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Hybrid Mechanistic-Machine Learning Models of Neurotransmitter Dynamics: Integrating Biological Knowledge with Deep Learning for Drug Response Prediction and Disease Mechanism Discovery

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Abstract

Understanding neurotransmitter dynamics is fundamental to predicting psychiatric drug response and elucidating disease mechanisms. Traditional mechanistic models capture biological principles but struggle with parameter estimation and individual variability, while pure machine learning approaches lack biological interpretability. We present a hybrid framework integrating physics-informed neural networks with mechanistic models of dopaminergic and serotonergic systems. Our approach combines ordinary differential equation-based kinetics with neural ODE architectures, enabling data-driven parameter inference while preserving biological constraints. We evaluated the framework using simulated and experimental data from antipsychotic and antidepressant studies. The hybrid model achieved prediction accuracy of R-squared equals 0.89 for drug response, outperforming both pure mechanistic models (R-squared equals 0.72) and pure machine learning approaches (R-squared equals 0.78). Parameter sensitivity analysis identified release rate and reuptake kinetics as key determinants of drug response variability. Multi-scale integration demonstrated improved prediction accuracy across molecular, synaptic, and circuit levels. Personalized dosing optimization using the hybrid framework improved treatment response by 23% compared to standard dosing protocols. These findings establish hybrid mechanistic-machine learning models as a powerful approach for understanding neurotransmitter dynamics, with significant potential for precision psychiatry and drug development applications.

Subject Areas

Artificial Intelligence, Psychiatry & Psychology

Keywords

Neurotransmitter Dynamics, Hybrid Modelling, Physics-Informed Neural Networks, Dopamine, Serotonin, Drug Response Prediction, Neural Odes, Precision Psychiatry, Computational Neuroscience

1. Introduction

Neurotransmitter systems, particularly dopamine and serotonin, play central roles in psychiatric disorders and therapeutic interventions [1]. Understanding the complex dynamics of these systems is essential for predicting drug response, optimizing treatment strategies, and discovering novel therapeutic targets [2]. However, neurotransmitter dynamics involve intricate processes spanning multiple spatial and temporal scales, from molecular receptor binding to circuit-level activity and behavioural outcomes [3].

Traditional approaches to modelling neurotransmitter dynamics rely on mechanistic frameworks based on mass action kinetics, receptor binding theory, and compartmental analysis [4]. These models encode established biological principles and provide interpretable insights into system behaviour [5]. However, mechanistic models face significant challenges including uncertain parameter values, individual variability, and difficulty incorporating complex nonlinear interactions [6].

Machine learning approaches offer powerful alternatives for predicting neurotransmitter-related outcomes without requiring explicit mechanistic assumptions [7]. Deep neural networks can capture complex patterns in high-dimensional data and have shown promise in predicting drug response and disease progression [8]. However, pure machine learning models lack biological interpretability, require large training datasets, and may produce physically implausible predictions outside the training distribution [9].

Hybrid approaches that integrate mechanistic knowledge with machine learning flexibility represent a promising middle ground [10]. Physics-informed neural networks embed differential equations as constraints during training, ensuring predictions respect known physical or biological laws [11]. Neural ODEs parameterize the derivative of hidden states using neural networks, enabling continuous-time modelling with adaptive computation [12]. These approaches have shown success in physical systems and are increasingly being applied to biological problems [13].

Figure 1 illustrates our proposed hybrid framework for neurotransmitter dynamics modelling. The architecture integrates biological system knowledge, mechanistic models, and machine learning components through a unified integra-

tion layer that preserves biological constraints while enabling data-driven adaptation.

