, and arterial blood pool [56]. Each compartment is parameterised by tissue volume (V_i), tissue-specific blood flow (Q_i), and partition coefficient (K_p,i). Elimination occurs primarily in liver (cytochrome P450-mediated oxidation, UGT-mediated glucuronidation, and biliary excretion) and kidney (glomerular filtration and active tubular secretion/reabsorption) [57].

Patient-specific parameterisation proceeds through a three-step pipeline. First, a reference physiological database is instantiated using values from the International Commission on Radiological Protection (ICRP) reference human, stratified by age and sex [58]. Second, covariate scaling equations adjust organ volumes and blood flows to the individual patient using validated allometric and morphometric relationships [59]. Third, genomic scaling factors from the pharmacogenomic layer modify metabolic and transport clearance terms [60].

Individual Patient Covariate Scaling

Liver volume (V_liver) is estimated from total body weight (BW) and height (HT) using the formula derived by Vauthey et al. from CT volumetric studies in 1827 patients:

$$V_{liver} = 0.0158 \times BW + 0.2099 \times BSA - 0.0029 \times Age + intercept$$

where BSA is body surface area in m² [61]. Hepatic blood flow is scaled proportionally to cardiac output, which is itself estimated from validated regression equations incorporating sex, age, and body composition [62]. Renal function—critically important for renally-excreted drugs—is parameterised using the patient's estimated glomerular filtration rate (eGFR) computed from serum creatinine or cystatin C using the CKD-EPI equation, with active tubular secretion parameters scaled to GFR [63].

For paediatric patients, additional maturational scaling functions are applied to both hepatic enzyme activity (using published ontogeny functions for CYP3A4, CYP2D6, and UGT enzymes) and renal clearance (using GFR ontogeny from birth through adolescence) [64]. Geriatric patients require scaling for reduced hepatic blood flow, altered body composition (increased adiposity, reduced lean mass), diminished renal reserve, and polypharmacy-mediated inhibition, all of which are incorporated as age-dependent covariate modifiers [65]. **Table 1. Pharmacogenomic Genotype-to-Phenotype Translation and PBPK Parameter Scaling Factors for Key Drug-Metabolising Enzymes and Transporters**

Selected clinically actionable pharmacogenes integrated within the PSDT genomic layer. Activity scores follow CPIC standardised nomenclature [48]. CL_int = intrinsic clearance; AUC = area under the concentration–time curve; NM = normal metaboliser; IM = intermediate metaboliser; PM = poor metaboliser; UM = ultra-rapid metaboliser; WGS = whole-genome sequencing.

Gene / Allele	Diplotype Example	Activity Score	Phenotype	CL_int Scaling Factor	Expected AUC Change vs NM	Clinical Implication
CYP2D6 (Metabolises: codeine, tamoxifen, atomoxetine, metoprolol, antidepressants)						
CYP2D6	*1/*1	2.0	Normal Metaboliser (NM)	1.00 (reference)	—	Standard dosing applicable
	*4/*4	0.0	Poor Metaboliser (PM)	0.05–0.15	↑ 400–800%	Dose reduction; consider alternative
	*4/*41	0.5	Intermediate Metaboliser (IM)	0.40–0.70	↑ 100–150%	Reduced dose; monitor levels
	*1×N/*1	>2.0	Ultra-Rapid Metaboliser (UM)	2.50–5.00	↓ 50–70%	Therapeutic failure risk; increase dose or switch
CYP2C19 (Metabolises: clopidogrel, PPIs, voriconazole, escitalopram, diazepam)						
CYP2C19	*1/*1	2.0	Normal Metaboliser (NM)	1.00 (reference)	—	Standard dosing applicable

	*2/*2	0.0	Poor Metaboliser (PM)	0.08–0.20	↑ 300–600%	Clopidogrel ineffective; switch to prasugrel/ticagrelor
	*17/*17	>2.0	Ultra-Rapid Metaboliser (UM)	2.00–3.50	↓ 40–65%	PPI failure; increased PUD risk
CYP2C9 (Metabolises: warfarin, phenytoin, NSAIDs, glipizide, losartan)						
CYP2C9	*1/*1	2.0	Normal Metaboliser (NM)	1.00 (reference)	—	Standard warfarin dosing
	*2/*3	0.5	Intermediate Metaboliser (IM)	0.25–0.45	↑ 150–200%	Lower warfarin initiation dose; frequent INR monitoring
	*3/*3	0.0	Poor Metaboliser (PM)	0.05–0.10	↑ 500–1000%	Very high bleeding risk; strongly consider alternative
SLCO1B1 (Transporter: statins — simvastatin, atorvastatin, rosuvastatin)						
SLCO1B1	*1a/*1a	—	Normal Function	1.00 (reference)	—	Standard statin dosing
	*5/*5	—	Poor Function	0.20–0.40 (uptake↓)	↑ 220–340%	High myopathy risk; use rosuvastatin or pravastatin

First-Pass and Intestinal Absorption

Oral drug absorption represents one of the most patient-variable steps in pharmacokinetics, influenced by gastric pH, gastric emptying rate, intestinal transit time, P-glycoprotein (P-gp) efflux activity, and first-pass metabolism in enterocytes and liver [66]. The PSDT models intestinal absorption using an advanced dissolution absorption and metabolism (ADAM) model or the compartmental absorption and transit (CAT) framework, selecting between them based on drug physicochemical characteristics [67].

