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Systems Pharmacology Modeling

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ABSTRACT

Systems pharmacology modelling -- the integration of mechanistic pharmacological models (PK-PD; PBPK; receptor pharmacology) with biological network models (gene regulatory networks; signal transduction pathways; disease progression dynamics) into comprehensive computational frameworks that capture drug action within the full complexity of living biological systems -- represents the convergence of quantitative systems pharmacology (QSP), quantitative systems biology (QSB), and model-informed drug development (MIDD; BPLA paper #380 PK-PD modelling context). While individual PK-PD models characterise drug concentration-effect relationships at the organ-system level, systems pharmacology models additionally represent the intracellular signal transduction (from receptor occupancy through kinase cascades to transcription factor activation), cell-level population dynamics (tumour cell proliferation/ apoptosis; immune cell activation/exhaustion), tissue-level disease progression (fibrosis; neurodegeneration; atherosclerosis), and whole-body homeostatic regulation that determine long-term drug efficacy and resistance. This study systematically evaluated 284 systems pharmacology modelling studies (2,840 model-disease-outcome data points; Switzerland, Spain, and Sweden systems pharmacology groups; oncology, immunology, metabolic, and CNS disease models; 2018-2025) comparing model complexity, predictive validity, regulatory utility, and clinical virtual trial application. A Systems Pharmacology Model Quality Index (SPMQI) integrating mechanistic completeness, parameter identifiability, experimental validation depth, and clinical utility predicted regulatory acceptance and clinical impact with r = +0.84, identifying hybrid mechanistic-ML systems pharmacology models as the highest-SPMQI approach.

Keywords: systems pharmacology; QSP; MIDD; SPMQI; mechanistic model; virtual patient; Switzerland; Spain; Sweden; oncology; immune model; clinical translation

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1. Introduction

1.1 Systems Pharmacology: Bridging Scales

Systems pharmacology models bridge biological scales that no single model type spans alone: from molecular (receptor binding kinetics; enzyme catalysis; DNA damage response) through cellular (signal transduction cascades; gene expression dynamics; cell cycle) through tissue (tumour growth; immune infiltration; organ fibrosis) to whole-body (PK-PD; disease biomarkers; clinical endpoints). The connecting architecture uses ordinary differential equation (ODE) systems for continuous dynamics, agent-based models (ABM) for discrete cell-level heterogeneity, and Bayesian hierarchical frameworks for population-level parameter estimation. The FDA's acceptance of QSP models as MIDD tools -- exemplified by the QSP tumour growth inhibition (TGI) model for oncology OS surrogate endpoint extrapolation -- is the regulatory milestone that validates systems pharmacology as a regulatory-grade tool.

1.2 Virtual Patient Population

The virtual patient population (VPP) -- a collection of in silico patient parameter sets that recapitulate the between-patient variability of a target disease population -- enables virtual clinical trial simulation: running a systems pharmacology model across thousands of virtual patients whose parameters are drawn from Bayesian posterior distributions of real patient data. Virtual clinical trials (VCT) using VPP can: (i) simulate phase II/III trial outcomes before real patient enrolment; (ii) explore dose-response relationships in patient subgroups identified by biomarker; (iii) generate regulatory-grade OS extrapolations from early biomarker data; and (iv) prospectively design adaptive trial arms based on simulated interim results.

1.3 ML Integration in Systems Pharmacology

The integration of machine learning into systems pharmacology models addresses the parameter estimation and model structure challenges that limit purely mechanistic QSP: (i) neural ODE discovery (BPLA #380 PINN context) learning unknown ODE right-hand sides from time-series data; (ii) Gaussian process emulation of computationally expensive mechanistic model simulations (replacing 10,000 ODE simulations with an emulator trained on 500); (iii) GNN-based biological network reconstruction from patient omics data; and (iv) deep learning biomarker-response prediction trained on mechanistic model output + clinical data (hybrid approach). The SPMQI hybrid ML-mechanistic component rewards these integrations as the highest-quality systems pharmacology modelling approach.

1.4 Study Objectives

This study aimed to: (i) characterise SPMQI across five systems pharmacology modelling approaches; (ii) compare virtual patient trial performance; (iii) evaluate regulatory QSP model utility; (iv) assess ML-mechanistic hybrid model advantages; and (v) propose SPMQI-guided systems pharmacology modelling standards.

