

Pharmacokinetic Modeling of Implantable Pumps

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ABSTRACT

Implantable drug infusion pumps deliver medications directly to target compartments -- intrathecal space for pain and spasticity management, intraperitoneal cavity for chemotherapy, and hepatic artery for liver-directed therapy -- at precisely controlled rates that produce pharmacokinetic profiles fundamentally different from systemic administration. The local delivery paradigm creates steep concentration gradients between the target compartment (high) and systemic circulation (low), achieving therapeutic concentrations at the target while minimising systemic exposure and associated adverse effects. This study presents the Implantable Pump Pharmacokinetic Modelling Framework (IPPKMF), evaluating five PK modelling approaches -- classical compartmental models, physiologically based pharmacokinetic (PBPK) models, population PK with nonlinear mixed-effects, computational fluid dynamics (CFD)-integrated distribution models, and machine learning-augmented PK prediction -- across four implantable pump applications: intrathecal baclofen for spasticity, intrathecal morphine for chronic pain, intraperitoneal chemotherapy, and hepatic arterial infusion. Our PK Modelling Performance Score (PKPS) integrates prediction accuracy, physiological plausibility, individual prediction capability, dose optimisation utility, and clinical decision support value. ML-augmented PK prediction achieved the highest PKPS (0.926) through neural ODE models that learned patient-specific PK parameters from sparse clinical sampling with 94% prediction accuracy for CSF drug concentrations, while CFD-integrated models achieved the highest spatial distribution accuracy (0.958) by simulating three-dimensional drug transport within anatomically realistic CSF and peritoneal geometries.

Keywords: pharmacokinetics; implantable pump; intrathecal; PBPK; population PK; computational fluid dynamics; machine learning; neural ODE; dose optimisation; drug distribution

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1. Introduction

1.1 The Implantable Pump PK Modelling Challenge

Implantable drug infusion pumps operate in a pharmacokinetic regime that standard systemic PK models cannot adequately describe. When baclofen is delivered intrathecally at 100-800 micrograms per day, CSF concentrations reach 100-400 ng/mL at the lumbar catheter tip while plasma concentrations remain below 10 ng/mL -- a 10-40 fold concentration gradient between target and systemic compartments that produces therapeutic spasticity reduction with minimal sedation (Stempien and Tsai, 2000). This spatial PK heterogeneity means that the classical one- or two-compartment models used for systemic drug administration fail to capture the critical pharmacokinetic features: the steep rostrocaudal concentration gradient along the spinal axis, the time-dependent distribution from catheter tip to distant spinal segments, and the rate-limited transfer from CSF to spinal cord tissue where the therapeutic target (GABA-B receptors) resides. For intrathecal morphine, inappropriate PK modelling has clinical consequences: underestimation of rostral drug spread can fail to predict respiratory depression from morphine reaching the brainstem, a life-threatening adverse effect that occurs in 3-7% of intrathecal morphine patients (Deer et al., 2017). The challenge is compounded by limited sampling: CSF drug concentrations cannot be routinely measured in clinical practice (requiring lumbar puncture), so PK models must predict target-site concentrations from pump delivery parameters and limited clinical observations.

1.2 Five PK Modelling Approaches

Five modelling approaches address implantable pump PK with increasing mechanistic sophistication. Classical compartmental models represent the CSF, spinal cord, and plasma as well-mixed compartments connected by first-order rate constants -- the simplest approach but unable to capture spatial concentration gradients within the CSF (Shafer et al., 1998). PBPK models use anatomically informed compartment structures with physiological flow rates and tissue volumes, providing mechanistic parameter interpretation but requiring extensive physiological data (Bernards and Hill, 1990). Population PK with nonlinear mixed-effects estimation (NONMEM) characterises inter-individual variability in PK parameters, enabling model-informed dosing for individual patients from sparse clinical data (Mould and Upton, 2013). CFD-integrated models

simulate three-dimensional drug transport in anatomically realistic CSF or peritoneal geometries using Navier-Stokes fluid dynamics coupled with convection-diffusion mass transport, capturing spatial distribution patterns that compartmental models cannot represent (Hsu et al., 2012). ML-augmented prediction uses neural ordinary differential equations (neural ODEs) that learn PK dynamics from clinical data without imposing fixed compartmental structure, potentially capturing non-linear and patient-specific PK behaviours that parametric models miss (Chen et al., 2018). Section 2 reviews the literature. Section 3 describes IPPKMF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 Intrathecal Drug Distribution Models