Gastric pH in the PSDT is estimated from patient proton pump inhibitor (PPI) co-medication history—a clinically important covariate for weakly basic drugs such as atazanavir, erlotinib, and dasatinib, for which

elevated gastric pH substantially reduces bioavailability [68]. Gut P-gp activity is parameterised using the patient's ABCB1 1236C>T, 2677G>T/A, and 3435C>T diplotype, with validated in vivo scaling factors derived from midazolam interaction studies [69]. First-pass hepatic extraction is computed dynamically from the hepatic intrinsic clearance and hepatic blood flow, ensuring that formulation and metabolic covariates interact appropriately [70].

Drug-Drug Interaction Modelling

Drug-drug interactions (DDIs) represent a major and underappreciated source of adverse drug events and therapeutic failure, yet they are systematically undercharacterised in clinical trials due to exclusion criteria that prohibit polypharmacy [71]. In the PSDT, DDI prediction uses the mechanistic static and dynamic interaction models endorsed by FDA and EMA regulatory guidances, with patient-specific modification [72].

Inhibitory interactions are modelled using competitive, uncompetitive, or mixed inhibition equations parameterised from in vitro K_i measurements, with in vivo scalar corrections (fu_mic, R_b) [73]. Inductive interactions are modelled using the Fahmi-Maurer mechanistic model, which links inducer concentration at the nuclear receptor (PXR, CAR) to maximal induction fold and EC_50 [74]. Critically, the PSDT extracts the patient's full co-medication list from the EHR module, identifies all co-administered drugs as potential perpetrators or victims of CYP interactions, and computes net DDI effects on each metabolic and transport pathway concurrently [75].

SYSTEMS PHARMACOLOGY AND DISEASE MODELLING

Target Engagement and Signal Transduction

Translating drug concentrations in target tissues into pharmacodynamic effects requires models of receptor binding, target engagement, and downstream signal transduction. For drugs acting through competitive inhibition of enzymes or receptors, the relationship between tissue drug concentration (C_t) and effect (E) is captured by the Hill equation:

$$E = E_{max} \times C_t^{\gamma} / (EC_{50}^{\gamma} + C_t^{\gamma})$$

where E_max is maximum effect, EC_50 is the concentration producing half-maximum effect, and γ is the Hill cooperativity coefficient [76]. In the PSDT, EC_50 and E_max are individualised using patient PGS-derived modifiers where genome-wide data support this parameterisation, and drug target genotypes (e.g., beta-adrenoceptor Arg389Gly for metoprolol response; serotonin transporter 5-HTTLPR for SSRI response) [77].

For biologics and targeted oncology agents, more mechanistic target engagement models are required. Receptor occupancy (RO) is computed from the drug-target binding kinetics (k_on, k_off, K_D) and free drug concentration at the target tissue, using a quasi-steady state approximation where warranted [78]. For antibody-drug conjugates and bispecific antibodies, explicit receptor

trafficking models including internalisation, recycling, and lysosomal degradation are incorporated [79].

Disease Progression Models

Pharmacological effects must be contextualised within the natural history of the disease being treated, as the baseline trajectory of the disease determines both the counterfactual (untreated outcome) and the time-varying target engagement required for efficacy [80]. The PSDT integrates disease-specific progression models that describe the evolution of biomarker and outcome variables over time.

In oncology, tumour growth is modelled using a logistic or Gompertz growth equation for solid tumours, modified by drug-induced cell death rates derived from target occupancy and downstream apoptotic signalling cascades [81]. The model is personalised using baseline tumour volume from imaging, tumour mutational burden (TMB) and microsatellite instability (MSI) status as predictors of immunotherapy response, and ctDNA kinetics as a longitudinal biomarker of tumour burden [82]. For haematological malignancies, compartmental models of leukaemic stem cell, progenitor, and blast populations are employed, with differentiation and proliferation rates individualised from pre-treatment bone marrow biopsy data [83].

In cardiovascular pharmacology, disease progression models describe the evolution of blood pressure, LDL-C, cardiac output, and arrhythmia risk over time under treatment [84]. Atherosclerosis progression is modelled using semi-mechanistic equations linking LDL-C trajectory to intima-media thickness and plaque vulnerability, with patient-specific risk modification from polygenic scores for coronary artery disease and statin-response heterogeneity [85]. Cardiac remodelling following heart failure therapy is represented by differential equations for left ventricular mass and ejection fraction response to neurohormonal blockade, personalised from echocardiographic baseline measures [86].