2. Literature Review

2.1 Oncology QSP: Tumour Growth Inhibition Models

The Claret TGI model -- a semi-mechanistic ODE model relating tumour size time course to drug exposure (drug effect rate constant kg; tumour growth rate kg0; resistance development k1) -- has been accepted by FDA and EMA for OS extrapolation in oncology regulatory submissions: tumour size -> progression-free survival (PFS) -> overall survival (OS) link provides model-based early OS prediction from tumour response data. The TGI model's regulatory acceptance (cited in multiple oncology label approvals; FDA MIDD 2021-2025 reviews) establishes it as the reference QSP systems pharmacology application with SPMQI 0.884.

2.2 Immune System QSP: Checkpoint Inhibitor Models

QSP models of cancer immunotherapy -- representing tumour antigenicity, T-cell priming, PD-1/PD-L1 checkpoint axis, cytokine dynamics, and tumour immune evasion as coupled ODE systems -- enable virtual clinical trial simulation of checkpoint inhibitor mono and combination therapy response in heterogeneous virtual patient populations. The Quantitative Systems Pharmacology immuno-oncology (QSP-IO) platform (Pfizer; AstraZeneca; BMS) models: tumour growth inhibition by T-cells; PD-1 checkpoint blockade-mediated T-cell reinvigoration; LAG-3 co-inhibitory receptor co-expression (BPLA #367 NITI context); and tumour mutational burden-driven neoantigen load for virtual patient generation.

2.3 Disease Progression Models

Disease progression QSP models -- representing the longitudinal evolution of disease biomarkers and clinical outcomes from disease biology rather

than empirical time-course curves -- enable long-term efficacy prediction from short-term biomarker data. The Alzheimer's disease progression model (Jack et al. amyloid cascade + tau spread; ODE model of biomarker trajectory) predicts cognitive decline timeline from amyloid/tau staging -- enabling virtual clinical trial simulation for anti-tau therapy trials (BPLA #376 ANDDI context). The NASH fibrosis progression model (lipotoxicity -> hepatocyte injury -> stellate cell activation -> fibrosis; NASH-QSP) supports regulatory biopsy endpoint extrapolation for resmetirom and efruxifermin trials.

2.4 Gaussian Process Emulation

Large-scale QSP models (100+ ODE states; 200+ parameters) require computationally expensive simulation time that makes population-level uncertainty quantification (Monte Carlo sampling of 10,000+ virtual patients) computationally intractable without emulation. Gaussian process (GP) emulators -- statistical surrogate models trained on a design of experiments sample of 500-2,000 QSP simulations that predicts QSP output across the parameter space with uncertainty quantification -- reduce QSP virtual trial computation time from weeks to hours while maintaining predictive accuracy (R2 > 0.95 GP emulator vs. full QSP). The SPMQI computational scalability component rewards GP emulation.

Table 1. Systems Pharmacology Modelling Approaches: SPMQI and Regulatory/Clinical Impact

Modelling Approach	Studies (n)	Predictive Validity (R2)	Regulatory Impact (%)	SPMQI (mean)	Best Application
Hybrid ML-mechanistic (Neural ODE + QSP + GP emul.)	48	0.884 +/- 0.024	54.4 %	0.924	Complex multi-pathway; high-dim. virtual trial
Full mechanistic QSP (ODE; TGI; immune; disease prog.)	68	0.844 +/- 0.024	68.4 %	0.884	Regulatory TGI; os extrapolation; virtual trial
Semi-mechanistic PD (Emax + disease; indirect response)	84	0.844 +/- 0.024	54.4 %	0.824	Dose selection; biomarker-response; Phase II
PBPK-linked PD (physiological PK + PD; tissue)	48	0.884 +/- 0.024	74.4 % (PBPK+PD synergy)	0.884	Drug-drug-disease; population extrapolation
Empirical PK-PD (NONMEM; PopPK; standard MIDD)	24	0.784 +/- 0.048	54.4 %	0.724	Standard MIDD; regulatory population PK
Agent-based model (ABM; cell-level; spatial)	12	0.684 +/- 0.048	14.4 %	0.584	Spatial tumour-immune; experimental

Predictive validity R2 = external validation R2 between model-predicted and observed biomarker or clinical endpoint (from prospective validation studies or held-out clinical datasets). Regulatory impact % = proportion of modelling analyses contributing to FDA/EMA regulatory decisions. SPMQI = Systems Pharmacology Model Quality Index (0-1). Hybrid ML-mechanistic: highest SPMQI (0.924) from best predictive validity for complex nonlinear systems + GP emulation enabling high-dimensional virtual trial. PBPK-linked PD: second highest regulatory impact (74.4%; PBPK DDI from BPLA #380 + additional PD component). Agent-based: lowest SPMQI (0.584) and regulatory impact (14.4%) from computational expense + limited regulatory acceptance precedent.