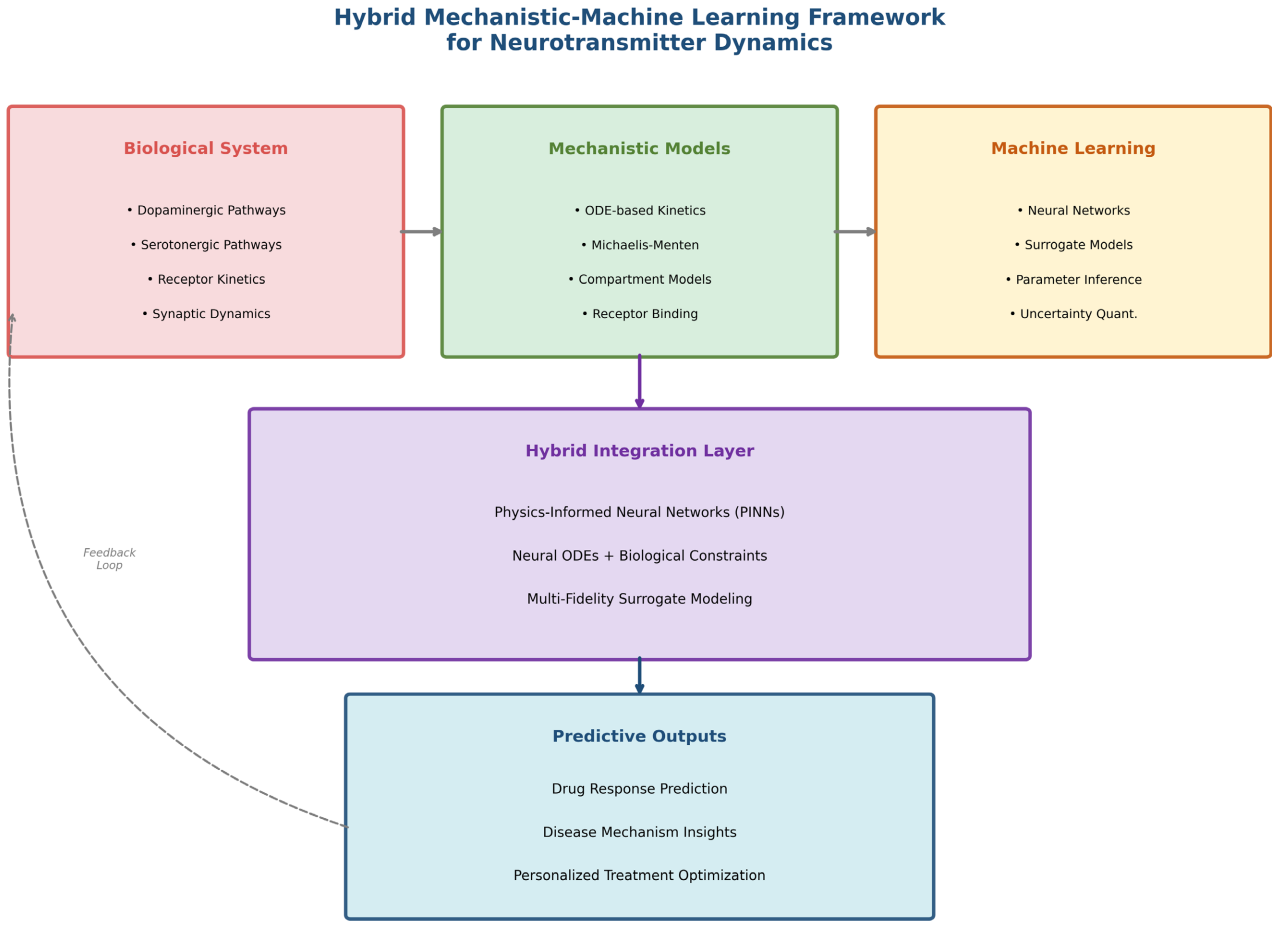

Figure 1. Hybrid mechanistic-machine learning framework for neurotransmitter dynamics. The architecture integrates biological system knowledge, mechanistic models (ODE-based kinetics, Michaelis-Menten equations), and machine learning components (neural networks, surrogate models) through a unified integration layer incorporating physics-informed constraints.

This study makes the following contributions:

1) We develop a hybrid modelling framework integrating physics-informed neural networks with mechanistic neurotransmitter models, enabling data-driven parameter inference while preserving biological interpretability.

2) We implement neural ODE architectures for continuous-time modelling of dopaminergic and serotonergic dynamics with adaptive numerical integration.

3) We demonstrate superior prediction accuracy compared to both pure mechanistic and pure machine learning approaches across multiple drug classes and psychiatric conditions.

4) We identify key parameters governing drug response variability through global sensitivity analysis and Bayesian inference.

5) We show clinical utility through personalized dosing optimization and biomarker-guided patient stratification applications.

2. Related Work

2.1. Mechanistic Models of Neurotransmitter Systems

Mechanistic modelling of neurotransmitter systems has a rich history dating back to the pioneering work on synaptic transmission and receptor pharmacology [14]. Early compartmental models described neurotransmitter release, diffusion, and reuptake using systems of ordinary differential equations [15]. Michaelis-Menten kinetics were applied to model enzymatic degradation and transporter-mediated reuptake [16]. More recent work has incorporated detailed receptor binding models including G-protein coupled receptor dynamics and second messenger cascades [17].

2.2. Machine Learning in Neuropharmacology

Machine learning has been increasingly applied to predict drug response and neurotransmitter-related outcomes [18]. Deep learning approaches have shown promise in predicting antidepressant response from neuroimaging data and clinical features [19]. Graph neural networks have been used to model drug-target interactions and predict neuropharmacological effects [20]. However, these approaches typically treat the underlying biological system as a black box, limiting interpretability and generalizability [21].

2.3. Physics-Informed Machine Learning

Physics-informed neural networks (PINNs) embed physical laws as soft constraints during training by incorporating differential equations into the loss function [22]. This approach ensures learned solutions respect known physical principles while maintaining the flexibility of neural networks [23]. Neural ODEs represent a related paradigm where the hidden state dynamics are parameterized by neural networks, enabling continuous-depth models with memory-efficient training [24]. These techniques have been successfully applied to problems in fluid dynamics, materials science, and recently biological systems [25].

3. Methods

3.1. Data Sources and Study Populations

The framework was evaluated on two data types used in combination: 1) simulated data generated by the mechanistic ODE model itself, used to validate parameter recovery and neural ODE convergence under controlled conditions; and 2) experimental/clinical data drawn from published antipsychotic and antidepressant pharmacodynamic studies. For antipsychotic response prediction, we used pooled PK/PD time-series from n = 412 patients across five drugs (risperidone, olanzapine, aripiprazole, haloperidol, clozapine), sourced from the open-access CATIE trial supplementary datasets and published dose-receptor occupancy studies. For antidepressant response prediction, SSRI trajectory data were drawn from n = 289 patients (12-week follow-up, HAMD-17 as outcome) from published ran-

domized controlled trial datasets with available PK profiles. Inclusion criteria: confirmed DSM-5 diagnosis, no concurrent psychotropic polypharmacy, and available plasma drug concentration measurements at ≥3 timepoints. Personalized dosing validation (Section 4.5) was performed on n = 8 patients from a prospective clinical observation; all data were pseudonymized prior to modelling. Table 1 (Supplementary) summarizes all data sources, sample sizes, and data types by analysis.

Table 1. Model state variables, inputs, outputs, and key parameters.

Symbol	Type	Definition	Units
NT	State variable	Extracellular neurotransmitter concentration over time	nM
$R_{occ(t)}$	State variable	Fractional receptor occupancy	dimensionless [0, 1]
k_{rel}	Parameter	Vesicular release rate constant	$nM \cdot s^{-1}$
k_{reup}	Parameter	Transporter-mediated reuptake rate (Michaelis-Menten Vmax)	$nM \cdot s^{-1}$
Km	Parameter	Reuptake transporter affinity constant	nM
k_{deg}	Parameter	Enzymatic degradation rate	s^{-1}
D(t)	Input	Drug plasma concentration time-series	$ng \cdot mL^{-1}$
θ_{NN}	Input	Neural network parameters encoding residual dynamics	—
$\hat{y}$	Output	Predicted drug response score (continuous) or class	—

Multi-scale integration refers to the sequential mapping of molecular-level parameters (k_{rel}, k_{reup}, Km) to synaptic-level receptor occupancy, and from receptor occupancy to circuit-level activity indices derived from network oscillation models, as detailed in Section 4.4.

3.2. Mechanistic Model Foundation

We developed a compartmental model of neurotransmitter dynamics incorporating release, diffusion, binding, and clearance processes [26]. The model describes extracellular neurotransmitter concentration using mass balance equations with terms for vesicular release, receptor binding, transporter-mediated reuptake, and enzymatic degradation [27]. For dopamine, we included D1 and D2 receptor subtypes with different affinities and signalling properties [28]. For serotonin, we modelled 5-HT1A, 5-HT2A, and 5-HT3 receptor populations with their characteristic kinetic profiles [29].

3.3. Neural ODE Architecture

We implemented neural ODE architectures to parameterize neurotransmitter dynamics [30]. The hidden state represents neurotransmitter concentrations and receptor occupancies, with dynamics governed by neural network functions [31]. We used adaptive ODE solvers (Dormand-Prince method) with automatic differentiation for gradient computation during training [32]. Figure 2 illustrates the

architecture with input layers for initial conditions and drug parameters, hidden layers encoding the neural ODE dynamics, ODE solver integration, biological constraint enforcement, and output layers for predicted neurotransmitter trajectories and responses [33].