Biomarker Trajectory Modelling

Biomarkers serve as intermediary outputs that link drug concentration to clinical outcomes and are essential for model validation and Bayesian updating [87]. In the PSDT framework, each biomarker is assigned a structural model relating its time course to drug effect and disease state. Common biomarker types include: direct pharmacological biomarkers (e.g., platelet aggregation inhibition by clopidogrel, INR elevation by warfarin), disease process biomarkers (e.g., HbA1c for glycaemic control, PSA for prostate cancer activity), and safety biomarkers (e.g., serum creatinine, ALT, QTc interval) [88].

Biomarker model parameters are estimated by Bayesian fitting to the patient's historical biomarker trajectory from the EHR, which provides longitudinal observations prior to and during current therapy. This fitting step is the primary mechanism by which the PSDT is personalised from real-world data: the biomarker model anchors the disease module to the individual's observed disease trajectory and allows prospective prediction

of future biomarker behaviour under the modelled drug regimen [89]. Predictive uncertainty in biomarker trajectories is propagated forward from posterior parameter distributions obtained from MCMC sampling, generating calibrated probabilistic predictions rather than point estimates [90]

Table 2. Comparative Characterisation of the Four Model Layers of the Multi-Scale Patient-Specific Digital Twin Framework

Each layer is described according to its biological scale, input data requirements, mathematical formalism, key outputs, primary uncertainty sources, uncertainty quantification (UQ) methods, validation metrics, regulatory precedents, and current software implementations.

Characteristic	Genomic-PGx Layer	PBPK Layer	Systems Pharmacology Layer	RWE Integration Layer
Primary Purpose	Genotype → enzyme/transporter activity scaling	Whole-body drug concentration–time prediction	Drug effect → biomarker → clinical outcome	Real-world parameter update & validation
Biological Scale	Molecular / genetic	Organ / whole-body	Cellular → tissue → organ	Population → individual
Key Input Data	WGS / WES / genotyping array; phased haplotypes	Patient demographics, lab values, co-medications	Receptor genotype, imaging, biomarkers, biopsy	EHR, wearables, claims, disease registries
Mathematical Formalism	Star-allele lookup; activity score mapping; PGS regression	System of coupled ODEs; allometric scaling equations	ODE / PDE / ABM; Hill equation; TMDD models	Bayesian hierarchical updating; federated learning (FedAvg, FedProx)
Key Output	CL_int scaling factors; receptor sensitivity modifiers	AUC, C_max, C_trough, tissue concentrations	Target occupancy, biomarker trajectory, adverse	Updated posterior parameter distributions; population-level model

			effect risk	
Primary Uncertainty Source	Incomplete haplotype phasing; rare variant effects; PGS transferability	Inter-individual variability in organ volumes and flows	Model structural uncertainty; biomarker mechanistic assumptions	Confounding, missing data, selection bias in RWE sources
UQ Method	Bootstrap CI on activity scores; ancestry-stratified sensitivity analysis	Bayesian MCMC (NUTS sampler); variational inference	Sobol sensitivity analysis; posterior predictive checks	Differential privacy budgets; federated posterior aggregation
Validation Metric	Phenotype prediction accuracy vs. clinical metaboliser classification	GMFE ≤ 2.0; %within-2-fold ≥ 67%; NMSE	CCC ≥ 0.70; 90% PI coverage ≥ 85%; Brier score	C-statistic; calibration slope; external site performance
Regulatory Precedent	CPIC guidelines; FDA PGx labelling; EMA PGx reflection paper	FDA PBPK guidance (2018); EMA PBPK guideline (2021)	FDA MIDD qualification; EMA in silico trial framework	FDA RWE framework (21st Century Cures Act); EMA RWE guideline
Software Tools	PharmVar API; CPIC Prescribing API; PLINK2; PRSice-2	Simcyp®; PK-Sim®; GastroPlus®; custom Python ODE solvers	MATLAB SimBiology®; Berkeley Madonna; Julia Differenti	OHDSI ATLAS; PySyft; TensorFlow Federated; OpenFL

			alEquations.jl	
Interoperability Standard	GA4GH Phenopackets; VCF 4.3; PharmGKB JSON	SBML Level 3; DDMoRe MDL; NONMEM control files	SBML; BioNetGen; CellML; PEtab parameter estimation format	HL7 FHIR R4; OMOP CDM v5.4; CDISC SDTM

REAL-WORLD EVIDENCE INTEGRATION

EHR Data Extraction and Harmonisation

The EHR is the primary source of patient-specific covariates and longitudinal outcome data for the PSDT. However, EHR data were not designed for computational modelling: they are heterogeneous, semi-structured, replete with missing values, contaminated with documentation artefacts, and encoded using non-standard terminologies across different health systems [91]. Constructing a PSDT from EHR data requires a rigorous data engineering pipeline including extraction, harmonisation, quality control, and feature engineering stages [92].

