

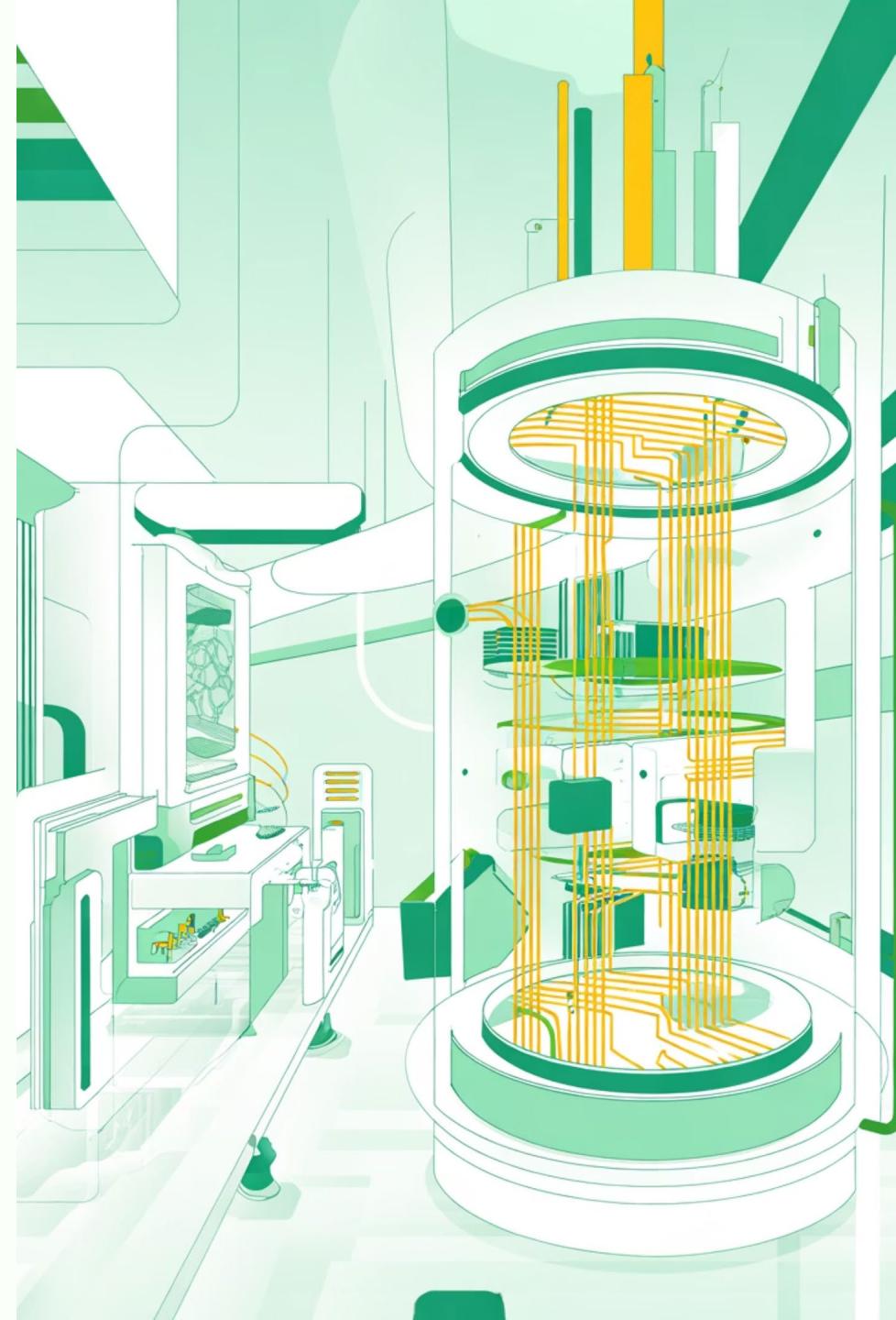
Quantum-Enhanced Pharmacometric Modeling

Team Entangled Angle

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Integrating Variational Quantum Circuits into SAEM for Improved PK/PD Parameter Inference

Aim: Use quantum variational circuits to enhance parameter sampling in nonlinear mixed-effects effects pharmacokinetic–pharmacodynamic modeling, improving exploration of complex posterior posterior distributions and enabling more efficient parameter estimation.