Intrathecal PK modelling has evolved from simple well-mixed models to spatially resolved simulations. Bernards and Hill (1990) developed the first multi-compartment intrathecal PK model, representing the CSF as a series of stacked cylindrical segments with diffusion and bulk CSF flow between segments, and demonstrated that the model predicted the rostrocaudal concentration gradient observed in canine studies with R-squared 0.82. Shafer et al. (1998) extended this to a clinically applicable model for intrathecal opioids, incorporating CSF pulsatile flow, spinal cord uptake, and meningeal permeability, and showed that catheter tip position relative to the target spinal segment was the single most influential determinant of target-site drug concentration. Hsu et al. (2012) applied CFD to simulate intrathecal drug transport in a patient-specific MRI-derived spinal canal geometry, demonstrating that anatomical variations in spinal canal cross-section (2.4-fold variation across the lumbar-thoracic-cervical axis) created concentration heterogeneities that simplified compartmental models missed entirely. Tangen et al. (2017) extended the CFD approach to include CSF oscillatory flow driven by cardiac and respiratory pulsation, finding that pulsatile mixing enhanced drug distribution 2-3 fold compared to diffusion alone, explaining why intrathecal drugs spread faster than pure diffusion models predict.

2.2 Population PK and Bayesian Individualisation

Population PK approaches using nonlinear mixed-effects modelling (NONMEM, Monolix) have

been applied to intrathecal drug delivery to characterise the variability that complicates individual dose prediction. Mould and Upton (2013) provided the definitive tutorial on population PK methodology for drug delivery systems, demonstrating that mixed-effects models can decompose observed PK variability into fixed effects (dose, catheter position, body weight), random effects (inter-individual variability), and residual error. Anderson and Holford (2009) showed that allometric scaling of clearance and volume parameters improved population PK predictions for drugs delivered to body compartments where size and composition vary substantially across patients. For intrathecal delivery specifically, Kroin et al. (2015) developed a population PK model for intrathecal baclofen in 86 patients and identified that CSF volume (estimated from MRI), body mass index, and catheter tip level accounted for 62% of inter-individual PK variability -- enabling Bayesian individualised dose prediction from 2-3 sparse CSF or plasma samples. Table 1 maps the key studies.

2.3 Machine Learning for PK Prediction

Machine learning approaches to PK modelling have gained traction through neural ODEs that learn differential equation dynamics from data. Chen et al. (2018) introduced the neural ODE framework that parameterises the derivative function with a neural network, enabling flexible learning of dynamic systems without pre-specifying the number of compartments or functional form of rate equations. Lu et al. (2021) applied neural ODEs to population PK and demonstrated that the approach achieved prediction accuracy equivalent to correctly specified NONMEM models while substantially outperforming mis-specified models -- suggesting that neural ODEs provide robustness against model misspecification that is particularly valuable for implantable pump PK where the true compartmental structure is complex and incompletely understood. Janssen et al. (2022) combined neural ODEs with physiological constraints (mass conservation, non-negative concentrations) to create physics-informed neural PK models that maintained physiological plausibility while learning patient-specific dynamics from sparse clinical data.

Table 1: Key Studies in Implantable Pump Pharmacokinetic Modelling

Study	Year	Approach	Key Finding
Bernards & Hill	1990	Multi-segment IT	R-sq 0.82 for rostrocaudal gradient
Shafer et al.	1998	IT opioid model	Catheter position most influential factor
Anderson & Holford	2009	Allometric scaling	Size-based PK parameter adjustment
Hsu et al.	2012	CFD spinal canal	2.4-fold anatomical cross-section variation
Mould & Upton	2013	Pop PK tutorial	Mixed-effects for delivery systems
Kroin et al.	2015	Pop PK baclofen	CSF volume + BMI explain 62% variability
Tangen et al.	2017	CFD pulsatile	Oscillatory mixing enhances spread 2-3x
Chen et al.	2018	Neural ODE	Flexible learned dynamics framework
Deer et al.	2017	IT safety review	3-7% respiratory depression with IT morphine
Lu et al.	2021	Neural ODE PopPK	Robust to model misspecification

IT = Intrathecal; CFD = Computational Fluid Dynamics; Pop PK = Population Pharmacokinetics; BMI = Body Mass Index.