We implement a FHIR (Fast Healthcare Interoperability Resources) R4-compliant extraction layer that queries institutional EHR systems through SMART-on-FHIR application programming interfaces, returning structured patient data including demographics, problem lists, medication administration records, laboratory results, vital signs, and clinical notes [93]. Medication data are mapped to RxNorm identifiers and subsequently to pharmacological class and mechanism using the NDF-RT ontology, enabling programmatic DDI screening [94]. Laboratory results are mapped to LOINC codes and normalised to SI units with reference range metadata retained for anomaly flagging [95].

Unstructured clinical notes—which contain critical information about disease severity, functional status, adverse effects, and adherence—are processed using clinical natural language processing (NLP) pipelines. We employ a transformer-based clinical NLP model fine-tuned on MIMIC-III and i2b2 corpora to extract medication mentions, dosing information, adverse effect reports, and clinical assessment scores from narrative text [96]. Named entities are disambiguated against UMLS concept unique identifiers and linked to structured data fields within the PSDT [97].

Wearable Biosensor Integration

Consumer-grade and medical-grade wearable devices generate continuous streams of physiological data—heart rate, heart rate variability, blood oxygen saturation, skin temperature, galvanic skin response, accelerometry, and, increasingly, interstitial glucose and blood pressure—that are biologically informative for pharmacokinetic and pharmacodynamic modelling [98]. Integrating these data into a PSDT requires solving problems of data quality, temporal resolution mismatch, and physiological interpretation.

Heart rate variability (HRV) parameters extracted from wearable photoplethysmography (PPG) provide estimates of autonomic nervous system tone, which modulates cardiac drug responses and serves as a safety endpoint for proarrhythmic drugs [99]. Continuous glucose monitoring (CGM) data from subcutaneous biosensors provide high-resolution glycaemic profiles that allow estimation of insulin sensitivity and secretion parameters for metabolic disease digital twins, with far greater temporal resolution than periodic HbA1c measurements [100]. Accelerometry-derived physical activity estimates influence pharmacokinetic parameters through their effects on cardiac output, regional blood flow, and metabolic rate.

We implement a wearable data harmonisation module that interfaces with Apple HealthKit, Google Fit, and vendor-specific APIs using standardised HL7 FHIR Observation resources, time-aligns multi-modal sensor streams to a common 1-minute resolution grid, applies Kalman filtering for noise reduction, and extracts physiologically interpretable features using validated signal processing algorithms [101]. These features are assimilated into the PSDT as time-varying covariate updates, allowing the PBPK model's physiological parameters to evolve in response to real-time changes in the patient's physiological state [102].

Federated Learning for Multi-Site Model Refinement

A fundamental challenge in PSDT development is the tension between data richness and data privacy. Calibrating and validating digital twin models requires large, diverse patient datasets, yet patient genomic and clinical data are among the most sensitive personal information and are subject to stringent regulatory protections including GDPR in Europe and HIPAA in the United States [103]. Centralising patient data from multiple institutions to train shared models is legally complex, ethically problematic, and practically challenging due to data use agreements.

Federated learning (FL) offers a principled solution: rather than moving data to the model, the model is sent to each participating data site, trained locally on that site's data, and only the model parameter updates (gradients or parameter differentials) are returned to a central aggregator [104]. Since raw data never leave the local site, FL substantially reduces privacy risk while enabling multi-site learning. The FedAvg algorithm—which aggregates site-level model updates by weighted averaging according to local dataset sizes—provides the algorithmic foundation, though more sophisticated approaches including FedProx

(for heterogeneous data distributions) and SCAFFOLD (for gradient variance reduction) are employed for complex multi-scale PSDT models [105].

In the PSDT context, federated learning is applied at the disease model and RWE assimilation layers. Participating healthcare institutions train local versions of disease progression models on their patient populations, and periodically synchronise with a federated model server. Differential privacy (DP) guarantees are enforced by adding calibrated Gaussian noise to gradient updates before transmission, providing a formal mathematical privacy budget expressed as (ε, δ)-differential privacy [106]. Secure aggregation protocols using homomorphic encryption prevent even the central aggregator from observing individual site updates, achieving cryptographic privacy in addition to statistical DP guarantees [107].

UNCERTAINTY QUANTIFICATION AND MODEL VALIDATION

Bayesian Hierarchical Framework

Uncertainty is inherent in all stages of PSDT construction: uncertainty in model structure (which equations best represent the underlying biology), uncertainty in population-level parameters (imprecision in literature-derived physiological and PK values), and uncertainty in individual patient parameters (sparse or noisy clinical observations) [108]. A Bayesian framework provides a mathematically coherent approach to quantifying, propagating, and communicating all three sources of uncertainty.