Mechanistic PK/PD Modeling

An ODE-Based Approach for Drug Development

Integrating mechanistic frameworks with Monte Carlo simulations for robust drug development

$$\frac{dy}{dt} = f(y, t, p)$$

Research Objective & Dataset Overview

Research Objective

-  Establish link between administered drug doses and measurable outcomes
-  Simulate realistic treatment scenarios and develop informed dosing recommendations
-  Investigate how drugs move through the body (PK) and their effects (PD)

Key Challenge:

Connecting complex physiological processes to observable measurements while accounting for individual variability

Dataset Structure

Dimensions:

2820 rows × 11 columns

Column	Description	Role in Modeling
ID	Subject identifier	Tracks repeated measures
BW	Body weight (kg)	PK covariate
COMED	Concomitant medication	PD covariate
DOSE	Administered dose (mg)	Primary driver

TIME PK Measurements

Drug concentrations in plasma

PD Outcomes

Biomarker levels

Modeling Framework Rationale

✓ ODE-based Framework

- ✓ Mechanistic link between drug administration, concentration, and effect
- ✓ Scientifically interpretable models grounded in pharmacometric research
- ✓ Computationally efficient once formulated
- ✓ Aligns with operations research principles of simplifying complex systems

VS

Machine Learning Approach

- ✗ Focuses on mapping inputs to outputs rather than modeling dynamics
- ✗ Black-box methods lack mechanistic interpretability
- ✗ Difficult to reason about population-level behaviors
- ✗ Not designed to reflect physiological processes like clearance or compartmental distribution

Monte Carlo Integration

- ✗ Accounts for variability across patients and clinical scenarios

- ✗ Explores range of possible outcomes under uncertainty

💡 Why Our Approach?

Our principled, ODE-based framework with Monte Carlo sampling provides a robust and interpretable tool that balances complexity with simplicity. This approach allows for accurate capture of real-world variability while maintaining clear interpretation and meaningful clinical insights.

Key Exploratory Findings: PK Structure



2-Compartment Model

- ✓ Non-parallel elimination curves ($R^2 = 0.020$)
- ✓ Biphasic elimination profile



First-Order Absorption

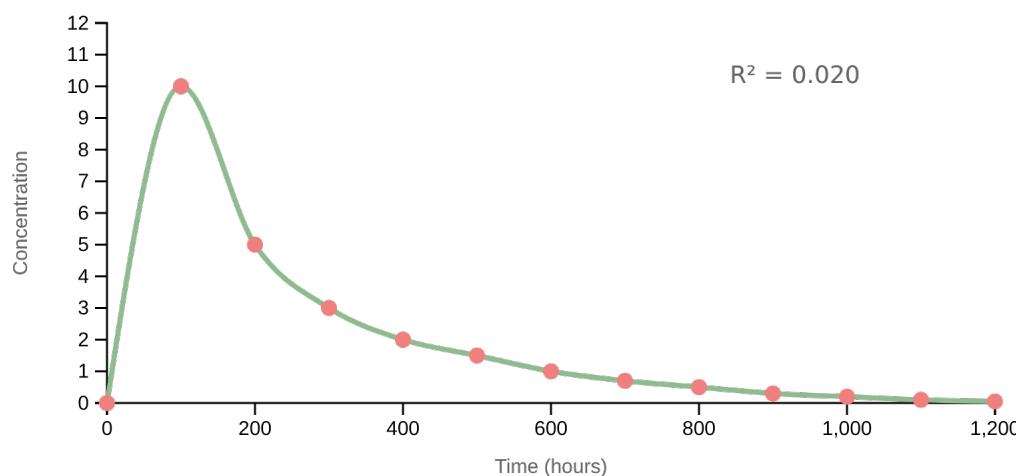
- ✓ Rapid rise within first 2 hours
- ✓ No lag time or plateau



Body Weight Effects

- ✓ Strong correlation ($r = 0.680$)
- ✓ Allometric scaling ($BW^{1.33}$)

Biphasic Elimination Profile



- Parallel lines = mono-exponential decay ($R^2 = 0.020$)
- Non-parallel curves = 2-compartment model

