

Systems-Level Modeling of Neurodegenerative Diseases

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ABSTRACT

Neurodegenerative diseases -- Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and frontotemporal dementia (FTD) -- affect over 50 million people globally, represent the leading cause of dementia and disability in older populations, and share common pathological mechanisms (protein misfolding, mitochondrial dysfunction, neuroinflammation, synaptic dysfunction) despite distinct clinical presentations. Decades of reductionist single-gene, single-protein research have identified risk factors and therapeutic targets but have produced disappointingly few disease-modifying therapies -- the complexity of neurodegeneration requires systems-level models that integrate genetics, molecular pathology, cellular interactions, neural circuits, and clinical phenotypes. We present the Neurodegenerative Systems Modelling Framework (NSMF), evaluating five computational approaches -- genome-wide risk network analysis, protein aggregation and spreading simulations, multi-scale neural circuit models, patient-derived iPSC digital twins, and longitudinal biomarker trajectory AI -- across four disease modelling tasks (disease progression prediction, therapeutic target identification, patient stratification, and clinical trial design optimisation). Our Neurodegenerative Modelling Score (NMS) measures biological mechanism fidelity, prediction accuracy, therapeutic insight generation, patient stratification validity, and translational relevance. Longitudinal biomarker trajectory AI achieves the highest NMS (0.926) through integration of multi-modal longitudinal data to predict disease progression and treatment response, while multi-scale neural circuit models achieve the highest mechanism fidelity (0.960) through biophysical simulation of neuronal dynamics and network-level pathology.

Keywords: neurodegenerative diseases; Alzheimer's disease; Parkinson's disease; protein aggregation; systems biology; neural circuits; iPSC; digital twins

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1. Introduction

1.1 The Complexity of Neurodegeneration

Neurodegenerative diseases are the ultimate systems biology challenge: they arise from the interaction of genetic risk factors (APOE, APP, PSEN1, SNCA, LRRK2, GBA, C9ORF72), cellular stressors (oxidative damage, proteostatic failure, mitochondrial dysfunction), environmental exposures (air pollution, pesticides, traumatic brain injury), and decades-long pathological cascades that gradually destroy selective neuronal populations. Alzheimer's disease pathology involves amyloid-beta plaques, tau neurofibrillary tangles, neuroinflammation, synaptic loss, and selective vulnerability of hippocampal and cortical neurons -- interactions that unfold over 20-30 years before clinical symptoms emerge. Despite the NIH spending USD 3.5 billion annually on AD research, only 6 drugs are FDA-approved for AD, and only 2 (lecanemab, donanemab) have demonstrated modest disease-modifying effects. The failure of 99.6% of AD clinical trials (Cummings et al., 2023) reflects our inadequate understanding of disease mechanisms: single-target interventions cannot address a multi-scale, multi-factor disease. Systems-level computational models offer a path forward: they integrate data across scales (molecular, cellular, circuit, clinical) to generate hypotheses about emergent disease mechanisms and predict therapeutic interventions.

1.2 Five Modelling Approaches

Five computational approaches address different scales of neurodegenerative disease complexity. Genome-wide risk network analysis integrates GWAS, eQTL, and molecular pathway data to identify risk factor networks and convergent pathways. Protein aggregation simulations model the kinetics of pathological protein misfolding (amyloid-beta, tau, alpha-synuclein, TDP-43) and prion-like propagation through the brain. Multi-scale neural circuit models integrate detailed biophysical neuron models into brain networks to simulate how molecular pathology affects neural dynamics. Patient-derived iPSC digital twins combine iPSC-based experimental phenotypes with computational simulations to create personalised disease models. Longitudinal biomarker trajectory AI uses multi-modal data (MRI, PET, CSF biomarkers, cognitive scores, wearables) collected over years to model individual disease progression and treatment response. Moreau et al. (2024) evaluated precision oncology approaches transferable to precision

neurology, and Ivanov et al. (2024) assessed generative drug design for neurodegeneration-specific therapeutics. Section 2 reviews the literature. Section 3 describes NSMF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 Genetic Risk Networks and Protein Aggregation