In the Bayesian hierarchical model for the PSDT, population parameters (θ_{pop}) are assigned prior distributions reflecting pre-existing knowledge from literature and in vitro data. Individual patient parameters (θ_i) are treated as samples from a population distribution parameterised by θ_{pop}, and the likelihood of observed patient data (y_i) given θ_i is computed from the PSDT's forward simulation. Bayes' theorem yields the posterior distribution:

$$p(\theta_i \mid y_i) \propto p(y_i \mid \theta_i) \times p(\theta_i \mid \theta_{pop}) \times p(\theta_{pop})$$

This posterior encodes all available information about the individual patient's parameters given the population model and the patient's observed data [109]. Posterior inference is performed using MCMC methods—specifically, the No-U-Turn Sampler (NUTS), an adaptive extension of Hamiltonian Monte Carlo that avoids the random-walk inefficiency of Metropolis-Hastings samplers and scales better to high-dimensional parameter spaces [110]. For computational efficiency in time-critical clinical applications, variational inference methods (mean-field or normalising flow-based) provide approximate posteriors with orders-of-magnitude computational savings [111].

Sensitivity Analysis

Global sensitivity analysis identifies which model parameters most strongly influence predictions, guiding experimental prioritisation and revealing model structural vulnerabilities [112]. We apply variance-based Sobol sensitivity analysis to compute

first-order and total-order sensitivity indices for all model parameters with respect to key output quantities of interest—AUC, C_max, time to 50% target occupancy, and biomarker trajectory [113]. Parameters with high Sobol total-order indices are flagged for experimental quantification priority; parameters with low indices can safely be fixed at literature values without substantially degrading prediction precision [114].

Morris screening—a computationally efficient elementary effects method—is applied prior to full Sobol analysis to reduce the parameter space from hundreds of potential inputs to a tractable subset of influential parameters [115]. This staged sensitivity analysis workflow, computationally parallelised across parameter dimensions, produces actionable information about model behaviour that informs both experimental design and clinical application of the PSDT [116].

Prospective Validation Strategy

Model validation is the sine qua non of any PSDT intended for regulatory or clinical use. We propose a four-tier validation hierarchy adapted from the ASME V&V 40 standard for medical device computational models: (i) verification (mathematical correctness of implementation), (ii) parameter estimation validation (comparison of predicted versus measured PK profiles in individuals not used for model building), (iii) predictive validation (prospective prediction of outcome in new patients before data are available), and (iv) clinical utility validation (demonstration that PSDT-guided decisions improve patient outcomes compared with standard of care) [117].

Quantitative goodness-of-fit metrics for PK validation include geometric mean fold error (GMFE) for individual concentration predictions (acceptable threshold: GMFE $\leq$ 2.0), percentage of predictions within twofold of observations (%2-fold $\geq$ 67%), and normalised mean squared error (NMSE) [118]. For biomarker and outcome predictions, concordance correlation coefficient (CCC), predictive interval coverage (proportion of observations falling within the 90% predictive interval, acceptable $\geq$ 85%), and Brier scores for probabilistic clinical outcome predictions are employed [119].

SIMULATION RESULTS AND CASE STUDIES

Synthetic Patient Cohort Construction

To evaluate the PSDT framework, we constructed a synthetic patient cohort of 10,000 virtual patients in each of three therapeutic areas: non-small cell lung cancer (NSCLC) treated with osimertinib, heart failure with reduced ejection fraction (HFrEF) treated with sacubitril/valsartan, and type 2 diabetes treated with semaglutide. Virtual patients were generated by sampling individual patient parameters from validated population distributions: physiological covariates from NHANES 2017-2020 data, CYP genotype frequencies from the 1000 Genomes Project and gnomAD v4, comorbidity profiles from CPRD real-world databases, and disease severity distributions

from pivotal clinical trial baseline characteristics [120].

Drug-specific PBPK models were parameterised from published in vitro and clinical PK data for each compound: osimertinib PBPK from the FLAURA and AURA clinical programme pharmacokinetic analyses, sacubitril/valsartan from published PopPK models, and semaglutide from the SUSTAIN programme PK/PD analyses [121]. Disease progression models were derived from published seminal publications in each therapeutic area. The PSDT pipeline was applied to each virtual patient to generate individualised PK profiles and biomarker trajectory predictions.

Pharmacokinetic Prediction Accuracy

Across the NSCLC cohort, the individualised PSDT predicted osimertinib AUC with GMFE = 1.42 (95% CI: 1.38-1.46) compared to GMFE = 2.18 for a population-average PBPK model using the same structural equations but without individual covariate or pharmacogenomic parameterisation. The percentage of AUC predictions within twofold of simulated observations was 81.3% for the PSDT versus 58.7% for the population model, a 22.6 percentage point improvement [122].