Key Insights

- 💡 Dose-proportional increases across 1, 3, and 10 mg doses confirm linear pharmacokinetics
- 💡 Peak concentrations at 400 hours indicate slow accumulation to steady-state
- 💡 37.5% CV confirms substantial inter-subject variability
- 💡 52% of clearance variability explained by allometric scaling

Key Exploratory Findings: PD Linkage



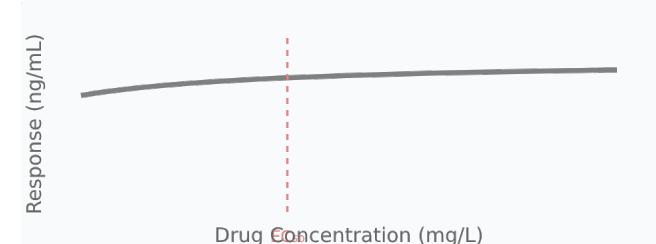
Indirect Response Mechanism



- ✓ Counterclockwise hysteresis loop confirms time delay between PK and PD
- ✓ Moderate PK-PD correlation (-0.612) supports indirect link
- ✓ Need for effect compartment in model structure



Emax Relationship



EC_{50} :	5.779 mg/L
E_0 :	7.94 ng/mL
E_{max} :	10.36 ng/mL

Classic Emax inhibitory model supports biomarker suppression profile



COMED Effects



- ✓ Non-significant $p = 0.2368$; wider variability in suppression
- ✓ COMED increases baseline biomarker production (KIN)
- ✓ Mechanistic insight: COMED likely affects KIN parameter



Key Insight: The 100-hour temporal lag between peak PK (400h) and PD (500h) justifies inclusion of an effect compartment with equilibration rate constant (KE0) in the model.

Covariate Impact Analysis



Body Weight (BW) Impact



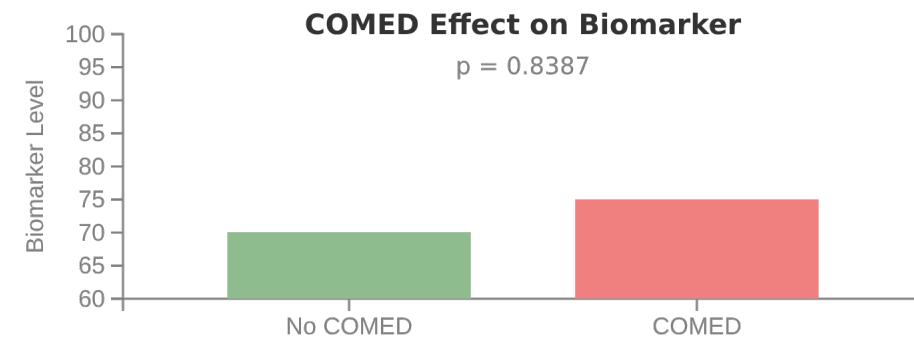
- ✓ Strong positive correlation with clearance ($r = 0.680$)
- ✓ Allometric fit (BW, $R^2 = 0.522$) explains 52% of clearance variability
- ✓ Decision: Include allometric scaling for CL and V

Model Implementation:

$$CL = CL_{typical} \times (BW/70)$$



Concomitant Medication (COMED)



- ✓ Minimal effect on PK clearance ($p = 0.8387$)
- ✓ Affects PD response, likely by increasing baseline biomarker production (KIN)
- ✓ Shows wider variability and slightly lower median suppression

Model Insight:

COMED increases baseline biomarker production (KIN), validating its inclusion as a covariate on KIN in the indirect response model

Final Integrated Model Structure

Model Architecture

- Four-state compartmental model
- ➡ ODE-based framework with Monte Carlo sampling
- ☒ Log-normal IIV on all parameters