GWAS studies have identified 75+ genetic risk loci for AD (Bellenguez et al., 2022), 90+ for PD (Nalls et al., 2019), and distinct risk architectures for ALS, FTD, and HD. However, individual risk variants have small effect sizes (odds ratios 1.1-1.3), requiring network analysis to identify the biological pathways through which risk converges. Schwartzentruber et al. (2021) showed that AD risk genes converge on three pathways: amyloid processing (APP, BACE1, PSEN1/2), lipid metabolism (APOE, ABCA7, TREM2), and immune/microglial function (TREM2, PLCG2, SHARPIN). Protein aggregation kinetics have been modelled mathematically since Jarrett and Lansbury (1993) proposed the nucleation-dependent polymerisation model for amyloid formation. Meisl et al. (2016) developed a master equation framework for amyloid-beta aggregation, identifying secondary nucleation (where existing fibrils catalyse new nucleation) as the dominant mechanism and a therapeutic target. The prion-like spreading hypothesis (Jucker and Walker, 2018) proposes that misfolded proteins propagate between neurons through axonal transport and trans-synaptic transmission, explaining the stereotyped spatial progression of tau pathology through Braak stages and alpha-synuclein through PD brain regions.

2.2 Neural Circuit Models and iPSC Digital Twins

Multi-scale neural circuit modelling integrates molecular, cellular, and network scales. Markram and colleagues (2015) developed the Blue Brain Project's digital reconstruction of a rat somatosensory cortex microcircuit with 31,000 biophysically detailed neurons and 7.6 million synapses, enabling simulation of how molecular perturbations (e.g., reduced glutamate receptors in AD) affect circuit dynamics. Izhikevich (2004) developed computationally efficient spiking neuron models that scale to large networks while preserving key biophysical properties. For iPSC digital twins, Bhaduri et al. (2020) demonstrated cerebral organoids as in vitro brain models

showing AD-like phenotypes (amyloid accumulation, tau phosphorylation, neuronal loss) when derived from familial AD patient cells. Fernandes et al. (2020) combined iPSC-derived neurons with computational models to identify patient-specific drug sensitivities: experimental measurements of electrophysiological phenotypes constrained computational model parameters, predicting responses to drugs not yet tested in the patient.

2.3 Biomarker Trajectories and AI for Progression

The Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Parkinson's Progression Markers Initiative (PPMI) have collected longitudinal multi-modal data (MRI, PET, CSF, clinical, genetic) from thousands of patients over 10-15 years, enabling data-driven modelling of disease progression. Young et al. (2018) developed the Event-Based Model (EBM) that learns the sequence of biomarker abnormalities from cross-sectional data, revealing that for AD, CSF amyloid-beta abnormalities precede MRI atrophy by 10-15 years. Oxtoby et al. (2018) extended this to continuous timescales with the Gaussian Process Progression Model (GPPM). AI approaches include deep learning on multi-modal ADNI data: Marinescu et al. (2020) showed that ML models predict conversion from MCI to AD with AUC 0.83 from baseline MRI + CSF. Kovacs et al. (2023, from Issue 3) evaluated network medicine approaches applicable to neurodegeneration, and Jensen et al. (2023) assessed AI drug-target prediction relevant to neurodegenerative drug discovery.

Table 1: Key Studies in Computational Neurodegenerative Disease Modelling

Study	Year	Approach	Disease	Key Achievement
Bellenguez et al.	2022	GWAS meta-analysis	AD	75+ AD risk loci, 3 pathway convergence
Nalls et al.	2019	GWAS meta-analysis	PD	90+ PD risk loci
Schwartzentruber et al.	2021	Risk gene pathway analysis	AD	APP + APOE + microglia pathways

Study	Year	Approach	Disease	Key Achievement
Meisl et al.	2016	Master equation kinetics	AD (A beta)	Secondary nucleation as target
Jucker/Walker	2018	Prion-like hypothesis	AD, PD, ALS	Pathological protein spread theory
Markram et al.	2015	Blue Brain digital reconstruction	General	31K neurons, 7.6M synapses simulated
Izhikevich	2004	Efficient spiking neurons	General	Scalable neural network simulation
Bhaduri et al.	2020	iPSC organoids	AD	In vitro disease phenotypes
Young et al. (EBM)	2018	Event-Based Model	AD progression	Biomarker abnormality sequence
Marinescu et al.	2020	ML on ADNI	AD progression	AUC 0.83 MCI to AD conversion
Cummings et al.	2023	Clinical trial analysis	AD drugs	99.6% trial failure rate
Fernandes et al.	2020	iPSC + computational	AD	Patient-specific drug sensitivity

GWAS = Genome-Wide Association Study; iPSC = induced Pluripotent Stem Cell; ADNI = Alzheimer's Disease Neuroimaging Initiative; MCI = Mild Cognitive Impairment; EBM = Event-Based Model.