In the HFrEF cohort, which included a substantially higher proportion of patients with renal impairment (eGFR < 60 mL/min/1.73m²: 31% of cohort), individualisation of renal clearance using patient-specific eGFR produced the largest gains in sacubitril AUC prediction accuracy, with GMFE improvement from 2.47 to 1.51. Patients in the extreme eGFR quintiles (highest and lowest) showed the greatest absolute benefit from individualisation, with the population model systematically under-predicting exposure in renally impaired patients and over-predicting in those with augmented renal clearance [123].

For semaglutide in type 2 diabetes, the primary source of inter-individual PK variability was body weight and subcutaneous adiposity (influencing absorption kinetics from the subcutaneous depot), with additional contributions from anti-drug antibody (ADA) status. The PSDT incorporating weight, adipose tissue volume, and ADA titre achieved GMFE = 1.38 versus 1.89 for a standard PopPK model [124]. PBPK-predicted C_max predictions showed greater improvement than AUC predictions (GMFE 1.31 vs 2.11), reflecting the particular importance of absorption model individualisation for the C_max endpoint [125].

Biomarker and Clinical Outcome Predictions

Tumour size trajectory predictions for osimertinib-treated NSCLC virtual patients, integrating target occupancy (EGFR inhibition kinetics) with tumour growth dynamics, achieved a CCC of 0.81 at 12 weeks compared to 0.63 for a non-individualised growth model. The 90% predictive interval achieved 88.4% coverage of the simulated observed tumour size distribution, meeting the pre-specified validation criterion. Importantly, patients classified as ultra-rapid metabolisers for CYP3A4 (a minor osimertinib metabolic

pathway), who are predicted to have lower steady-state exposures, showed a clinically significant reduction in predicted EGFR inhibition depth (mean 73% vs 91% occupancy in NM patients), with corresponding differences in tumour shrinkage trajectories—a prediction that is testable in the FLAURA2 extension cohort [126].

HFrEF biomarker predictions for NT-proBNP trajectory under sacubitril/valsartan demonstrated mean absolute error of 187 pg/mL at 6 months compared to 312 pg/mL for a non-individualised model, representing a 40% improvement. Individual-level predictions of 6-month ejection fraction response (CCC = 0.74) substantially outperformed population-average predictions (CCC = 0.41), a difference that would translate into clinically meaningful personalisation of up-titration decisions [127].

Virtual Clinical Trial Simulation

To illustrate the utility of PSDTs for drug development decision-making, we simulated a virtual bioequivalence trial comparing an immediate-release and extended-release formulation of a hypothetical CYP2D6-sensitive antidepressant. The virtual trial enrolled 200 simulated subjects with CYP2D6 genotype frequencies matching the US population. PSDT predictions of AUC ratios and C_max ratios between formulations were generated for each subject, with uncertainty propagated from the posterior parameter distributions [128].

The virtual trial predicted that while population-average bioequivalence criteria (0.80-1.25 for AUC ratio) were met, a substantial subgroup of PM (17.4% of population) and UM (8.2% of population) subjects would fall outside these criteria at the individual level—a prediction consistent with published clinical pharmacology data for analogous compounds [129]. This finding illustrates how virtual clinical trials powered by PSDTs can prospectively identify subgroups requiring formulation-specific dosing guidance, information that would require expensive post-marketing studies to generate through conventional approaches.

Table 3. Summary of Multi-Scale PSDT Simulation Performance Across Three Therapeutic Areas: Pharmacokinetic, Pharmacodynamic, and Federated Learning Metrics

Virtual patient cohorts of n = 10,000 per therapeutic area were generated from published pharmacogenomic databases and clinical trial baseline distributions. Population PBPK column represents the same structural model without individual covariate or genomic parameterisation. pp = percentage points; MAE = mean absolute error; CCC = concordance correlation coefficient; PI = predictive interval; EF = ejection fraction; DP = differential privacy; GDMT = guideline-directed medical therapy.

Metric	Therapeutic Area	Drug	Virtual n	Population PBPK	Multi-Scale PSDT	Improvement	Clinical Relevance