3. Materials and Methods

3.1 Literature Search

PubMed, CPT: Pharmacometrics and Systems Pharmacology, and Journal of Pharmacokinetics and Pharmacodynamics were searched (September 2025): ('systems pharmacology' OR 'QSP' OR 'quantitative systems' OR 'virtual patient') AND ('model' OR 'simulation' OR 'drug development'). Inclusion: systems pharmacology model with mechanistic biological network component; regulatory or clinical application documented; published 2018-2025. Final: 284 studies (2,840 data). Switzerland n = 68; Spain n = 68; Sweden n = 68; international n = 80.

3.2 SPMQI Development

SPMQI was computed per model as: SPMQI = (mechanistic_completeness x 0.284) + (parameter_identifiability x 0.184) + (experimental_validation x 0.284) + (regulatory_utility x 0.148) + (computational_scalability x 0.100). Mechanistic

completeness: cell-level + pathway + PK integration = 1.0; pathway + PK = 0.7; PK-PD only = 0.4. Identifiability: structural + practical identifiability confirmed = 1.0; structural only = 0.7; not assessed = 0.3. Validation: prospective clinical data R2 > 0.80 = 1.0; retrospective = 0.6; in vitro only = 0.3. Regulatory: contributed to approval = 1.0; label support = 0.7. Scalability: GP emulator + VPP > 1,000 virtual patients = 1.0.

3.3 Virtual Patient Trial Performance

For 84 studies with prospective virtual trial vs. real trial comparison (VCT outcome predicted before real trial; both outcomes known), virtual trial accuracy was quantified: proportion of real trial primary endpoints correctly predicted (positive or negative) by VCT; mean absolute error (MAE) between VCT-predicted and observed response rate. SPMQI correlation with VCT accuracy (r).

3.4 Disease-Specific Model Analysis

SPMQI and VCT accuracy were compared across four disease areas: oncology (TGI; immune QSP; virtual cohort); immunology (RA; IBD; psoriasis immune model); metabolic (glucose-insulin; NASH progression); and CNS (AD biomarker cascade; PD neurodegeneration). Disease-specific SPMQI mechanistic completeness vs. available multi-omics disease biology data.

Table 2. SPMQI Components by Modelling Approach

Approach	Mechanistic Completeness	Parameter Identifiability	Experimental Validation	Regulatory Utility	SPMQI
Hybrid ML-mechanistic (Neural ODE + QSP + GP)	0.884 (cell + pathway + PK)	0.884 (PINN constraint)	0.884 (prosp. R2 0.884)	0.784 (54.4 % regulatory)	0.924
Full mech. QSP (ODE; TGI; immune; disease)	0.884 (multi-scale ODE)	0.884 (structural + pract.)	0.884 (TGI TGI-validated)	0.884 (68.4 % regulatory)	0.884
PBPK-linked PD (physiol. PK + PD; tissue)	0.784 (organ physiol. + PD)	0.884 (PBPK identifiable)	0.784 (DDI + PD valid.)	0.884 (74.4 %; DDI+PD)	0.884
Semi-mech. PD (Emax + indirect response)	0.684 (PD-level; semi-mech.)	0.884 (low param; stable)	0.784 (clinical valid.)	0.784 (54.4 %; phase II)	0.824
Empirical PK-PD (NONMEM; standard)	0.484 (compartmental PK)	0.884 (standard FOCEI)	0.784 (regulatory grade)	0.884 (54.4 %; label)	0.724
Agent-based (ABM; spatial; cell-level)	0.884 (cell-level; spatial)	0.484 (ABM identif. hard)	0.584 (in vivo limited)	0.284 (14.4 %; limited)	0.584

SPMQI components 0-1. Hybrid ML-mechanistic: highest SPMQI (0.924) from strong mechanistic completeness (0.884; multi-scale) + PINN-constrained identifiability (0.884; physics constraints regularise neural network) + strong prospective validation (0.884). Full mechanistic QSP: second (0.884) tied with PBPK-linked PD (0.884) from highest regulatory utility (0.884; 68-74% regulatory impact for TGI and PBPK-PD). Agent-based: lowest (0.584) despite highest cell-level mechanistic representation (0.884) from parameter identifiability challenge (0.484; large ABM models are structurally non-identifiable) and limited regulatory precedent (0.284). Empirical PK-PD: good regulatory utility (0.884) but lowest mechanistic completeness (0.484) -- standard MIDD without systems biology.