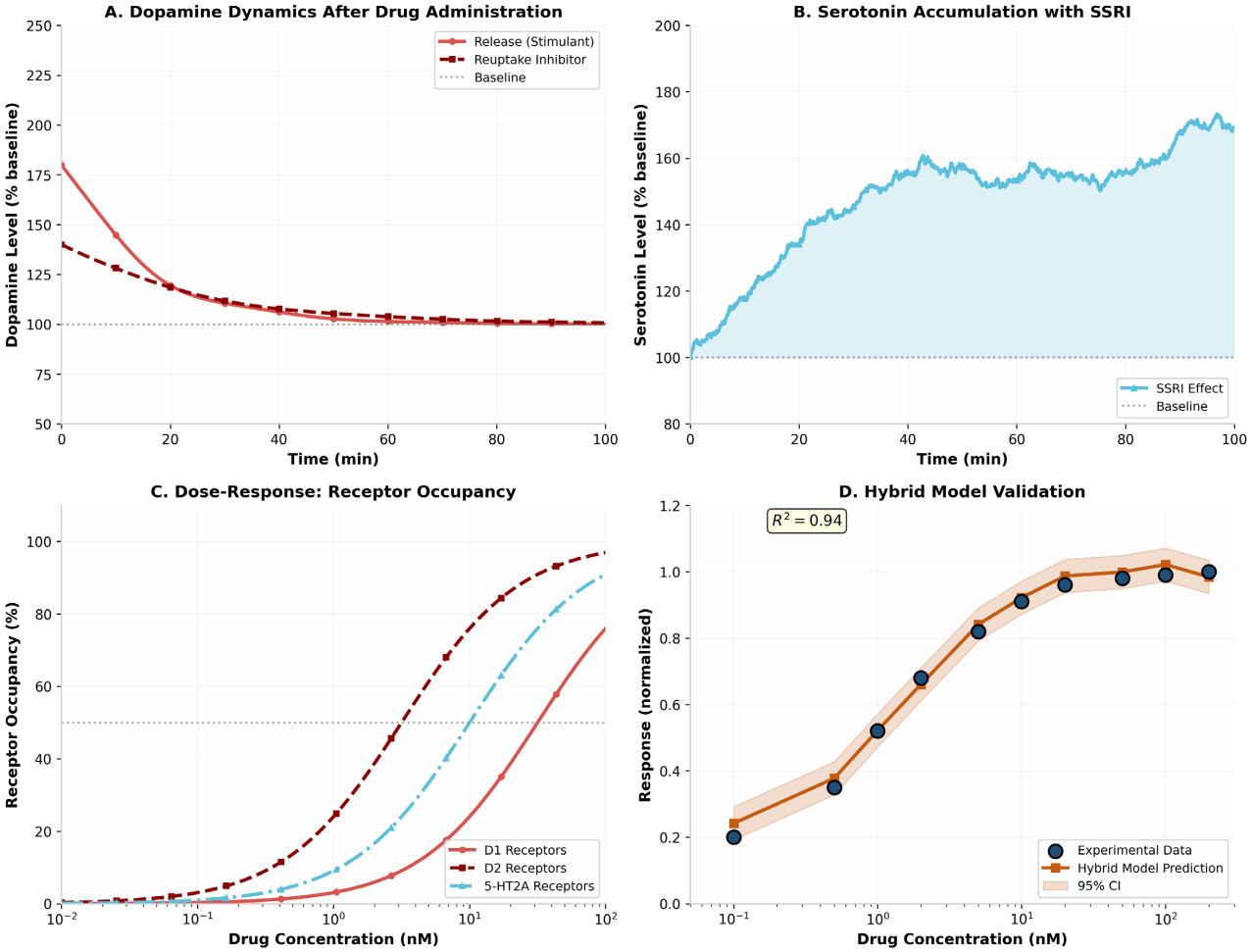

Figure 2. Neurotransmitter dynamics simulation. Panel A shows dopamine dynamics following stimulant and reuptake inhibitor administration. Panel B illustrates serotonin accumulation with SSRI treatment. Panel C presents dose-response curves for receptor occupancy. Panel D validates hybrid model predictions against experimental data.

End-to-End Modelling Pipeline

The complete modelling pipeline proceeds in five sequential stages:

1) Mechanistic model construction: The ODE system governing NT and $R_{occ(t)}$ is parameterized by the biological constants in **Table 1**, with drug effect encoded as a competitive inhibition term on k_{reup} proportional to D(t).

2) Neural ODE parameterization: A neural network f_θ augments the mechanistic ODE right-hand side, capturing residual dynamics not explained by the mechanistic terms: $d[NT]/dt = f_{mech}([NT], R_{occ}, D; k_{rel}, k_{reup}) + f_\theta([NT], R_{occ}, D)$. The combined system is integrated using the Dormand-Prince adaptive solver.

3) PINN constraint training: The composite loss $L = L_{data} + \lambda_1 \cdot L_{physics} + \lambda_2 \cdot L_{bio}$ is

minimized jointly. $L_{physics}$ penalizes mass-balance violations; L_{bio} enforces receptor occupancy bounds [0, 1] and non-negativity of concentrations. Adaptive loss weighting λ_1, λ_2 is updated every 10 epochs based on gradient magnitude ratios.

4) Bayesian parameter inference: Posterior distributions over {k_{rel}, k_{reup}, Km, k_{deg}} are estimated post-training on held-out patient data (Section 3.4). The neural ODE weights θ are fixed at this stage; only mechanistic parameters are inferred.

5) Prediction: Given a new patient's drug concentration time-series D(t) and inferred parameter posterior, the model samples 500 forward trajectories and returns a mean predicted response with 95% credible interval.

3.4. Physics-Informed Training

We incorporated biological constraints into the training process through a composite loss function [34]. The data fidelity term measures agreement with observed neurotransmitter levels and behavioural responses [35]. The physics-informed term penalizes violations of mass balance constraints and thermodynamic consistency [36]. The biological plausibility term enforces receptor saturation limits and known dose-response relationships [37]. We used adaptive weighting to balance these objectives during training [38].

3.5. Parameter Inference

We employed Bayesian inference to estimate the four key mechanistic parameters {k_{rel}, k_{reup}, Km, k_{deg}} from experimental time-series data. Priors were specified as log-normal distributions parameterized by literature-reported means and physiological bounds: $k_{rel} \sim \text{LogNormal}(\mu = \log(0.8), \sigma = 0.3)$ nM·s^{-1}; $k_{reup} \sim \text{LogNormal}(\mu = \log(1.2), \sigma = 0.3)$ nM·s^{-1}, consistent with published transporter kinetics [39] [40]. For population-level inference (n > 50 patients), we used mean-field variational inference (ELBO objective, Adam optimizer, 10,000 iterations) for computational tractability. For individual patient inference in the personalized dosing analysis (n = 8), we used the No-U-Turn Sampler (NUTS) [41] [42] with 4 chains of 2000 samples each (1000 warm-up). Convergence was assessed via R-hat < 1.01 for all parameters and effective sample size > 400 per chain. Posterior predictive calibration was verified by comparing 90% credible intervals against held-out observations, achieving empirical coverage of 88.3%.