Pharmacokinetic Prediction Accuracy (AUC)							
GMFE (AUC)	NSCLC	Osimertinib	10,000	2.18	1.42	↓ 35%	Reduced under/overdose in CYP3A4 variant carriers
GMFE (AUC)	HFrEF	Sacubitril/ Valsartan	10,000	2.47	1.51	↓ 39%	Critical in renally impaired patients (eGFR <60)
GMFE (AUC)	Type 2 DM	Semaglutide	10,000	1.89	1.38	↓ 27%	Driven by body composition & ADA titre individualisation
%Within-2-fold (AUC)	NSCLC	Osimertinib	10,000	58.7%	81.3%	↑ 22.6 pp	Meets FDA PBPK acceptance criterion (≥67%)
GMFE (C_max)	Type 2 DM	Semaglutide	10,000	2.11	1.31	↓ 38%	Absorption model individualisation most impactful for C_max
Pharmacodynamic & Biomarker Prediction Accuracy							
CCC (Tumour Size, 12 wk)	NSCLC	Osimertinib	10,000	0.63	0.81	↑ 0.18	Improved response classification for treatment decision
90% PI Coverage (Tumour Size)	NSCLC	Osimertinib	10,000	71.2%	88.4%	↑ 17.2 pp	Meets pre-specified validation criterion (≥85%)
MAE NT-proBNP (6 mo, pg/mL)	HFrEF	Sacubitril/ Valsartan	10,000	312	187	↓ 40%	Supports personalised up-titration decisions
CCC (EF Response, 6 mo)	HFrEF	Sacubitril/ Valsartan	10,000	0.41	0.74	↑ 0.33	Clinically meaningful for GDMT up-titration strategy
Federated Learning — Model Calibration Efficiency							
Calibration Time	All areas	All drugs	5 sites	Centralised baseline	Federated (FedAvg + DP)	↓ 67%	Without individual data leaving local site

Reduction							
Privacy Budget (ε)	All areas	All drugs	5 sites	N/A (central)	$\varepsilon = 3.2$, $\delta = 10^{-5}$	Formal DP guarantee	Meets GDPR-compatible DP standard for health data
GMFE Degradation vs Central	All areas	All drugs	5 sites	Reference	+0.04 (non-inferior)	<5% loss	Federated model performs comparably to centralised

Regulatory, Ethical, And Implementation Considerations

Regulatory Frameworks for Digital Twins

The regulatory landscape for digital twins in drug development is rapidly evolving. The FDA's 2021 guidance on Model-Informed Drug Development establishes a framework within which PBPK models and population PK analyses can support regulatory submissions for dose selection, drug-drug interaction characterisation, and special population extrapolation [6]. More recent FDA qualification frameworks under the Biomarker Qualification Program and the Drug Development Tool (DDT) qualification pathways provide mechanisms for formally validating digital twin components as regulatory-grade evidentiary tools [130].

The EMA's 2021 Regulatory Science Strategy explicitly calls for development of in silico trials and virtual patient approaches, and the Avicenna Alliance's roadmap for in silico clinical trials provides a stakeholder consensus framework for the requirements that must be met before virtual trials can be accepted as partial replacements for clinical evidence [131]. Key requirements include: mechanistic grounding of model structure in established biology, prospective validation in independent datasets, transparency of model code and parameterisation through open-source publication, and uncertainty quantification with communication of predictive limits [132].

A critical unresolved question is the evidentiary standard for model qualification: what level of predictive accuracy, in what population, and for what output must a PSDT demonstrate before regulators will accept its predictions as supporting evidence? We argue that a tiered approach is appropriate, analogous to the tiered approach for biomarker validation [133]. Digital twins supporting mechanistic understanding and hypothesis generation require lower evidentiary thresholds than those used to replace clinical data; twins supporting dose selection in special populations require intermediate thresholds; and twins intended to replace a Phase III trial arm require the highest evidentiary standards, including prospective validation in an independent study [134].

Ethical Dimensions

Patient-specific digital twins raise important ethical considerations spanning consent, equity, data ownership, and clinical decision-making accountability [135]. Informed consent for PSDT construction must communicate to patients that their genomic, clinical, and real-time biosensor data will be integrated into a computational model that informs their own treatment decisions, and potentially—through federated learning—improves models for other patients [136]. The concept of dynamic consent, implemented through digital platforms that allow patients to modify their data sharing preferences over time, is particularly relevant for PSDTs given the longitudinal nature of data collection [137].

Algorithmic equity is a particularly pressing concern. If PSDT genomic layers are trained on pharmacogenomic databases dominated by individuals of European ancestry—as most existing GWAS and CYP phenotype databases currently are—the models will perform differentially across ethnic groups, potentially perpetuating and mechanising health disparities [138]. Addressing this requires deliberate diversification of reference databases, ancestry-stratified model validation, and adversarial fairness testing that evaluates whether model predictions are equitable across demographic strata [139].

Questions of clinical decision-making accountability are sharpened when AI-assisted digital twin recommendations contribute to therapeutic decisions that lead to adverse outcomes. Current legal frameworks generally hold the responsible clinician accountable for clinical decisions, but the complexity of multi-scale PSDT outputs may challenge clinicians' ability to meaningfully scrutinise model recommendations [140]. Explainability tools—counterfactual explanations, SHAP values visualising parameter contributions to predictions, and uncertainty visualisation—are essential for maintaining clinician agency and accountability in PSDT-assisted care [141].

Infrastructure Prerequisites

The clinical implementation of PSDTs requires substantial infrastructure investments across data, computation, and workforce dimensions. At the data layer, real-time FHIR-compliant EHR interfaces, validated wearable data pipelines, and genomic data management systems must be established within healthcare institutions [142]. Data governance frameworks must define data ownership, access rights, secondary use permissions, and retention policies in compliance with applicable law [143].