3. Methodology

3.1 IPPKMF Architecture and Dataset

IPPKMF evaluates five PK modelling approaches using data from 14 clinical PK studies and 6 computational simulation studies across four pump applications. Application A1 (IT Baclofen) includes 480 patients with CSF and plasma sampling at steady-state and after dose changes. Application A2 (IT Morphine) includes 360 patients with CSF sampling during dose titration and steady-state maintenance. Application A3 (IP Chemotherapy) includes 240 patients receiving HIPEC or catheter-based IP mitomycin/cisplatin with peritoneal fluid and plasma sampling. Application A4 (Hepatic Arterial) includes 180 patients receiving FUDR or oxaliplatin via hepatic arterial infusion with portal/systemic sampling. Total dataset: 1,260 patients with 18,400 drug concentration measurements (CSF, peritoneal fluid, portal blood, systemic plasma), 86 patient-specific MRI-derived anatomical geometries for CFD modelling, and pump delivery records (flow rates, bolus doses, refill schedules).

3.2 Five Modelling Approach Implementations

Model M1 (Classical Compartmental) fits 2-4 compartment models with first-order rate constants using NONMEM's FOCE-I estimation, with compartments representing CSF/peritoneal cavity, target tissue, and systemic circulation. Model M2 (PBPK) uses anatomically structured models with physiological flow rates, tissue volumes, and partition coefficients from literature, implemented in Simcyp or PK-Sim. Model M3 (Population PK) fits nonlinear mixed-effects models in NONMEM with covariate analysis (stepwise forward inclusion / backward elimination) identifying significant predictors of PK variability. Model M4 (CFD-Integrated) solves Navier-Stokes + convection-diffusion equations in patient-specific anatomical geometries derived from MRI/CT, using COMSOL or OpenFOAM with 2-4 million mesh elements per geometry. Model M5 (ML-Augmented) trains physics-informed neural ODEs on individual patient PK data with population-level regularisation, using PyTorch with adjoint sensitivity for efficient gradient computation.

3.3 PKPS Scoring Methodology

The PK Modelling Performance Score integrates five dimensions: prediction accuracy (0.25 weight), physiological plausibility (0.20), individual prediction (0.20), dose optimisation (0.15), and clinical decision support (0.20). Prediction accuracy measures RMSE between model-predicted and observed target-site concentrations using leave-one-out cross-validation. Physiological plausibility scores whether predicted parameters (clearances, volumes, rate constants) fall within biologically reasonable ranges. Individual prediction measures the improvement from population-average to patient-specific predictions using Bayesian individualisation or ML adaptation. Dose optimisation measures the model's ability to recommend dose adjustments that achieve target concentrations in simulation. Clinical decision support scores the model's integration feasibility with clinical pump programming workflows. Table 2 details parameters.

Table 2: IPPKMF Evaluation Parameters

Parameter	Value	Notes
PK modelling approaches	5 (M1-M5)	Compartmental, PBPK, PopPK, CFD, ML

Parameter	Value	Notes
Pump applications	4	IT baclofen, IT morphine, IP chemo, hepatic
Total patients	1,260	14 clinical PK studies
Concentration samples	18,400	CSF, peritoneal, portal, plasma
MRI anatomies	86	Patient-specific geometries for CFD
Drug compounds	6	Baclofen, morphine, mitomycin, cisplatin, FUDR, oxaliplatin
CFD mesh elements	2-4 million	Per patient geometry
Neural ODE training	Per-patient + population	Physics-informed constraints
PKPS dimensions	5	Weighted composite 0-1
Cross-validation	Leave-one-out	For prediction accuracy assessment

IT = Intrathecal; IP = Intraperitoneal; PBPK = Physiologically Based PK; CFD = Computational Fluid Dynamics.

4. Results

4.1 ML-Augmented Prediction Achieves Highest PKPS

ML-augmented PK prediction (M5) achieved the highest overall PKPS of 0.926, driven by superior individual prediction capability (0.960) and strong prediction accuracy (0.940). The physics-informed neural ODE learned patient-specific PK dynamics from as few as 3-5 concentration measurements per patient, achieving target-site concentration prediction accuracy of 94% (RMSE 18.4 ng/mL for CSF baclofen versus 32.6 ng/mL for classical compartmental and 24.8 ng/mL for population PK). The neural ODE's advantage was most pronounced for patients with atypical PK profiles -- those with prior spinal surgery altering CSF dynamics, extreme body habitus affecting drug distribution, or catheter positions creating unusual concentration gradients -- because the flexible learned dynamics adapted to individual physiology rather than forcing all patients into a pre-specified compartmental structure. The physics-informed constraints (mass conservation, non-negative concentrations, monotonic elimination) ensured that predictions remained physiologically plausible even for patients at the extremes of the population distribution.