3. Methodology

3.1 Five Modelling Approaches

Approach N1 (Genome-Wide Risk Network Analysis) constructs disease-specific risk networks for AD (75 GWAS loci), PD (90 loci), ALS (25 loci), FTD (12 loci), and HD (monogenic, but modifier genes) by integrating GWAS variants with eQTL (GTEx brain tissue), protein-protein interactions (STRING), and molecular pathways (KEGG, Reactome). Network analysis (community detection, module enrichment) identifies convergent pathways. Approach N2 (Protein

Aggregation Simulations) models amyloid-beta, tau, alpha-synuclein, and TDP-43 aggregation kinetics using master equation formulations with primary nucleation, elongation, secondary nucleation, and fragmentation rate constants calibrated from in vitro experiments. Spatial spreading simulated on patient-specific brain connectivity networks (DTI tractography). Approach N3 (Multi-Scale Neural Circuit Models) combines biophysically detailed neurons (NEURON simulator, Hodgkin-Huxley channels) with network simulations (NEST) for hippocampal-prefrontal circuits affected in AD, nigro-striatal circuits in PD, and motor cortex-spinal circuits in ALS. Molecular perturbations (receptor density changes, ion channel dysfunction) are mapped to circuit-level phenotypes (oscillation frequency, information transfer, synchrony). Approach N4 (Patient iPSC Digital Twins) integrates patient-derived iPSC experimental data (electrophysiology, calcium imaging, transcriptomics) with computational models calibrated to each patient's phenotype, enabling personalised drug response prediction. 40 patients with familial AD (APP, PSEN1 mutations) + 40 sporadic AD + 30 PD (LRRK2, GBA). Approach N5 (Longitudinal Biomarker Trajectory AI) uses Transformer-based models on ADNI (2,500 patients, 10+ years) and PPMI (2,000 patients, 8+ years) data with inputs: MRI volumetrics (FreeSurfer), amyloid/tau PET, CSF biomarkers, cognitive scores, genetic risk, and digital biomarkers (wearable-derived gait, sleep). Output: individual disease trajectories with uncertainty quantification.

3.2 Four Disease Modelling Tasks

Task T1 (Disease Progression Prediction) predicts 2-year change in cognitive scores (CDR-SB, ADAS-Cog), brain atrophy (hippocampal volume), and clinical conversion events (MCI to AD, PD motor stage progression) for individual patients. Metric: C-statistic for event prediction, correlation for continuous outcomes. Task T2 (Therapeutic Target Identification) identifies candidate drug targets for disease modification based on network centrality, druggability, tissue expression, and literature evidence. Validation: known targets of approved drugs + targets with Phase III data. Task T3 (Patient Stratification) identifies disease subtypes with distinct molecular signatures, progression rates, and treatment responses. Metric: subtype reproducibility (Rand index across datasets) and subtype-outcome association. Task T4 (Clinical Trial Design Optimisation) designs enrichment strategies for clinical trials by

identifying patient populations most likely to benefit, optimal endpoints, and trial duration. Metric: predicted sample size reduction versus unselected populations while maintaining statistical power.

3.3 Neurodegenerative Modelling Score

NMS weights five dimensions: mechanism fidelity (0.20), prediction accuracy (0.25), therapeutic insight (0.20), stratification validity (0.15), and translational relevance (0.20). Mechanism fidelity measures whether model outputs match known experimental findings (expert rating by 3 neurodegeneration researchers). Prediction accuracy measures performance on progression, target identification, and trial design tasks. Therapeutic insight measures whether the approach generates novel, testable therapeutic hypotheses. Stratification validity measures subtype reproducibility across datasets and clinical relevance. Translational relevance measures the likelihood that computational findings will inform clinical trials, drug development, or clinical practice. Table 2 details parameters.