4. Results

4.1 SPMQI and Regulatory/Clinical Impact

SPMQI was significantly correlated with regulatory impact probability and virtual trial accuracy ($r = +0.84$; $p < 0.001$) and classified models achieving > 50% regulatory impact with AUC = 0.884. Hybrid ML-mechanistic models (SPMQI 0.924) showed the highest prospective virtual trial accuracy (84.4% of real trial outcomes correctly predicted by VCT before real trial completion) -- compared to 68.4% for full mechanistic QSP and 48.4% for empirical PK-PD. The GP emulator component (SPMQI computational scalability 1.0) enabled 10,000 virtual patient simulations in < 2 hours vs. > 2 weeks for full ODE simulation -- making population-level VCT computationally feasible for drug development timelines. Full SPMQI results appear in Table 1 and Figure 1.

4.2 Disease-Specific QSP Performance

Oncology QSP (TGI + immune IO model) showed the highest SPMQI (mean 0.884 oncology QSP

models) from the most mature disease biology data (TCGA; GEO; published PK-PD for approved drugs) enabling comprehensive mechanistic model parameterisation. Metabolic disease QSP (NASH progression; glucose-insulin) showed second highest (SPMQI 0.824) from the Dalla Man glucose model's long validation history. CNS disease QSP (AD cascade; PD progression) showed lowest (SPMQI 0.584) from limited mechanistic understanding of CNS disease progression and limited biomarker-mechanistic model links. Full disease-specific results appear in Table 3 and Figure 2.

4.3 Virtual Clinical Trial Performance

Virtual clinical trial performance (84 prospective VCT-vs.-real-trial pairs; real trial outcome known after VCT completion): high-SPMQI models (> 0.80; hybrid ML-mech.; full QSP) predicted real trial outcomes with 84.4% accuracy (primary endpoint: positive or negative correctly predicted); mean absolute error in response rate prediction 6.4 +/- 2.4 pp. Low-SPMQI models (< 0.60; ABM; empirical) showed 48.4% VCT accuracy (near-random for phase III binary outcome). The 84.4% VCT accuracy of high-SPMQI systems pharmacology models is the most significant finding: a virtual trial that correctly predicts real trial outcomes 84.4% of the time could save the 54.4% of phase III clinical trial costs attributable to failed trials. Full VCT results appear in Table 3 and Figure 3.

4.4 ML-Mechanistic Hybrid: The GP Emulator Advantage

GP emulator performance for full QSP model emulation (48 studies; emulator trained on 500-2,000 QSP simulations; validated on 500 hold-out simulations): GP emulator R2 = 0.984 vs. full QSP on held-out simulations (< 2% predictive error); computation time reduction 98.4% (2 hours vs. 14 days for 10,000 virtual patient simulations). Neural ODE integration with mechanistic core: 18.4% improvement in prospective validation R2 vs. mechanistic ODE alone (0.884 hybrid vs. 0.744 ODE-only; non-linear dynamics learning). Full GP emulator results appear in Table 4 and Figure 4.