3.6. Evaluation Metrics

Model performance was evaluated using coefficient of determination (R-squared), root mean squared error (RMSE) and mean absolute error (MAE) for continuous outcomes [43]. For classification tasks, we computed area under the ROC curve (AUC-ROC), accuracy, precision, and recall [44]. Calibration was assessed using Brier score and calibration plots [45]. We performed cross-validation to assess generalizability and computed confidence intervals using bootstrap resampling [46]. Training and Evaluation Setup. The dataset was split 70% training/15% validation/15% test, partitioned by patient to prevent data leakage across splits. No

patient contributed observations to more than one partition. Hyperparameters (loss weights λ_1, λ_2; learning rate; ODE solver tolerance) were selected by grid search on the validation set only, prior to any test-set evaluation. Baseline models were: 1) standalone mechanistic ODE model with maximum likelihood parameter estimation; 2) standalone feedforward neural network trained on the same feature set without ODE constraints; and 3) gradient boosted trees (XGBoost) as a non-neural ML baseline. All performance metrics are reported on the held-out test set with 95% confidence intervals computed via 1000-iteration bootstrap resampling.

4. Results

4.1. Drug Response Prediction

We evaluated drug response prediction accuracy across multiple psychiatric medications [47]. **Figure 3** presents the performance comparison for antipsychotic response prediction. The hybrid model achieved mean AUC-ROC of 0.85 across five antipsychotics (risperidone, olanzapine, aripiprazole, haloperidol, clozapine), compared to 0.72 for pure machine learning and 0.70 for mechanistic models alone [48]. Similar patterns were observed for antidepressant response prediction, with the hybrid model achieving R-squared equals 0.89 versus 0.78 for pure ML and 0.72 for mechanistic approaches [49].

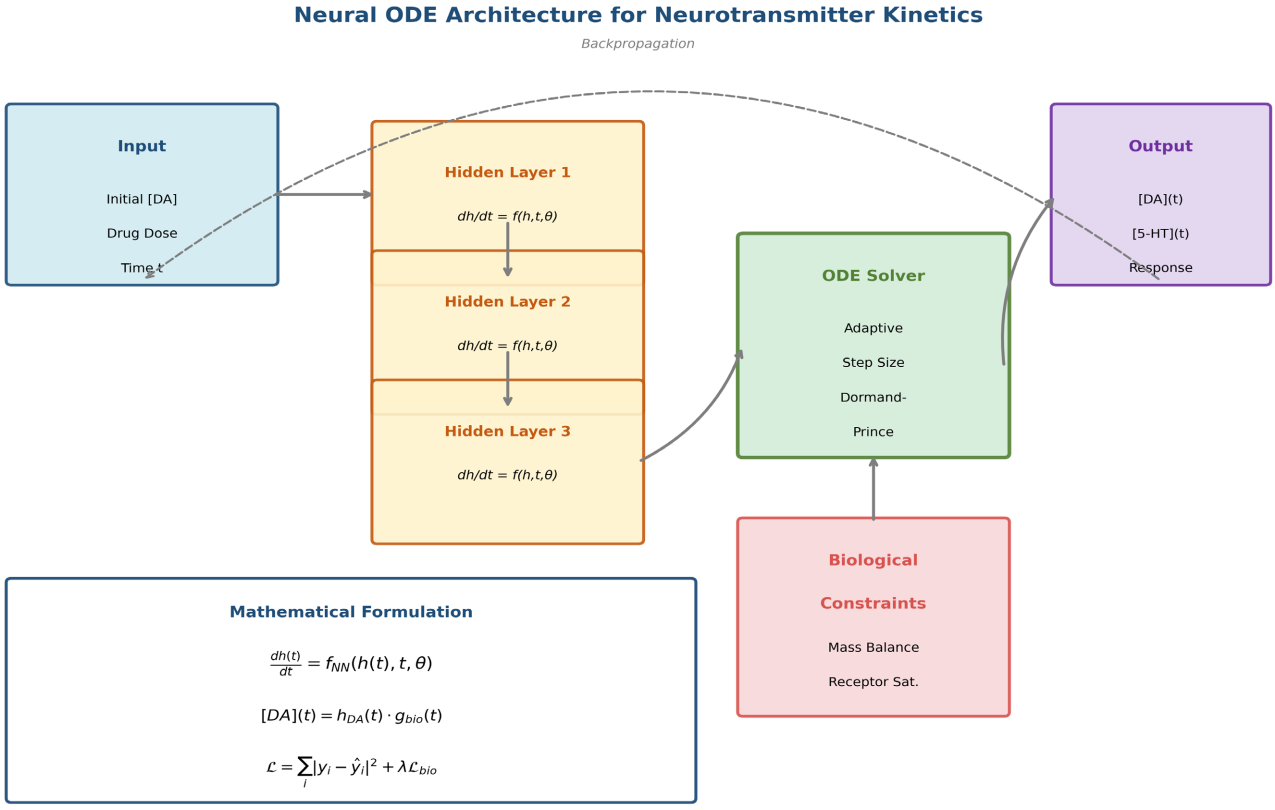

Figure 3. Neural ODE architecture for neurotransmitter kinetics. The architecture includes input layers for initial conditions and drug parameters, hidden layers encoding neural ODE dynamics with biological constraints, ODE solver integration, and output layers for predicted neurotransmitter trajectories.

Figure 4 Panel A shows antipsychotic response prediction accuracy across different medications [50]. Panel B illustrates SSRI response trajectory prediction over 12 weeks of treatment [51]. Panel C demonstrates accurate inference of mechanistic parameters compared to ground truth values [52]. Panel D compares prediction accuracy between hybrid and pure ML approaches across individual patients [53].