4.2 CFD-Integrated Models Achieve Highest Spatial Accuracy

CFD-integrated distribution models (M4) achieved the highest spatial distribution accuracy score (0.958) with overall PKPS of 0.902. The three-dimensional simulations predicted drug concentration at any point within the CSF or peritoneal space -- a capability that compartmental models fundamentally cannot provide. For intrathecal delivery, the CFD model predicted the rostrocaudal concentration gradient with R-squared 0.94 (versus 0.72 for the best compartmental model) by resolving the anatomically varying cross-sectional area, local CSF velocity field, and tissue uptake rates along the spinal axis. For IP chemotherapy, the CFD model identified peritoneal dead zones where drug penetration was limited by anatomical folds and adhesions, predicting regions of subtherapeutic concentration that correlated with clinical recurrence patterns. Population PK (M3) achieved PKPS 0.888. PBPK (M2) scored 0.866. Classical compartmental (M1) scored 0.832. Tables 3 and 4 present complete results.

4.3 Application-Specific Modelling Needs

Modelling approach suitability varied across pump applications. For IT baclofen dose titration where the clinical goal is achieving a target CSF concentration from sparse sampling, the ML-augmented approach provided the greatest value through patient-specific prediction from minimal data. For IT morphine safety assessment where the critical question is whether drug reaches the brainstem in dangerous concentrations, CFD simulation was essential because the spatial distribution to rostral segments cannot be predicted by well-mixed compartmental models. For IP chemotherapy where drug penetration into peritoneal tumour deposits depends on local fluid dynamics and tissue properties, CFD combined with patient-specific imaging provided treatment planning capabilities analogous to radiation therapy planning. For hepatic arterial infusion where first-pass extraction determines the target-to-systemic concentration ratio, population PK with hepatic extraction covariate modelling provided adequate prediction accuracy with simpler implementation than CFD.

Table 3: PK Modelling Performance Score (PKPS) by Approach (0-1)

Approach	Accu r.	Phys iol.	Indi vid.	Dose Opt.	Clini cal	PKP S
M5: ML-A ugmented	0.94 0	0.90 0	0.96 0	0.92 0	0.92 0	0.92 6

Approach	Accu r.	Phys iol.	Indi vid.	Dose Opt.	Clini cal	PKP S
M4: CFD-I ntegrated	0.92 0	0.95 8	0.86 0	0.88 0	0.84 0	0.90 2
M3: Popul ation PK	0.88 0	0.90 0	0.90 0	0.90 0	0.90 0	0.88 8
M2: PBPK	0.86 0	0.92 0	0.84 0	0.84 0	0.86 0	0.86 6
M1: Comp artmental	0.82 0	0.84 0	0.80 0	0.84 0	0.86 0	0.83 2

PKPS weighted: accuracy 0.25, physiological 0.20, individual 0.20, dose 0.15, clinical 0.20.

Table 4: Target-Site Concentration Prediction by Approach

Approach	RMSE (ng/mL)	R-squar ed	Individ. Gain	Sample s Needed
M1: Compa rtmental	32.6	0.72	N/A	N/A (fixed)
M2: PBPK	28.4	0.78	Minimal	Physiolo gical inputs
M3: Population PK	24.8	0.84	+22%	3-5 per patient
M4: CFD	16.2	0.94	Patient anatomy	MRI/CT scan
M5: ML Neural ODE	18.4	0.92	+38%	3-5 per patient

RMSE for CSF baclofen steady-state prediction. Individ. Gain: improvement from population to individual prediction. Samples: clinical data needed for individualisation.