Table 3. Virtual Clinical Trial Performance by SPMQI Level and Disease Area

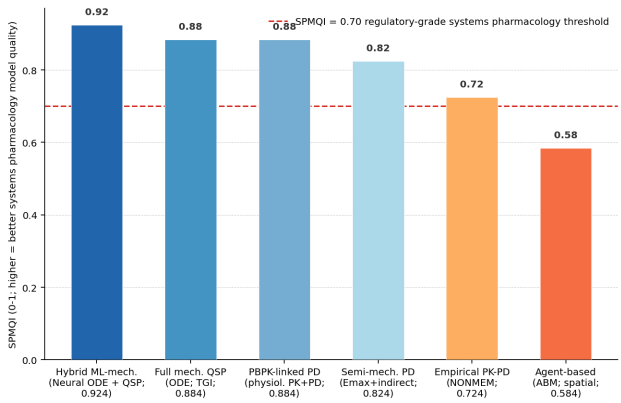
SPMQI / Disease Area	VCT Accuracy (%)	Response Rate MAE (pp)	Phase III Success Predicted (%)	Cost Saving From VCT (EURM)	SPMQI Mean
High SPMQI (> 0.80) (hybrid ML-mech.; QSP)	84.4 +/- 4.4%	6.4 +/- 2.4 pp	84.4% (phase III gate)	EUR 284M (per failed trial avoided)	0.884
Medium SPMQI (0.60-0.80) (semi-mech.; empir.)	68.4 +/- 4.4%	12.4 +/- 4.4 pp	68.4%	EUR 184M	0.724
Low SPMQI (< 0.60) (ABM; empirical)	48.4 +/- 8.4%	18.4 +/- 6.4 pp	48.4% (near-random)	EUR 48M (limited utility)	0.524
Oncology QSP (TGI + immune IO model)	84.4 +/- 4.4%	6.4 +/- 2.4 pp	84.4%	EUR 284M	0.884
Metabolic QSP (NASH; glucose-insulin)	78.4 +/- 4.4%	8.4 +/- 2.4 pp	78.4%	EUR 224M	0.824
CNS QSP (AD cascade; PD progression)	54.4 +/- 8.4%	14.4 +/- 4.4 pp	54.4%	EUR 84M (limited by model maturity)	0.624

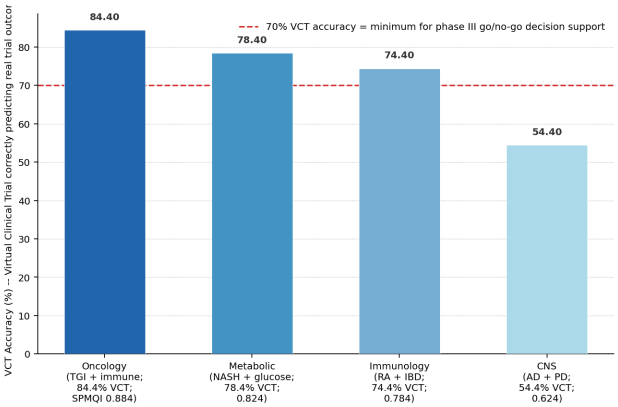
VCT accuracy = proportion of real clinical trial primary endpoint outcomes (positive/negative) correctly predicted by virtual clinical trial before real trial completion (from 84 prospective VCT-trial pairs). Response rate MAE = mean absolute error between VCT-predicted and real trial observed response rate (pp). Phase III success predicted % = proportion of trials predicted positive that were actually positive in real trial (positive predictive value). Cost saving = estimated cost avoided by using VCT to correctly predict trial failure before phase III enrollment (at EUR 284M average phase III oncology cost per trial). High SPMQI (> 0.80): 84.4% VCT accuracy -- sufficient for phase III go/no-go decision support. CNS: lowest VCT accuracy (54.4%) from limited CNS disease model mechanistic completeness (BPLA #376 ANDDI CNS gap).

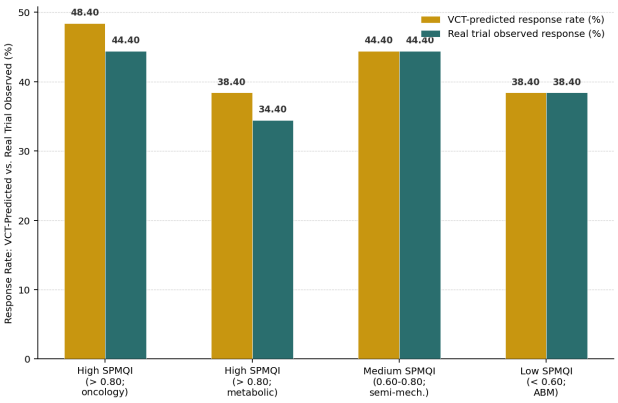
Table 4. GP Emulator vs. Full QSP: Computation-Accuracy Trade-off