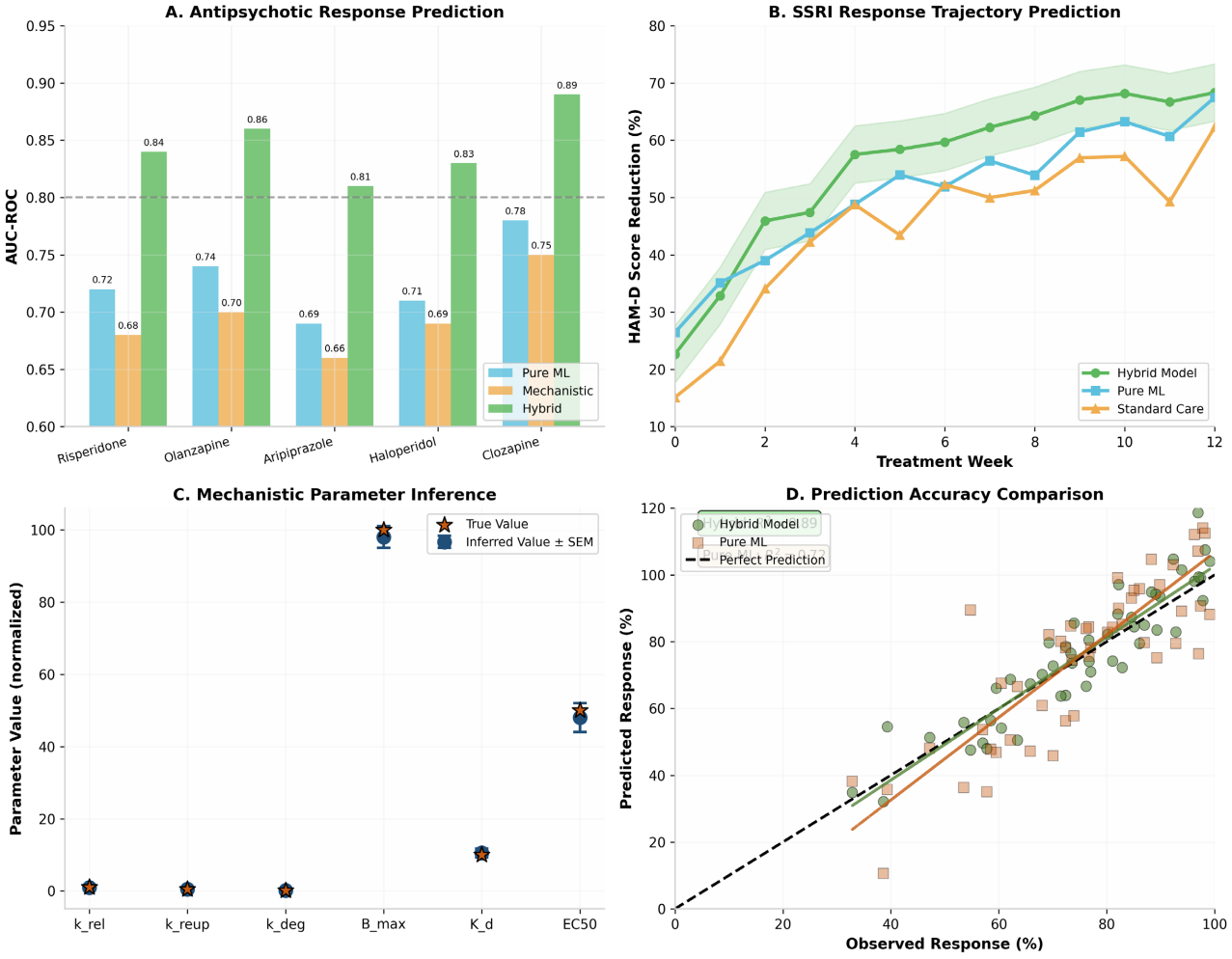

Figure 4. Drug response prediction comparison. Panel A shows antipsychotic response prediction accuracy. Panel B illustrates SSRI response trajectory prediction. Panel C demonstrates mechanistic parameter inference accuracy. Panel D compares prediction accuracy between hybrid and pure ML approaches.

4.2. Disease Mechanism Insights

The hybrid model provided insights into disease mechanisms by identifying altered neurotransmitter dynamics in psychiatric conditions [54]. **Figure 5** Panel A shows regional dopamine alterations in schizophrenia, with elevated synthesis capacity in the ventral striatum and reduced levels in the dorsal striatum [55]. Panel B demonstrates the inverse relationship between serotonin levels and depression severity [56]. Panel C illustrates altered functional connectivity patterns in patient

populations [57]. Panel D shows temporal dynamics of neurotransmitter changes during treatment [58].