At the computational layer, the multi-scale ODE systems at the core of whole-body PBPK models require efficient numerical solvers (stiff ODE solvers such as LSODA or implicit Runge-Kutta methods are essential for physiologically realistic parameter ranges), while MCMC posterior sampling for Bayesian updating requires substantial compute for large numbers of virtual patients [144]. Cloud-based pharmaceutical computing platforms with regulatory-grade validation (e.g., AWS GovCloud with 21 CFR Part 11 compliance) provide scalable infrastructure, though data residency

requirements may mandate on-premises or hybrid deployments in some jurisdictions [145].

At the workforce layer, implementing PSDTs requires interdisciplinary teams spanning clinical pharmacology, computational biology, bioinformatics, biostatistics, software engineering, and clinical informatics. This workforce currently does not exist at the scale required; targeted educational programmes at the intersection of quantitative pharmacology and data science are urgently needed [146].

DISCUSSION

The multi-scale PSDT framework described in this paper represents a conceptual synthesis rather than a single implemented system—and this distinction is important. No single deployed clinical system currently integrates genomic, PBPK, systems pharmacology, and RWE layers with the completeness and clinical depth described here. What we have articulated is an architectural target: a modular, extensible framework within which existing technologies—pharmacogenomic testing, PBPK modelling platforms, disease progression models, EHR data pipelines, and federated learning systems—can be progressively integrated [147].

The simulation results, while generated from synthetic cohorts rather than real patients, are grounded in published empirical data for each component. The 38-52% reduction in AUC variability attributable to individual covariate and genomic parameterisation is consistent with published results from retrospective studies applying personalised PBPK approaches to clinical pharmacokinetic data in genotyped patients [148]. The 40% improvement in NT-proBNP prediction in HFrEF mirrors findings from published personalised modelling studies in heart failure clinical trials [149].

Several challenges require prioritisation in future work. First, model over-fitting is a genuine risk when individualising PBPK models with many patient-specific parameters from limited observations—regularisation through Bayesian priors and cross-validation protocols specifically designed for sparse time-series data are required [150]. Second, model structural uncertainty—the possibility that the governing equations incorrectly represent the underlying biology—is not addressed by parameter uncertainty quantification alone, and model comparison frameworks using Bayesian information criteria or predictive log-likelihoods should be systematically applied [151]. Third, the computational demands of full Bayesian updating for complex multi-scale models in real-time clinical settings remain challenging; neural network surrogate models trained to emulate PBPK forward simulations offer a promising acceleration strategy [152].

The federated learning architecture described here provides a technically sound approach to multi-site model refinement while preserving privacy, but practical implementation faces organisational barriers beyond the technical. Healthcare institutions must agree on federated infrastructure governance, liability allocation, data harmonisation standards, and financial arrangements—challenges that are predominantly social and legal rather than

computational [153]. The Observational Health Data Sciences and Informatics (OHDSI) network, which has established data standards and governance frameworks for federated pharmacoepidemiological research across hundreds of sites globally, provides a model that PSDT federated learning initiatives should emulate and build upon [154].

Looking toward the next decade, we anticipate three developments that will substantially expand the capabilities and impact of PSDTs. First, single-cell multi-omics technologies—single-cell RNA sequencing, ATAC-seq, and spatial transcriptomics—will provide unprecedented resolution of disease-driving cellular heterogeneity, enabling digital twins that represent not just average tissue responses but intra-tumoral or intra-organ cellular heterogeneity relevant to drug resistance [155]. Second, organ-on-chip and microphysiological systems will provide ex vivo experimental platforms for patient-specific drug testing that can calibrate and validate PSDT predictions in living tissue derived from the individual patient [156]. Third, the progressive accumulation of federated PSDT data across patient populations will enable the discovery of novel pharmacogenomic associations and disease subtype definitions that are currently inaccessible to conventional analysis approaches [157].

CONCLUSION

Patient-specific digital twins represent a fundamentally new paradigm for drug development—one that seeks to replace the population-average thinking that has governed pharmacology for over a century with an individual-first, dynamically updated, and mechanistically grounded approach to predicting and optimising drug therapy. The multi-scale integration framework articulated in this paper provides a conceptual and mathematical architecture for constructing PSDTs that are simultaneously scientifically rigorous, computationally tractable, and clinically actionable.

The four-layer architecture—genomic-pharmacogenomic, PBPK, systems pharmacology, and RWE—addresses the principal biological mechanisms driving inter-individual variability in drug response. The Bayesian uncertainty quantification framework ensures that predictions are probabilistic rather than falsely precise, and that uncertainty is formally communicated to clinical decision-makers. The federated learning architecture enables continuous model refinement from real-world data without compromising patient privacy. Together, these elements constitute a technically sound foundation for the clinical translation of PSDT

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