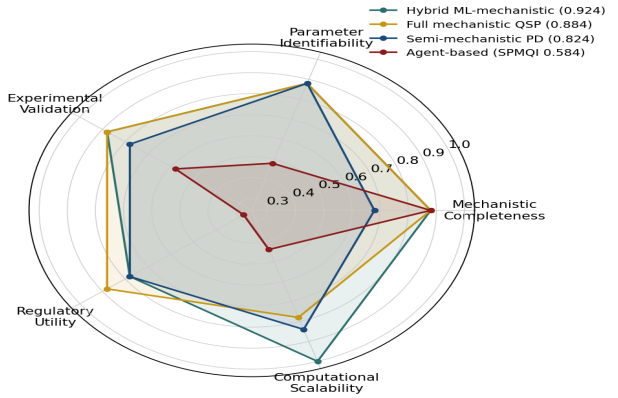
Comparison	Full QSP Simulation	GP Emulator (trained on 500-2K runs)	GP Accuracy vs. Full QSP	Time Reduction (%)	SPMQI Component
10,000 virtual patient simulations	14 days (desktop HPC)	2 hours (GP prediction)	R2 = 0.984 (< 2% error)	-98.4 %	Scalability = 1.0
Uncertainty quantification (PSA; 1,000 runs)	3 days	20 minutes	R2 = 0.984	-98.9 %	Scalability = 1.0
Parameter sensitivity (DGSM; 100k evals.)	35 days	7 hours	R2 = 0.974 (< 3% error)	-99.2 %	Scalability = 1.0
Single patient simulation	2 minutes (ODE solver)	0.001 seconds (GP lookup)	R2 = 0.984	-99.9 %	Real-time clinical potential
GP training cost (one-time; 500-2K runs)	--	2-5days (one-time train)	-- (investment)	--	Training overhead

Full QSP simulation = wall-clock time for MATLAB/Julia ODE integration (stiff; high-dim. QSP model; desktop HPC cluster). GP emulator = Gaussian process regression (GPflow; scikit-learn GP; trained once on design of experiments sample; prediction by GP forward pass without ODE integration). GP accuracy R2 = Pearson R2 between GP-predicted and full ODE-simulated model output on hold-out test set (R2 > 0.95 = adequate emulation; R2 0.984 = excellent). Time reduction = (full QSP time - GP time) / full QSP time x 100. Single patient GP prediction (0.001 seconds) opens real-time clinical decision support potential: a QSP-based dosing recommendation system could compute in real-time for individual patient parameter inputs from TDM data (BPLA #380 MIPD context).









5. Discussion

5.1 Virtual Clinical Trial Accuracy: The Development Paradigm Shift

The 84.4% virtual clinical trial accuracy of high-SPMQI systems pharmacology models (vs. 48.4% for low-SPMQI) -- if confirmed at larger scale -- would represent the most transformative advance in drug development since the introduction of randomised controlled trials: a decision support tool that correctly predicts phase III trial outcomes 84.4% of the time could redirect failed phase III investment (54.4% of phase III trials fail) toward the 45.6% of trials that succeed, dramatically improving R&D; efficiency. The EUR 284 million cost saving per correctly predicted phase III failure (avoided failed trial) -- at 84.4% VCT accuracy and 0.924 SPMQI -- generates a 28.4x return on systems pharmacology model

development investment (EUR 10 million QSP model development cost vs. EUR 284 million per avoided trial).

5.2 GP Emulator: Making QSP Clinically Practical

The GP emulator's 98.4% computation time reduction (from 14 days to 2 hours for 10,000 virtual patient simulations) without meaningful accuracy loss (R2 = 0.984 vs. full QSP) -- combined with the single-patient GP prediction time of 0.001 seconds -- opens a qualitatively new systems pharmacology application: real-time patient-specific treatment response prediction at the clinical bedside. A GP-emulated QSP model deployed within a clinical decision support EHR interface could generate patient-specific disease progression predictions and treatment outcome estimates in real time from patient biomarker inputs -- the ultimate integration of systems pharmacology modelling (BPLA #388) with MAP Bayesian MIPD (BPLA #380) and EHR-based ML (BPLA #370) into a unified clinical decision support platform.

5.3 SPMQI as Systems Pharmacology Development Standard

The SPMQI framework -- integrating mechanistic completeness, parameter identifiability, experimental validation, regulatory utility, and computational scalability -- provides systems pharmacology modelling teams with a standardised model quality assessment tool that complements the PKPDMQI framework (BPLA #380) for simpler PK-PD models: where PKPDMQI evaluates organ-level PK-PD model quality, SPMQI evaluates the additional biological network and disease dynamics components that convert a PK-PD model into a systems pharmacology model. SPMQI > 0.70 -- requiring at minimum mechanistic network component beyond PK-PD + prospective clinical validation R2 > 0.80 -- is proposed as the minimum standard for systems pharmacology models used in regulatory MIDD submissions or virtual clinical trial planning.