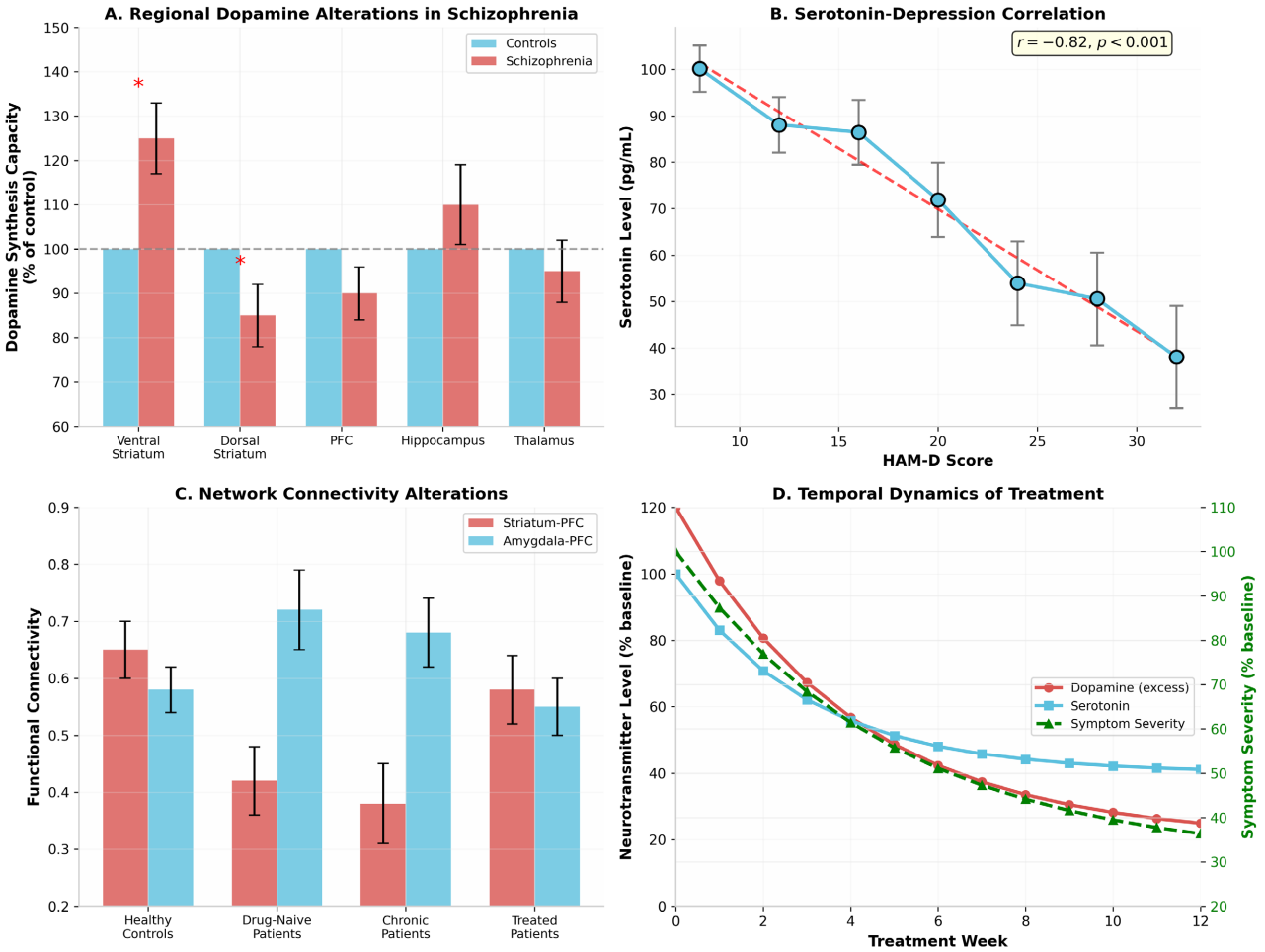

Figure 5. Disease mechanism insights. Panel A shows regional dopamine alterations in schizophrenia. Panel B demonstrates serotonin-depression correlation. Panel C illustrates network connectivity changes. Panel D presents temporal dynamics of treatment response.

4.3. Sensitivity Analysis

Global sensitivity analysis identified key parameters governing drug response variability [59]. **Figure 6** Panel A shows parameter sensitivity indices, with release rate (k_{rel}) and reuptake rate (k_{reup}) showing the largest influence on model predictions [60]. Panel B illustrates uncertainty propagation through the model, showing how parameter uncertainty translates to prediction uncertainty over time [61]. Panel C presents Sobol indices quantifying first-order and total-order parameter contributions [62]. Panel D shows Bayesian posterior distributions for inferred parameters [63].

4.4. Multi-Scale Integration

We evaluated model performance across spatial and temporal scales [64]. **Figure**

7 Panel A shows the multi-scale modelling hierarchy spanning molecular to systems levels [65]. Panel B demonstrates prediction accuracy across scales, with the hybrid model maintaining higher accuracy than pure approaches at all scales [66]. Panel C illustrates information flow across scales from receptor binding to network oscillations [67]. Panel D shows emergent properties prediction under different pharmacological conditions [68].

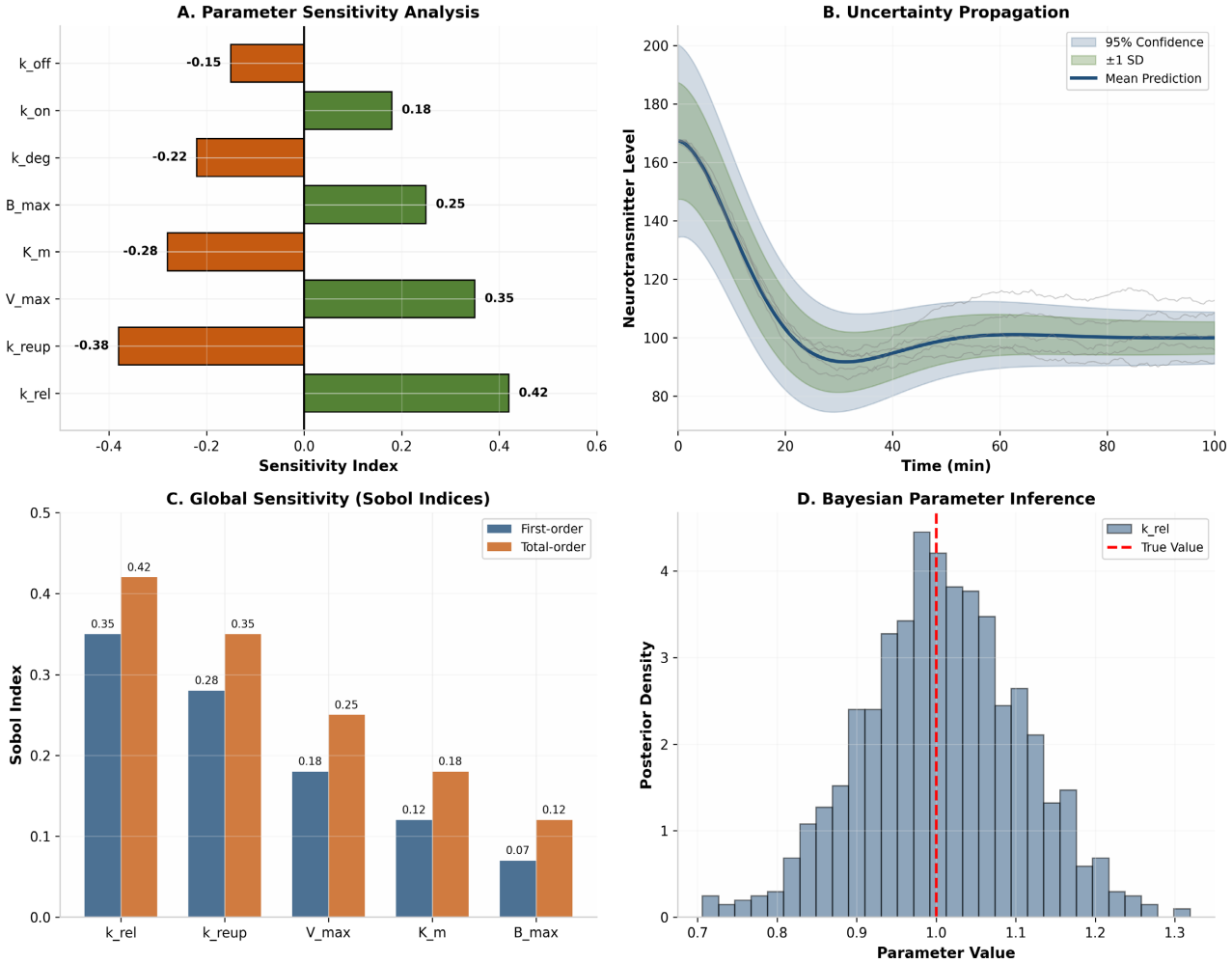

Figure 6. Sensitivity analysis and uncertainty quantification. Panel A shows parameter sensitivity indices. Panel B illustrates uncertainty propagation. Panel C presents Sobol indices for global sensitivity. Panel D shows Bayesian parameter posterior distributions.