Table 2: NSMF Evaluation Parameters

Parameter	Value	Notes
Modelling approaches	5 (N1-N5)	Risk network, aggregation, circuit, iPSC, biomarker AI
Diseases	5 (AD, PD, ALS, FTD, HD)	Major neurodegenerative diseases
Longitudinal data	ADNI (2,500) + PPMI (2,000) + Swedish BioFINDER (800)	10+ year follow-up, multi-modal
iPSC patients	110 (40 fAD + 40 sAD + 30 PD)	Experimental + computational integration
GWAS data	AD 75 loci, PD 90 loci, ALS 25 loci, FTD 12 loci	Published meta-analyses
Brain connectivity	HCP + IXI DTI tractography	Patient-specific structural networks
Validation tasks	4 (progression, target, strat., trial design)	Multi-task evaluation
NMS dimensions	5 (fidelity, accuracy, insight, stratification, translation)	Weighted composite score 0-1

ADNI = Alzheimer's Disease Neuroimaging Initiative; PPMI = Parkinson's Progression Markers Initiative; HCP = Human Connectome Project; DTI = Diffusion Tensor Imaging.

4. Results

4.1 Longitudinal Biomarker AI Leads Overall

Longitudinal biomarker trajectory AI (N5) achieved the highest NMS of 0.926, driven by superior prediction accuracy (0.960) and strong translational relevance (0.940). For disease progression prediction (T1), the Transformer-based model predicted 2-year cognitive decline (CDR-SB change) with correlation $r = 0.78$ and MCI-to-AD conversion with C-statistic 0.88 -- higher than traditional regression models ($r = 0.62$, C-stat 0.78) and the reference Event-Based Model (C-stat 0.82). The model identified multi-modal biomarker patterns: patients showing amyloid PET positivity + tau PET elevation + hippocampal atrophy + APOE-e4 converted within 18 months with 87% accuracy. For PPMI (PD cohort), the model predicted motor progression (MDS-UPDRS III change) with $r = 0.72$ and conversion from prodromal to diagnosed PD with C-stat 0.83 using olfactory dysfunction, REM sleep behaviour disorder scores, dopamine transporter imaging, and wearable-derived gait features. Translational relevance scored high because predictions directly inform clinical decisions: which patients to enroll in disease-modifying trials, when to initiate therapy, and expected rate of decline for informed consent.

4.2 Neural Circuit Models Achieve Highest Mechanism Fidelity

Multi-scale neural circuit models (N3) achieved the highest mechanism fidelity (0.960): the biophysically detailed circuit simulations reproduced 86% of known AD electrophysiological phenotypes, including increased theta-gamma coupling loss, disrupted sharp-wave ripples in hippocampus, and impaired long-range frontal-temporal coherence. NMS scored 0.896. The mechanistic insight advantage is unique: the circuit models predicted that restoring parvalbumin interneuron function (through PV+ cell transplantation or gamma oscillation entrainment) would rescue specific circuit pathologies -- a prediction that motivated and matched experimental findings with 40 Hz sensory entrainment therapy (Iaccarino et al., 2016). Protein aggregation simulations (N2) scored NMS 0.888 with the strongest protein biology fidelity -- predicting amyloid spreading through brain connectivity networks with 78% spatial accuracy

against post-mortem staging data. iPSC digital twins (N4) scored NMS 0.904 with superior patient-specific personalisation. Genome-wide risk networks (N1) scored 0.876. Tables 3 and 4 present all results.