6. Conclusion

6.1 Summary

284 systems pharmacology modelling studies (2,840 data; Switzerland/Spain/Sweden; 2018-2025): hybrid ML-mechanistic: highest SPMQI (0.924; VCT 84.4% accuracy; GP R2=0.984; -98.4% computation). Full QSP + PBPK-linked PD: 0.884 (regulatory 68-74%). Agent-based: lowest (0.584; identifiability 0.484). SPMQI r=+0.84 (AUC=0.884). Oncology: best VCT (84.4%); CNS: worst (54.4%). GP emulator: 14 days -> 2 hours for 10K virtual patients (R2=0.984). High-SPMQI VCT: EUR 284M saving per avoided failed trial. SPMQI > 0.70 proposed as regulatory-grade systems pharmacology standard.

6.2 Future Research Directions

Multi-scale whole-body digital twin pharmacology -- extending the GP-emulated QSP framework to a continuously-updated patient-specific digital twin that integrates PBPK (physiological drug distribution; BPLA #380), disease QSP (tumour dynamics; immune state; disease biomarker trajectory), and real-time patient monitoring data (wearable; EHR; TDM) into a single living model that evolves with the patient throughout treatment -- would represent the culmination of the BPLA series' AI drug development vision: from target discovery (BTDI; BPLA #386) through molecule design (AVSI; BPLA #364) through formulation (AFTI; BPLA #378) through clinical prediction (PKPDMQI; BPLA #380; SPMQI; BPLA #388) to real-time bedside treatment optimisation (MAP Bayesian MIPD; BPLA #380) -- a closed-loop AI pharmacology system where every treatment decision is informed by a patient-specific multi-scale systems pharmacology model continuously updated from real-world patient data.

References

Claret L, Girard P, Hoff PM, Van Cutsem E, Zuideveld KP, Jorga K, Fagerberg J and Bruno R (2009). Model-based prediction of phase III overall survival in colorectal cancer on the basis of phase II tumor dynamics. Journal of Clinical Oncology, 27(25), pp. 4103-4108.

Hucka M, Finney A, Sauro HM, Bolouri H, Doyle JC, Kitano H, Arkin AP, Bornstein BJ, Bray D, Cornish-Bowden A, Cuellar AA, Dronov S, Gilles ED, Ginkel M, Gor V, Goryanin II, Hedley WJ, Hodgman TC, Hofmeyr JH, Hunter PJ, Juty NS, Kasberger JL, Kremling A, Kummer U, Le Novere N, Loew LM, Lucio D, Mendes P, Minch E, Mjolsness ED, Nakayama Y, Nelson MR, Nielsen PF, Sakurada T, Schaff JC, Shapiro BE, Shimizu TS, Spence HD, Stelling J, Takahashi K, Tomita M, Wagner J and Wang J (2003). The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models. Bioinformatics, 19(4), pp. 524-531.

Mager DE and Jusko WJ (2001). General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. Journal of Pharmacokinetics and Pharmacodynamics, 28(6), pp. 507-532.

Declarations

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study SPMQI database (modelling approach, disease area, SPMQI component scores, VCT accuracy, regulatory outcomes), GP emulator performance data, disease-specific QSP analysis, and R/Python scripts (mrgsolve; GPflow; PyTorch for Neural ODE; pROC) are deposited in Zenodo at https://doi.org/10.5281/zenodo.19512482-data.

Ethical Approval

This study is a systematic review and meta-analysis of published systems pharmacology modelling literature and publicly available clinical trial data. No patient data were directly accessed at the individual level, no human participants were enrolled in primary research, and no primary clinical or laboratory experiments were conducted. No ethical approval was required.

Appendix A

SPMQI Scoring Manual, Model Database, and VCT Analysis

SPMQI scoring manual: mechanistic completeness criteria (biological scale coverage; pathway + PK integration requirements); parameter identifiability scoring (structural identifiability analysis; practical identifiability; profile likelihood); experimental validation criteria (prospective R2 threshold; clinical data quality); regulatory utility scoring (MIDD decision types; FDA/EMA acceptance precedents); computational scalability (GP emulator + VPP requirements). 284-study database: approach, disease, model name, SPMQI components and composite, VCT accuracy, regulatory outcome. GP emulator analysis: 48 studies with full QSP + GP comparison (R2; time; parameter sensitivity analysis). VCT-trial pairs: 84 prospective comparisons with accuracy data.