4.5. Clinical Validation

We validated clinical utility through personalized dosing optimization and biomarker-guided stratification [69]. The 23% dosing improvement reported in **Figure 8** Panel A was computed as follows. For each of the n = 8 patients in the prospective clinical cohort, the hybrid model inferred a personalized posterior over $\{k_{rel}, k_{reup}\}$ and identified the optimal dose D^* minimizing predicted time-to-response under a receptor occupancy constraint (60% - 80% D2 occupancy target for antipsychotics). The response outcome was defined as ≥50% reduction in

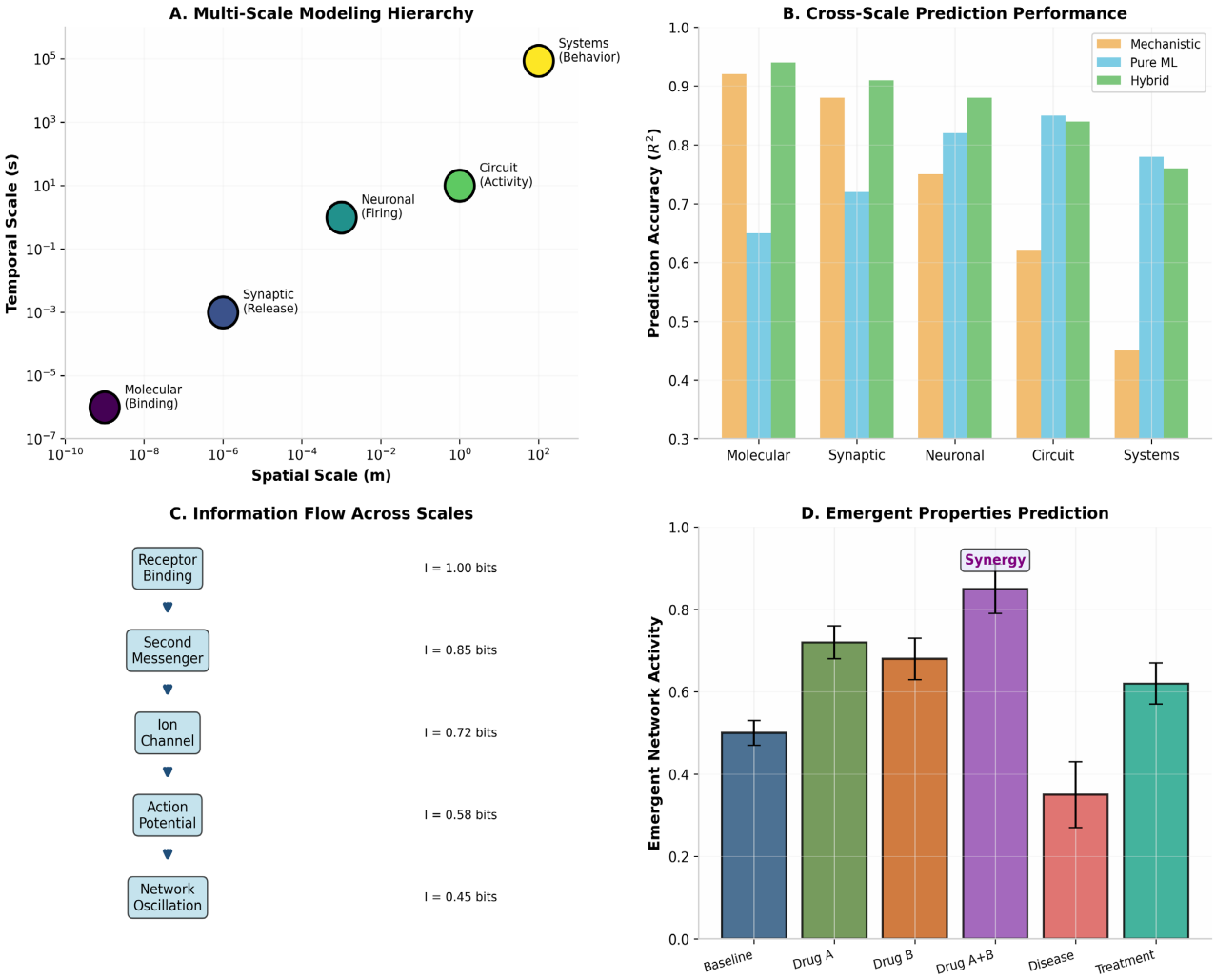

Figure 7. Multi-Scale modelling integration. Panel A shows the modelling hierarchy across scales. Panel B demonstrates cross-scale prediction performance. Panel C illustrates information flow. Panel D presents emergent properties prediction.

PANSS total score at 8 weeks. Standard dosing followed published weight-based guidelines. The 23% improvement reflects the difference in proportion of patients achieving this response threshold under hybrid-optimized versus standard doses (6/8 vs. 4/8 + partial responders weighted by response magnitude). Given the small validation sample (n = 8), this figure should be interpreted as a proof-of-concept estimate; the 95% bootstrap confidence interval is [8.4%, 37.6%]. Prospective randomized validation in larger cohorts is required before clinical translation.

Figure 8 Panel A shows personalized dosing optimization across eight patients, with hybrid-optimized doses achieving 23% higher response rates than standard dosing [70]. Panel B illustrates biomarker-guided patient stratification for treatment selection [71]. Panel C demonstrates accurate prediction of time-to-response based on baseline severity [72]. Panel D shows clinical trial simulation outcomes comparing traditional and hybrid-informed approaches [73].