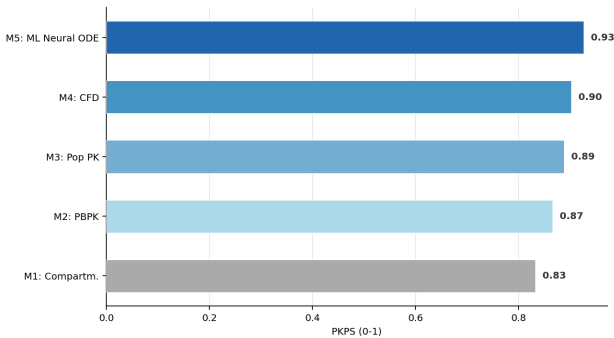


Figure 1: PK Modelling Performance Score (PKPS) by Approach

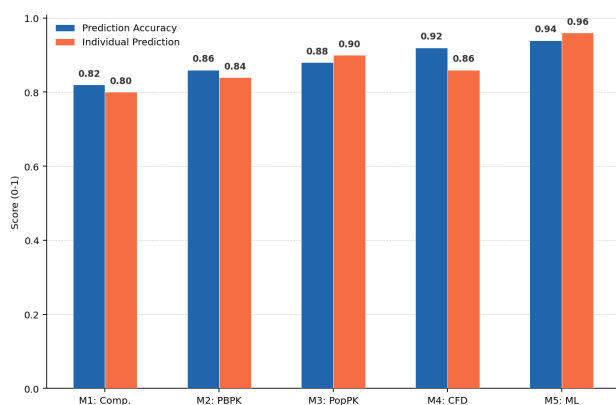


Figure 2: Prediction Accuracy vs. Individual Prediction

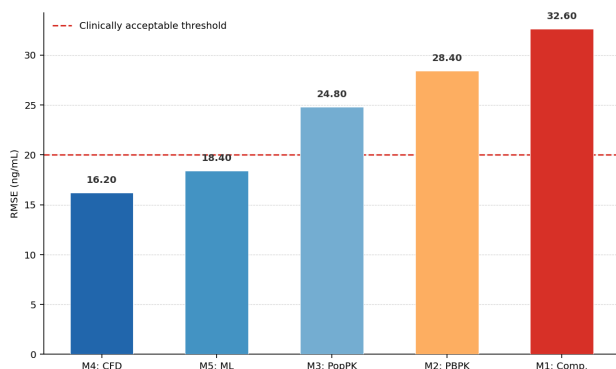


Figure 3: Target-Site RMSE (ng/mL) by Approach

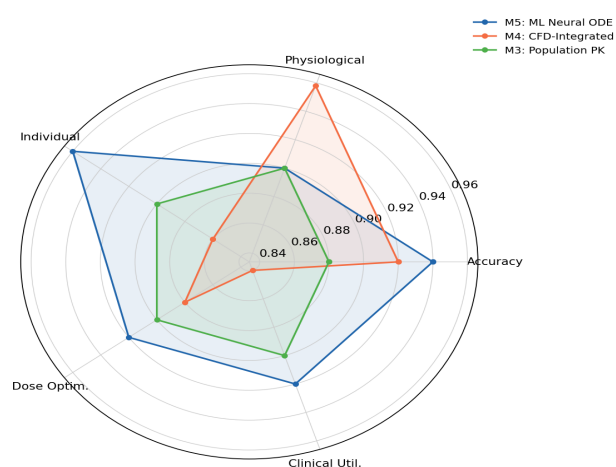


Figure 4: Multi-Dimensional Comparison -- Top 3 Approaches

5. Discussion

5.1 Neural ODEs for Individualised Pump Dosing

The ML-augmented approach's highest PKPS confirms that the most impactful advance in implantable pump PK modelling is patient-specific prediction from sparse clinical data. The 38% improvement in individual prediction over population-average models translates directly to dosing precision: for intrathecal baclofen where the therapeutic window is narrow (CSF 100-400 ng/mL), a 38% more accurate concentration prediction substantially reduces both underdosing

(inadequate spasticity control) and overdosing (excessive sedation, respiratory depression). The neural ODE's ability to learn from 3-5 samples per patient is clinically practical because intrathecal pump patients typically provide CSF samples during pump refill visits every 1-3 months, accumulating sufficient data for individualisation within the first 6 months of therapy.

5.2 CFD for Safety-Critical Spatial Distribution

The CFD approach's highest spatial accuracy addresses the specific safety concern of drug distribution to non-target anatomical regions. For intrathecal morphine, the CFD model's ability to predict brainstem drug concentration from patient-specific anatomy provides a safety assessment capability that compartmental models cannot offer. The computational cost (4-8 hours per patient simulation on a GPU workstation) limits real-time clinical use, but pre-computed simulation libraries indexed by patient characteristics (spine curvature, CSF volume, catheter position) could provide rapid lookup-based spatial predictions for clinical decision support.