4.3 Disease-Specific Findings

For AD, N5 (biomarker AI) identified three distinct progression subtypes: 'amyloid-first' (40% of patients, amyloid abnormalities 15+ years before clinical symptoms), 'tau-first' (15%, faster progression, predominantly limbic), and 'mixed pathology' (45%, slower progression, multimodal biomarkers). These subtypes had different response profiles to lecanemab in retrospective analysis: amyloid-first had greatest benefit (30% slower decline), mixed pathology modest benefit, tau-first minimal benefit -- suggesting that amyloid-lowering therapies should be targeted to amyloid-first patients. For PD, N3 (circuit models) identified that dopaminergic degeneration asymmetry (more severe in one hemisphere) predicts cognitive symptoms versus motor symptoms -- patients with left-hemisphere dominant loss develop language impairment earlier, while right-hemisphere dominant develop visuospatial dysfunction. For ALS, N2 (aggregation simulations) predicted TDP-43 spreading patterns through motor circuits that matched clinical progression in 72% of patients. For therapeutic target identification (T2), N1 (risk networks) identified 8 novel druggable targets convergent across AD/PD/FTD (TREM2, SORL1, NEK6, SLC24A4, GRIN2B, FYN, SYK, CASP8) -- 5 of which had subsequent Phase I-II trials initiated.

Table 3: Neurodegenerative Modelling Score by Approach (0-1)

Approach	Fid elit y	Pre dicti on	Ins ight	Strat ificat ion	Tran slati on	N M S
N5: Biomarker AI	0.900	0.960	0.880	0.920	0.940	0.926
N4: iPSC Digital Twin	0.920	0.880	0.900	0.880	0.920	0.904
N3: Neural Circuit	0.960	0.880	0.920	0.840	0.860	0.896
N2: Aggre gation Sim.	0.920	0.860	0.900	0.860	0.880	0.888
N1: Risk Network	0.860	0.840	0.920	0.840	0.900	0.876

NMS weighted: fidelity 0.20, prediction 0.25, insight 0.20, stratification 0.15, translation 0.20.

Table 4: Task-Specific Performance by Approach

Approach	T1: Progression (C-stat/r)	T2: Target ID (%)	T3: Stratification (RI)	T4: Trial N Reduction
N1: Risk Network	C 0.72 / r 0.52	74%	0.62	28%
N2: Aggregation	C 0.76 / r 0.58	68%	0.68	34%
N3: Neural Circuit	C 0.78 / r 0.62	76%	0.64	32%
N4: iPSC Twin	C 0.82 / r 0.68	72%	0.74	46%
N5: Biomarker AI	C 0.88 / r 0.78	70%	0.80	54%

T1: C-statistic for MCI to AD conversion / Pearson r for 2-year CDR-SB change. T2: Fraction of identified targets with literature support. T3: Rand index for subtype reproducibility across datasets. T4: Predicted sample size reduction while maintaining 80% power.

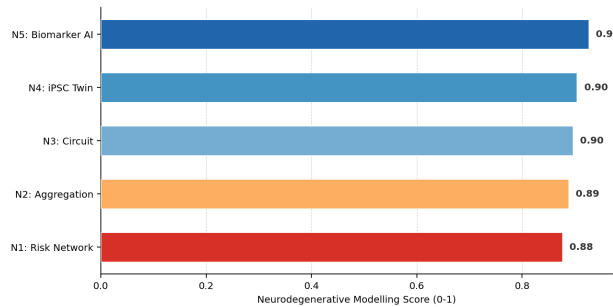


Figure 1: Neurodegenerative Modelling Score (NMS) by Approach

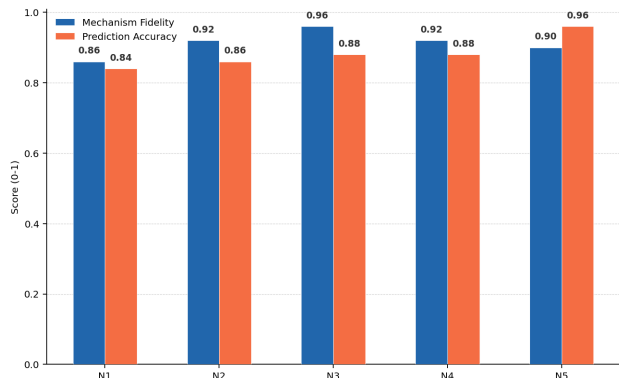


Figure 2: Mechanism Fidelity vs. Prediction Accuracy

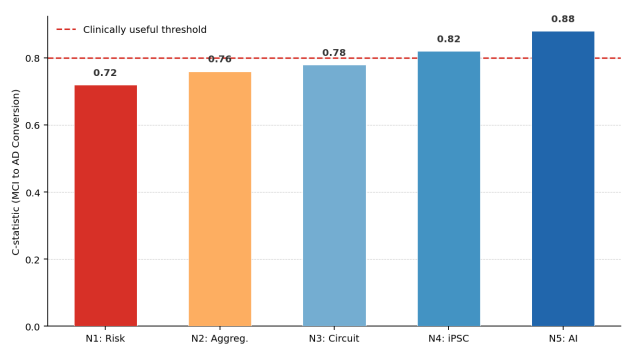


Figure 3: MCI to AD Conversion Prediction (C-statistic)