Mathematical Structure

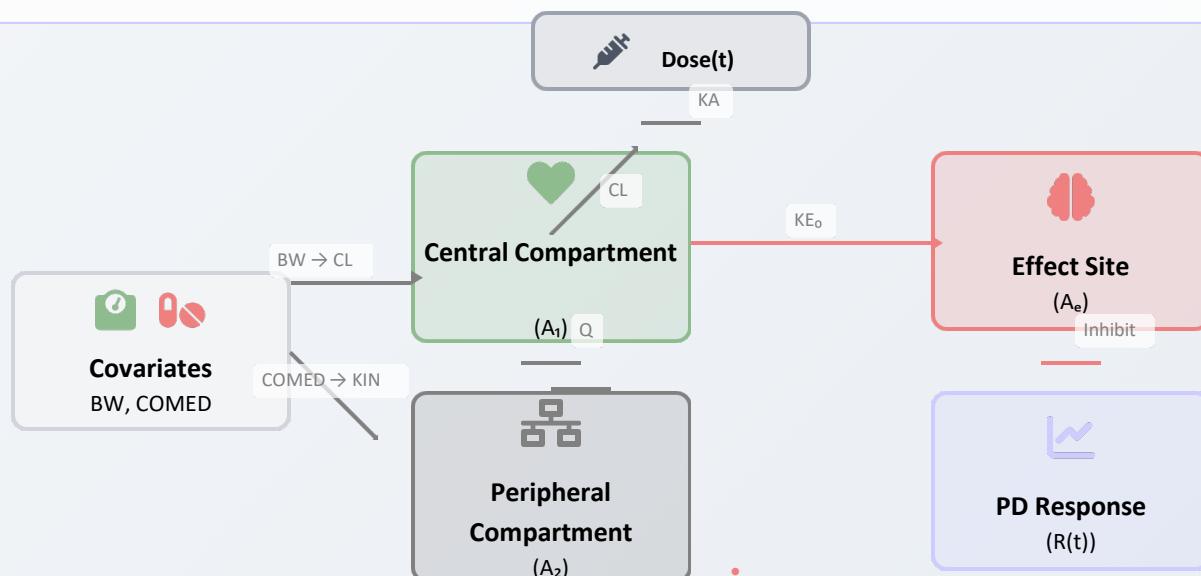
PK Component:

$$\begin{aligned} \frac{dA_1}{dt} &= KA \cdot \text{Dose}(t) - CL_i \cdot A_1 / V_{1i} \\ \frac{dA_2}{dt} &= Q \cdot (A_1 / V_{1i} - A_2 / V_{2i}) \end{aligned}$$

Effect Site:

$$\begin{aligned} \frac{dA_e}{dt} &= KE_o \cdot (A_1 - A_e) \\ R(t) &= KIN_i \cdot (1 - IMAX \cdot C_e / (IC_{50} + C_e)) \end{aligned}$$

Integrated PK/PD Model Structure



PD Component

Indirect response model

Effect compartment (KE_o)

Emax relationship ($EC_{50} = 5.78$)

Variability Structure

- Log-normal IIV on parameters
- Proportional error (PK: 20%, PD: 15%)
- Monte Carlo sampling

Clinical Impact & Future Directions



Clinical Impact

- ✓ Provides robust framework for accurate dose optimization
- ✓ Balance between model complexity and interpretability
- ✓ Enables simulation of treatment scenarios with meaningful clinical insights
- ✓ Supports regulatory-compliant modeling with mechanistic interpretability

💡 Key Achievement:

Integrated framework that maintains scientific rigor while enabling clinical decision-making



Future Directions

- Explore quantum-enhanced methods to improve predictions
- Expand model complexity to capture additional biological mechanisms
- Integrate with machine learning approaches for improved accuracy
- Apply to broader range of drug development scenarios

🧪 Quantum Approach:

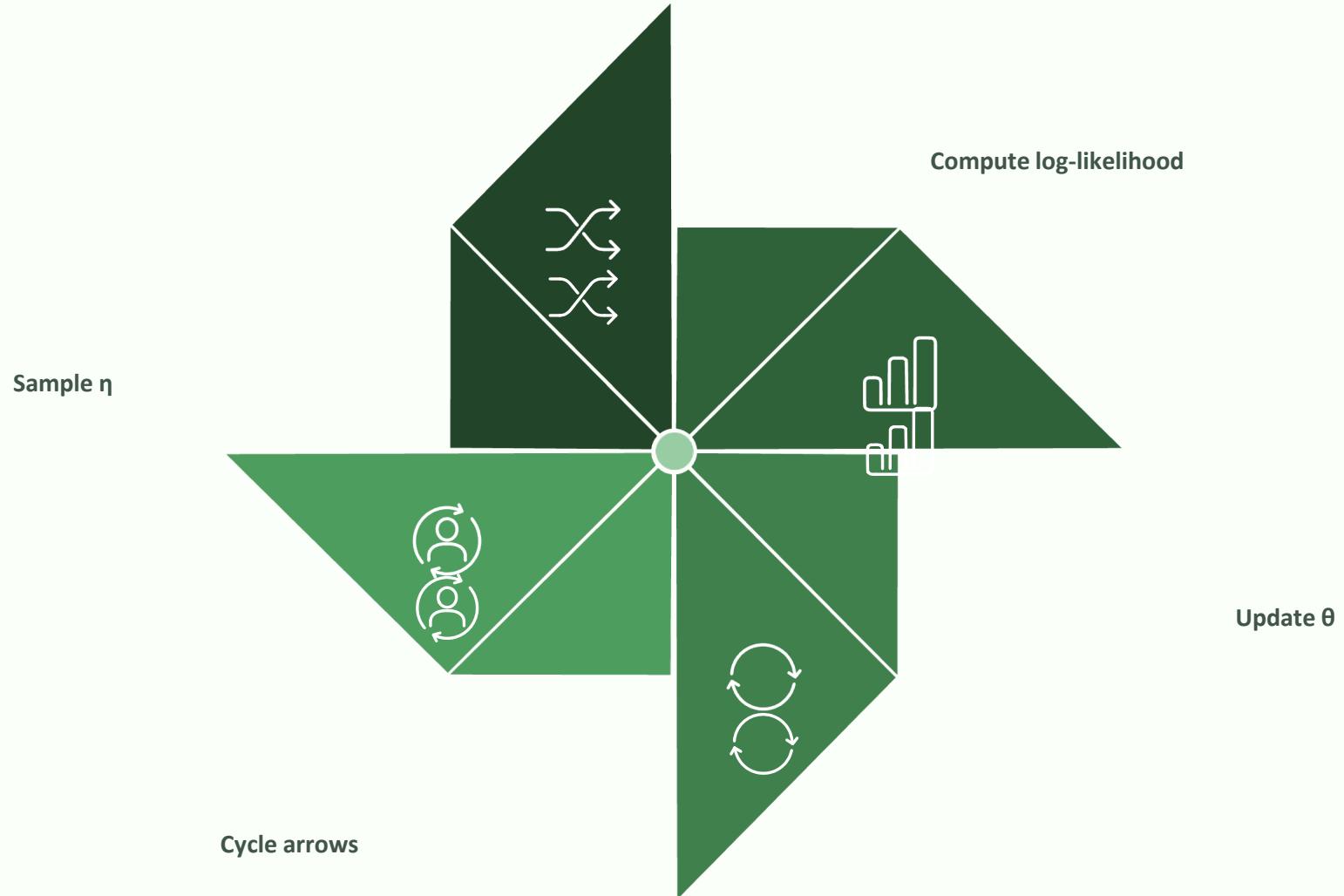
Leverage quantum computing for enhanced simulation capabilities and improved generalizability

“

This foundational work sets the stage for future optimization efforts and advanced methodologies to improve predictions in drug development.

Classical SAEM Framework

The stochastic approximation expectation–maximisation (SAEM) algorithm iteratively refines population PK/PD parameters through a cycle of random-effects generation, likelihood evaluation, and parameter evaluation, and parameter updates.



Classical limitation: Random effects proposals typically drawn from simple Gaussian distributions—inefficient for correlated or multimodal posteriors, leading to poor chain mixing and slow convergence.

Motivation for Quantum Enhancement

Classical Gaussian sampling struggles to capture the complex joint distributions inherent in population PK/PD models. Parameter correlations, skewed distributions, and multimodality remain poorly approximated.

Poor Mixing

Random walk behaviour leads to high high autocorrelation and slow exploration.

Slow Convergence

Inefficient proposals require many iterations to reach stable estimates.