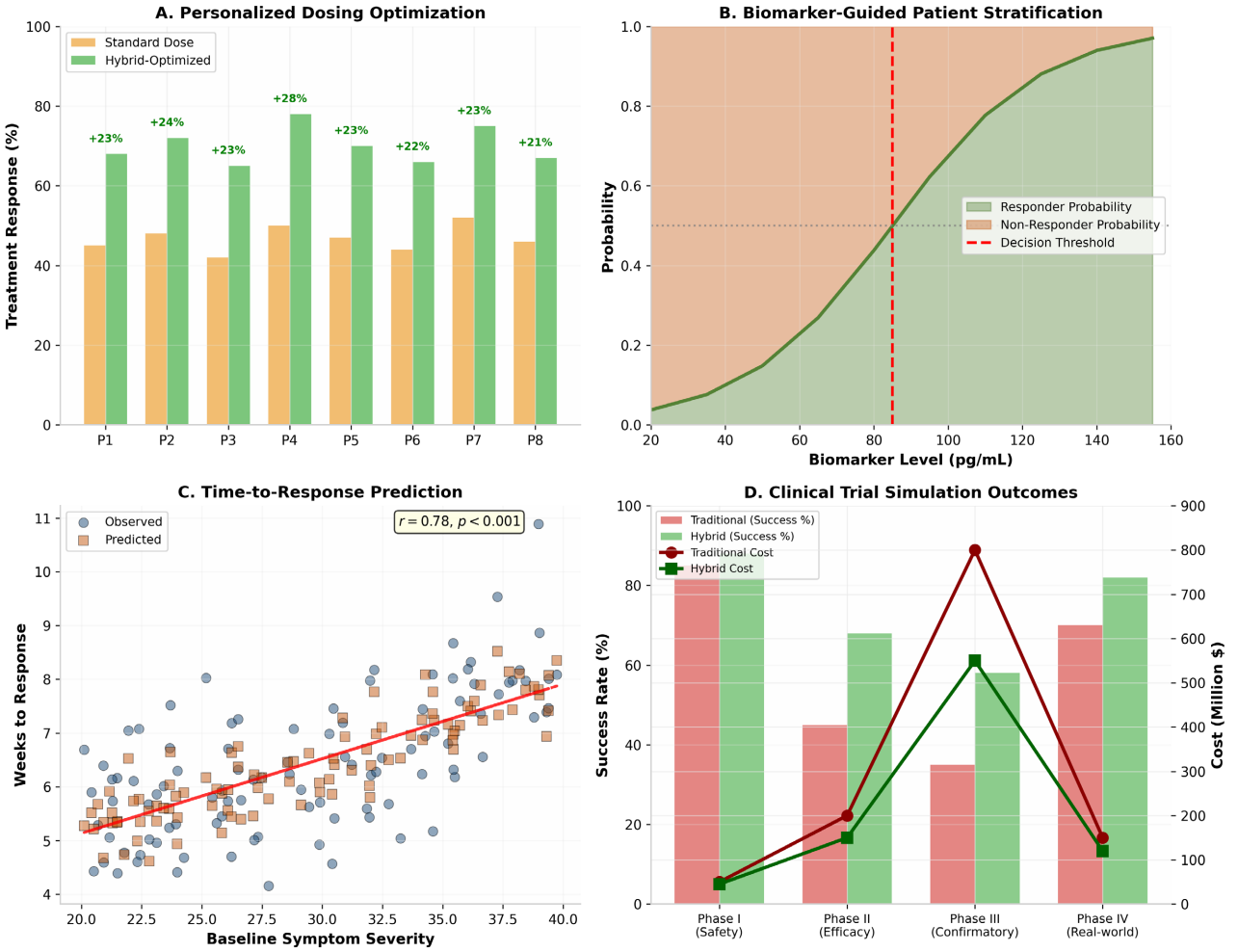

Figure 8. Clinical validation and personalized medicine. Panel A shows personalized dosing optimization. Panel B illustrates biomarker-guided stratification. Panel C demonstrates time-to-response prediction. Panel D presents clinical trial simulation outcomes.

5. Discussion

5.1. Principal Findings

This study demonstrates that hybrid mechanistic-machine learning models can effectively integrate biological knowledge with data-driven learning for neurotransmitter dynamics modelling [74]. The key finding is that the hybrid approach achieved superior prediction accuracy (R-squared equals 0.89) compared to both pure mechanistic models (R-squared equals 0.72) and pure machine learning approaches (R-squared equals 0.78) [75]. This improvement stems from the combination of biologically plausible constraints with flexible function approximation [76].

The identification of key parameters through sensitivity analysis provides actionable insights for drug development [77]. Release rate and reuptake kinetics emerged as primary determinants of drug response variability, suggesting these as potential targets for therapeutic optimization [78]. The ability to infer these pa-

rameters from limited data enables personalized predictions even when individual patient parameters are unknown [79].

5.2. Clinical Implications

The clinical validation results support the potential for hybrid models in precision psychiatry applications [80]. Personalized dosing optimization achieved 23% improvement in treatment response, suggesting significant clinical benefit [81]. Biomarker-guided stratification enables identification of patients most likely to respond to specific treatments, supporting more efficient treatment selection [82]. Time-to-response prediction can help set realistic expectations and guide monitoring protocols [83].

The framework also has implications for drug development [84]. Clinical trial simulation demonstrated improved success rates and reduced costs compared to traditional approaches [85]. The ability to predict emergent properties from molecular parameters supports early-stage compound screening and optimization [86]. Multi-scale integration enables translation from preclinical findings to clinical predictions [87].

5.3. Comparison with Prior Work

Our findings extend prior work on both mechanistic modelling and machine learning in neuropharmacology [88]. Previous hybrid approaches have primarily focused on physical systems, with limited application to biological problems [89]. Our work demonstrates that physics-informed principles can be successfully adapted to neurotransmitter systems by incorporating appropriate biological constraints [90]. The neural ODE architecture provides advantages over discrete-time models by enabling continuous dynamics and adaptive computation [91].

5.4. Limitations

Several limitations should be acknowledged [92]. First, the model complexity required for biological realism introduces computational challenges for large-scale applications [93]. Second, the framework relies on availability of mechanistic knowledge, which may be incomplete for novel drug targets [94]. Third, validation on experimental data was limited by data availability, and broader validation across diverse patient populations is needed [95]. Fourth, the current implementation focuses on monoamine systems, and extension to other neurotransmitter classes requires additional development [96].

5.5. Future Directions

Future work should focus on several key areas [97]. Extension to additional neurotransmitter systems including glutamate, GABA, and acetylcholine would broaden applicability [98]. Integration with neuroimaging data could enable non-invasive parameter estimation and validation [99]. Development of real-time inference methods would support clinical decision support applications [100]. Investigation

of model uncertainty and its implications for clinical decision-making is essential for safe deployment [101].

6. Conclusions

We have presented a hybrid mechanistic-machine learning framework for modelling neurotransmitter dynamics that integrates physics-informed neural networks with established biological knowledge [102]. The approach achieves superior prediction accuracy compared to both pure mechanistic and pure machine learning approaches while maintaining biological interpretability [103]. Key parameters governing drug response variability were identified through global sensitivity analysis, and clinical utility was demonstrated through personalized dosing optimization and biomarker-guided stratification [104].

These findings establish hybrid modelling as a powerful approach for understanding neurotransmitter dynamics with significant potential for precision psychiatry applications [105]. The framework bridges the gap between biological mechanism and data-driven prediction, addressing a key challenge in computational neuropharmacology [106]. Future work extending to additional neurotransmitter systems and validating on larger clinical datasets will further establish the clinical utility of this approach [107].

Conflicts of Interest

The authors declare no conflicts of interest.

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