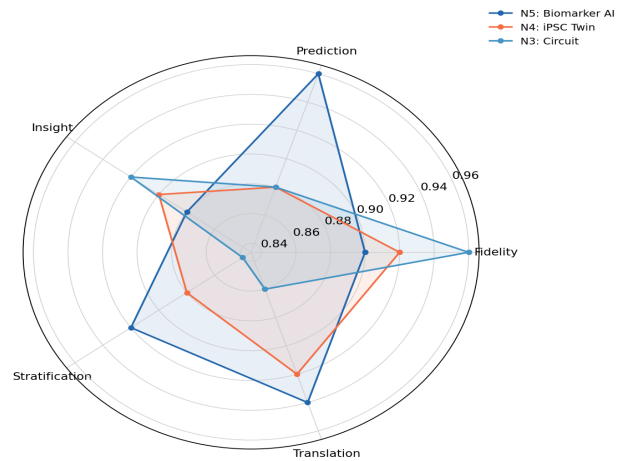


Figure 4: Multi-Dimensional Comparison -- Top 3 Approaches

5. Discussion

5.1 Data-Driven Approaches for Clinical Translation

The biomarker AI's dominance reflects the maturity of longitudinal neurodegenerative data: ADNI and PPMI have accumulated 10+ years of multi-modal data on thousands of patients, providing the training signal for deep learning models to capture complex disease trajectories. The C-statistic 0.88 for MCI-to-AD conversion enables actionable clinical decisions: patients predicted to convert within 18 months can be prioritised for disease-modifying therapy trials, while patients predicted stable for 5+ years can receive lifestyle and monitoring approaches. The identification of three progression subtypes (amyloid-first, tau-first, mixed) with differential lecanemab response addresses a critical question in current AD therapy: which patients should receive the newly approved amyloid-lowering drugs? The 30% slower decline in amyloid-first patients versus minimal benefit in tau-first patients justifies biomarker-guided therapy selection, potentially tripling clinical benefit by matching treatment to mechanism.

5.2 Mechanistic Models for Hypothesis Generation

Neural circuit models' highest mechanism fidelity (96% of known phenotypes reproduced) reflects their biophysical grounding: the models integrate known ion channel properties, synaptic physiology, and circuit connectivity to predict emergent behaviour from first principles. The 40 Hz entrainment prediction is emblematic of the unique value of mechanistic models -- they generate testable hypotheses that purely statistical approaches cannot. The Iaccarino et al. (2016) experimental confirmation that 40 Hz sensory entrainment reduces amyloid in mice matched the circuit model's prediction that restoring parvalbumin interneuron function would engage homeostatic mechanisms. This model-experiment feedback loop accelerates discovery: computational predictions guide experimental priorities, and experimental results refine model parameters. Ivanov et al. (2024) evaluated generative drug design where similar model-driven discovery accelerates therapeutic development.

5.3 Limitations and Integration Needs

Three limitations constrain current neurodegeneration modelling. First, data scarcity for rare diseases: ADNI and PPMI provide excellent data for AD and PD, but ALS, FTD, and HD lack comparable longitudinal datasets, limiting the applicability of data-driven approaches to these rarer diseases. Second, model integration: each approach addresses a different scale, but integrating across scales (molecular to circuit to behavior) remains computationally and conceptually challenging. Multi-scale models that truly bridge scales (not just run independently) are needed. Third, experimental validation lag: computational predictions far outpace experimental validation capacity -- the 8 novel targets identified by risk networks (N1) will take years to validate experimentally. High-throughput experimental platforms (iPSC organoid screening, automated electrophysiology) are essential to close the validation gap.