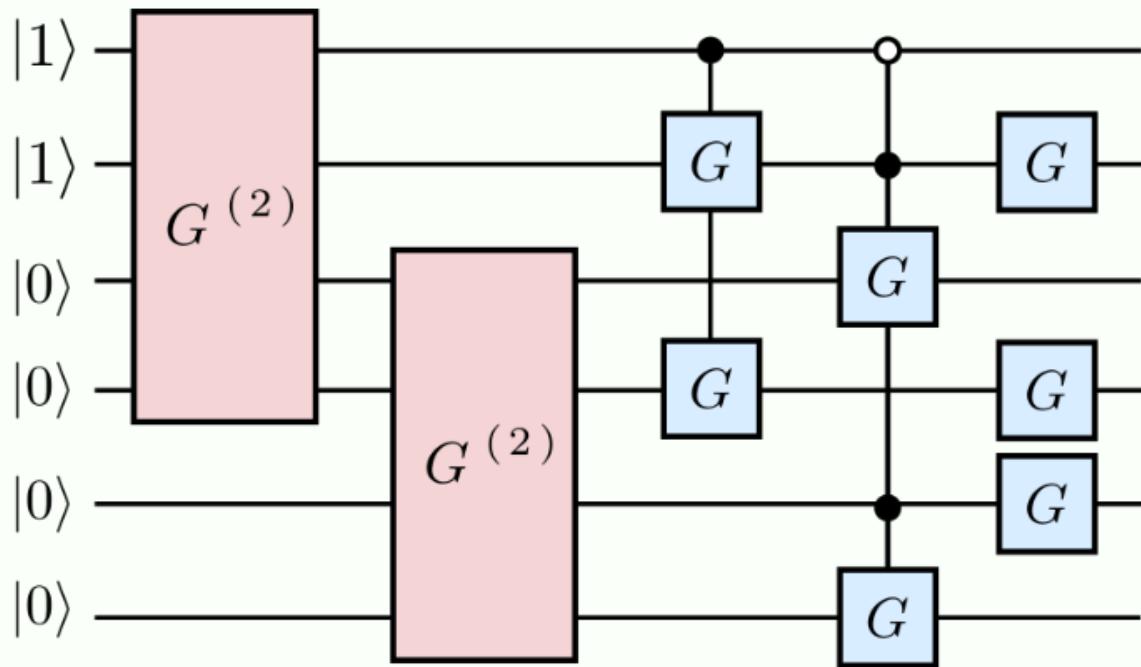
Missed Correlations

Independent Gaussian components fail to encode physiological parameter dependencies.

Solution: Variational Quantum Circuits (VQCs) learn expressive, correlated probability distributions over parameter space.

Variational Quantum Circuit

Design



A 6-qubit ansatz encodes the joint distribution of key PK/PD parameters: clearance (CL), volume of distribution (V1), elimination rates, and covariate-dependent effects.

Circuit structure: Initial state $|0\rangle \otimes^6 \rightarrow$ parameterised rotation layers (R_x, R_y, R_u) \rightarrow CNOT entanglement blocks \rightarrow measurement. Entanglement is crucial—it encodes parameter correlations reflecting true physiological dependencies.

Advantages & Expected Outcomes

Multimodal & Correlated Posteriors

Quantum circuits learn complex joint distributions impossible to approximate with simple Gaussians.

Faster Convergence & Mixing

Reduced autocorrelation and superior exploration lead to fewer to fewer SAEM iterations required.

Preserved Interpretability

PK/PD model structure unchanged. Quantum methods enhance sampling, not biology.

Workflow Compatibility

Seamlessly integrates with established pharmacometric pipelines and covariate adjustments.

Covariate Integration & Model Predictions

Covariates (body weight, concomitant medication) are incorporated classically into the structural model, whilst quantum-enhanced random enhanced random effects enable richer uncertainty capture.

Covariate Effects

- Body weight (BW) scales clearance and volume
- Concomitant medication (COMED) modulates kinetic rates
- Applied to fixed effects θ and random effects η_i

Prediction Framework

$$C_{\text{pred}}(t) = f(\theta, \eta_i, BW, COMED, t)$$

$$R_{\text{pred}}(t) = g(\theta, \eta_i, BW, COMED, t)$$

Quantum sampling enhances η_i estimation; structural biology remains intact.