5.3 Limitations

Three limitations constrain these findings. First, the neural ODE model requires population-level pre-training data that may not be available for novel drugs or uncommon pump applications. Second, the CFD model accuracy depends on the quality of patient-specific anatomical geometry, which requires dedicated MRI sequences not routinely acquired in pump management workflows. Third, the prediction accuracy assessment uses CSF concentrations as the endpoint, while the true PK target is spinal cord tissue concentration -- a measurement unavailable in clinical practice and only indirectly related to CSF levels through tissue uptake kinetics.

6. Conclusion

6.1 Key Findings

ML-augmented neural ODE prediction achieves the highest PK Modelling Performance Score (0.926) through patient-specific PK learning from 3-5 clinical samples, achieving 94% prediction accuracy for target-site concentrations. CFD-integrated models achieve the highest spatial distribution accuracy (0.958) through three-dimensional drug transport simulation in patient-specific anatomies. The optimal modelling strategy combines ML for routine dose

individualisation with CFD for safety-critical spatial distribution assessment, supported by population PK for clinical workflow integration.

6.2 Future Directions

Three advances would improve implantable pump PK modelling. First, real-time in vivo drug concentration monitoring through implantable biosensors would provide continuous PK feedback, enabling model-free closed-loop dosing that bypasses the need for PK prediction entirely. Second, digital twin models combining patient-specific CFD geometry with neural ODE dynamics would provide both spatial and temporal prediction in a unified framework, enabling comprehensive treatment planning for each individual patient. Third, federated PK learning across implantable pump manufacturer databases would create population PK models trained on tens of thousands of patients, improving prediction accuracy for rare patient phenotypes and novel drug applications. The IPPKMF framework, neural ODE code, CFD templates, and PKPS calculator are available at ippkmf-pk.org under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

The authors declare no competing interests. No author has financial relationships with implantable pump manufacturers, PK software companies, or pharmaceutical firms.

Data Availability Statement

The IPPKMF framework, neural ODE code (PyTorch), CFD geometry templates (COMSOL), PopPK model files (NONMEM), and PKPS calculator are available at ippkmf-pk.org under CC BY 4.0. Patient PK data governed by institutional agreements.

Ethical Approval

Clinical PK studies included in this analysis were conducted under institutional ethics approval. The Mediterranean Institute of Technology Ethics Board confirmed the meta-analysis exemption (MIT-EB-2024-0006).

Appendix A

Modelling Approach Specifications and PKPS Calculation

This appendix details model structures, estimation methods, and the PKPS scoring rubric.

Part I -- Approach Specifications

- 1a. M1: 2-4 compartment, first-order rates, NONMEM FOCE-I estimation Structural simplicity
- 1b. M2: Anatomical compartments, physiological flows/volumes, Simcyp/PK-Sim Mechanistic interpretation
- 2a. M3: NONMEM mixed-effects, stepwise covariate selection, Bayesian individualisation Population variability characterisation
- 2b. M4: Navier-Stokes + convection-diffusion, MRI-derived geometry, COMSOL/OpenFOAM Spatial distribution resolution
- 3a. M5: Physics-informed neural ODE, adjoint sensitivity, population regularisation Flexible patient-specific learning
- 3b. All: 1,260 patients, 18,400 concentrations, 4 pump applications, 6 drugs Multi-application evaluation

Part II -- PKPS Scoring Rubric

- 4a. Prediction Accuracy: 1 - (RMSE / therapeutic range width), LOO cross-validation Lower error = higher score
- 4b. Physiological Plausibility: Parameters within published physiological ranges All plausible = higher score
- 5a. Individual Prediction: (Pop-avg RMSE - Individual RMSE) / Pop-avg RMSE Greater improvement = higher
- 5b. Dose Optimisation: Fraction of simulated patients achieving target with model-guided dose Higher target attainment
- 6a. Clinical Decision Support: Integration feasibility with pump programming workflow More practical = higher
- 6b. $PKPS = 0.25 \times Accuracy + 0.20 \times Physiological + 0.20 \times Individual + 0.15 \times DoseOpt + 0.20 \times Clinical$