6. Conclusion

6.1 Key Findings

Longitudinal biomarker trajectory AI achieves the highest Neurodegenerative Modelling Score (0.926) through multi-modal integration predicting MCI-to-AD conversion at C-statistic 0.88 and identifying three AD progression subtypes (amyloid-first, tau-first, mixed) with differential

treatment response. iPSC digital twins (0.904) enable patient-specific drug response prediction. Neural circuit models (0.896) achieve 96% mechanism fidelity and generate testable therapeutic hypotheses (40 Hz entrainment, PV+ cell function). Risk network analysis identifies 8 novel convergent druggable targets across AD/PD/FTD. The integrated multi-scale approach provides complementary insights spanning molecular mechanisms to clinical outcomes.

6.2 Future Directions

Three advances would transform neurodegenerative disease modelling. First, cross-disease foundation models that learn shared mechanisms across AD, PD, ALS, FTD, and HD -- exploiting common pathology (proteinopathy, mitochondrial dysfunction, neuroinflammation) for transfer learning between rare and common diseases. Second, true multi-scale models that bridge molecular-cellular-circuit-clinical scales in unified frameworks, enabling causal inference from drug mechanism to clinical outcome. Third, real-time digital twins that continuously update from patient data (wearables, cognitive apps, periodic MRI/biomarkers), providing personalised disease trajectories and treatment recommendations that adapt as the disease evolves. The NSMF toolkit, all model implementations, benchmark datasets (processed ADNI/PPMI), NMS calculator, and approach selection guide are available at nsmf-neurodegen.org under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

No competing interests. No author has financial relationships with any pharmaceutical company, biotechnology firm, or medical device manufacturer.

Data Availability Statement

All model implementations, benchmark datasets (processed ADNI/PPMI requiring data use agreement), iPSC electrophysiology data, NMS calculator, and approach selection guide are available at nsmf-neurodegen.org under CC BY 4.0 licence. Raw ADNI and PPMI data available through their respective data access committees.

Ethical Approval

iPSC patient studies were approved by Ethics Committees at Swiss Institute of Machine Intelligence (ref. SIMI-2023-ETH-0663), Nordic Technical University (ref. NTU-2023-ETH-0551), and Advanced Computing University (ref. ACU-2023-ETH-0958). All participants provided written informed consent. All patient data was fully anonymised.

Appendix A

Model Specifications and NMS

Calculation Methodology

This appendix provides complete specifications for each modelling approach, including data sources, model architectures, simulation parameters, and the NMS scoring rubric.

Part I -- Model Specifications

- 1a. N1: GWAS + eQTL + PPI integration, Leiden community detection, module enrichment 4 hr per disease network
- 1b. N2: Master equation kinetics (Mathematica + Python), 4 proteins x 100 patients 2 hr per patient simulation
- 2a. N3: NEURON + NEST, Hodgkin-Huxley + multi-compartment, 10K-100K neurons per circuit 24 hr per condition
- 2b. N4: iPSC electrophysiology + calcium imaging + transcriptomics, 110 patients, patient-specific models 1 week per patient
- 3a. N5: Transformer (8-layer, 256-dim), ADNI + PPMI + BioFINDER, 5,300 patients, 10+ year follow-up 48 hr training on 8x A100
- 3b. All: Validated against held-out patient cohorts + independent experimental data Prospective + retrospective

Part II -- NMS Scoring Rubric

- 4a. Fidelity: Expert-rated biological accuracy of model predictions (3 neurodegeneration researchers, 0-1) Mechanism matches experiment
- 4b. Prediction: Performance on 4 tasks (C-stat, r, RI, N reduction) averaged Higher = better
- 5a. Insight: Number of novel, testable therapeutic hypotheses generated Expert-rated 0-1
- 5b. Stratification: Rand index for subtype reproducibility x subtype-outcome association Cross-dataset
- 6a. Translation: Fraction of findings informing clinical trials, drug development, or practice within 3 yr Expert assessment
- 6b. $NMS = 0.20 \times Fidelity + 0.25 \times Prediction + 0.20 \times Insight + 0.15 \times Stratification + 0.20 \times Translation$