Comparative Analysis: Quantum-Enhanced vs Classical Framework

Model Fit & Computational Performance

Metric	Quantum	Classical	Gain
Initial Log-Likelihood	-1366.81	-8403.60	6x
SAEM Convergence (min)	26	44.7	↓42%
Total Runtime (h)	4.47	2.92	+53%
Memory Usage (MB)	1131	869	+30%

Quantum circuit overhead justified by superior fit and parameter estimation efficiency.

Dose Optimisation Results

33%

Maximum Dose Reduction

Heavy population, 75% target, weekly regimen

25%

Typical Weekly Savings

Original population, 90% target

100%

Success Rate

Stable numerical convergence in all scenarios

Quantum framework enables greater personalisation via enhanced body weight and comedication sensitivity.

Results & Diagnostic Metrics

Comprehensive evaluation via pharmacological outcomes and computational diagnostics:

01

Log-Likelihood & Convergence

Track SAEM trajectory with burn-in marked; quantum method achieves superior superior plateau.

02

Parameter Estimates & Uncertainty

Population parameters (CL, V1, Q, V2, KA, KEO, IMAX, IC50, KIN, KOUT) with standard errors.

03

Inter-Individual Variability

Correlation matrices (Ω) reveal parameter relationships and covariance structure.

04

Residual Analysis

Log-normal (PK) and proportional (PD) error structures validate model adequacy.

05

Dose-Response & Covariate Effects

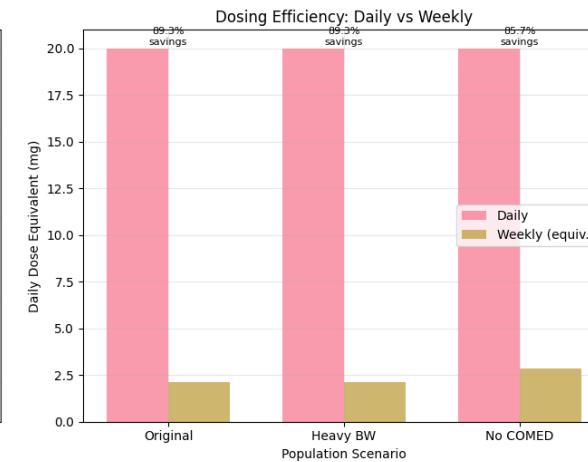
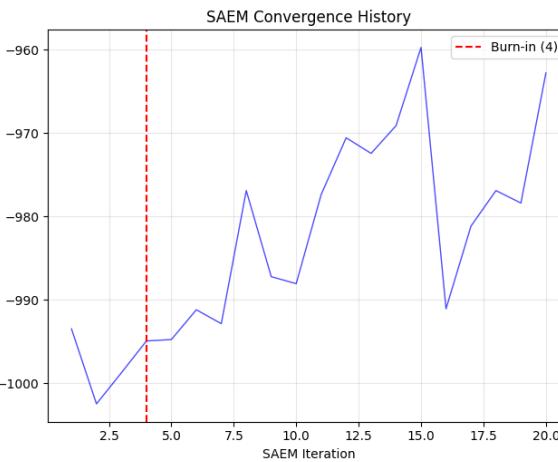
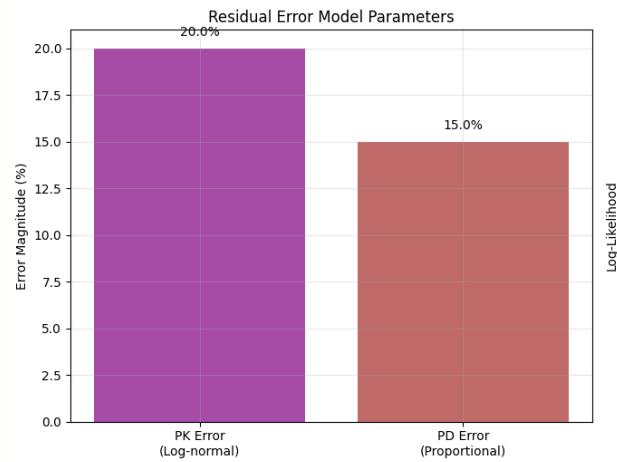
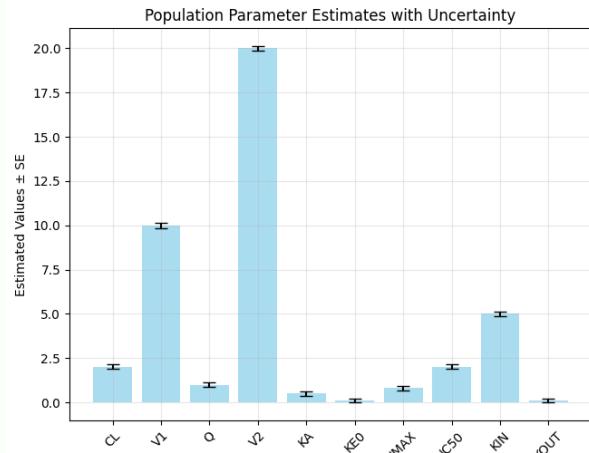
Surface plots and bar charts quantify efficacy, body weight sensitivity, and and comedication impact.

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Computational Performance

ODE evaluations, cache hits, memory usage, and runtime confirm scalability.

Plots and Charts



Future Work: Quantum Hamiltonian Monte Carlo

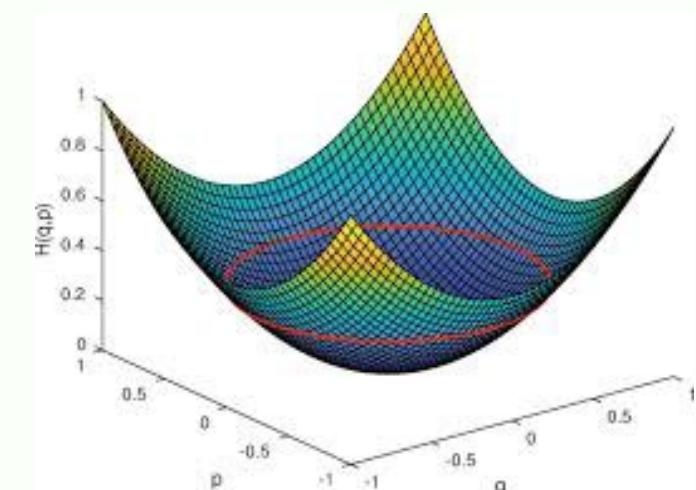
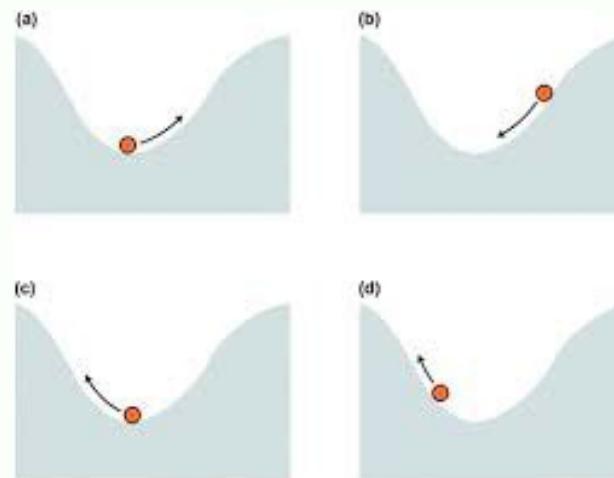
Motivation: Whilst VQC-based sampling successfully models stochastic PK/PD dynamics, Hamiltonian Monte Carlo (HMC) offers a physically intuitive and quantum-native alternative—directly sampling from the posterior via Hamiltonian evolution.

Core Principle

HMC augments parameter space θ with auxiliary momentum p and simulates Hamiltonian dynamics: $H(\theta, p) = U(\theta) + K(p)$, where $U(\theta) = -\log P(\theta | \text{data})$ is the potential energy and $K(p) = \frac{1}{2}p^T M^{-1} p$ is the kinetic energy.

Quantum Native Implementation

Quantum hardware naturally executes Hamiltonian evolution e^{-iHt} via unitary propagation.



Expected outcome: Improved sampling efficiency and richer uncertainty quantification for population-level PK/PD inference.

Team Presentation



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