

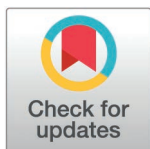
RESEARCH ARTICLE

Data-driven modeling of spatiotemporal dynamics using multimodal imaging data

Chunyan Li¹, Yutong Mao², Xiao Liu^{2,3}, Wenrui Hao^{1*}

1 Department of Mathematics, The Pennsylvania State University, University Park, Pennsylvania, United States of America, **2** Department of Biomedical Engineering, The Pennsylvania State University, University Park, Pennsylvania, United States of America, **3** Institute for Computational and Data Sciences, The Pennsylvania State University, University Park, Pennsylvania, United States of America

* wqh64@psu.edu



Abstract

Understanding how biological systems evolve across space and time remains a fundamental challenge, particularly when dynamic processes vary substantially across individuals. We present a personalized graph-based dynamical modeling framework for characterizing spatiotemporal biological dynamics from longitudinal multimodal imaging data. The framework constructs individualized brain graphs from MRI and PET measurements and learns patient-specific dynamical parameters governing regional structural and molecular changes. Applied to 1,891 participants from the Alzheimer's Disease Neuroimaging Initiative, the model captures the coordinated evolution of amyloid- β , tau, neurodegeneration, and cognition and accurately predicts their future trajectories, outperforming established clinical and neuroimaging benchmarks. Patient-specific dynamical parameters reveal distinct patterns of biological progression and provide improved prediction of future cognitive decline compared with standard biomarkers. Sensitivity analysis further identifies regional network features associated with the propagation of pathological and structural changes, recovering known temporolimbic and frontal vulnerability patterns. These results demonstrate how data-driven dynamical modeling can integrate multimodal longitudinal measurements to uncover individualized spatiotemporal patterns and latent mechanisms of biological change. The framework provides a quantitative approach for studying complex biological dynamics across heterogeneous individuals and establishes a foundation for personalized modeling of progressive biological processes.

OPEN ACCESS

Citation: Li C, Mao Y, Liu X, Hao W (2026) Data-driven modeling of spatiotemporal dynamics using multimodal imaging data. *PLoS Comput Biol* 22(9): e1014751. <https://doi.org/10.1371/journal.pcbi.1014751>

Editor: Jian Liu, University of Birmingham, UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

Received: March 11, 2026

Accepted: August 23, 2026

Published: September 18, 2026

Copyright: © 2026 Li et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data availability statement: All multimodal neuroimaging and clinical data used in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI; <http://adni.loni.usc.edu/>) following approval of our data use application. Regional A β -PET and tau-PET standardized uptake value

Author summary

Alzheimer's disease is a complex brain disorder that develops slowly over many years. Changes in the brain can begin long before memory and thinking problems become noticeable, but it remains difficult to predict how quickly the disease will progress in a particular person. In this study, we developed

ratios (SUVRs) were derived from the “UC Berkeley - AV45 analysis [ADNI1, GO, 2, 3] (version: 2020-05-12)” and “UC Berkeley - AV1451 analysis [ADNI1, GO, 2, 3] (version: 2022-04-26)” datasets. Cortical thickness measures were obtained from the “UCSF Cross-Sectional FreeSurfer (6.0) [ADNI3]” and “UCSF Cross-Sectional FreeSurfer (5.1) [ADNI1, GO, 2]” releases. The Mini-Mental State Examination (MMSE) scores were obtained from “Mini-Mental State Examination (MMSE) [ADNI1,GO,2,3,4]”. Resting-state fMRI data were collected from 3T scanners following standardized ADNI acquisition protocols, and functional connectivity was computed between DKT-68 atlas regions. The simulation study code of hierarchical structured training incorporating with homotopy regularization is openly available at <https://github.com/chunyanlimath/AD-DigitalTwin-Model>. The sensitivity analysis code is available at <http://salib.readthedocs.io/en/latest/>.

Funding: C. L. and W. H. were supported by the National Institute of General Medical Sciences (NIGMS) through Grant No. R35GM146894. W. H. was also supported by the National Science Foundation (NSF) through Grant No. DMS-2533995 and by the Huck Chair in AI Mathematical Modeling from The Pennsylvania State University's Huck Institutes of the Life Sciences. This work was also supported by the NSF under Grant No. DMS-2052685. Authors C. L. and W. H. received salary support from the NIGMS and NSF grants described above. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

a computer-based approach that creates a personalized “digital twin” of Alzheimer’s disease progression. The approach combines information from brain scans collected repeatedly over time with mathematical models of how disease-related changes develop and spread through the brain. We tested the framework using data from nearly 1,900 people participating in the Alzheimer’s Disease Neuroimaging Initiative. Our model predicted future changes in key disease indicators and cognitive function, outperforming several commonly used prediction approaches. It also identified differences in how individuals progress and highlighted brain regions that may play important roles in this process. This work provides a foundation for more personalized prediction of Alzheimer’s disease progression and could ultimately help researchers improve clinical trials and develop more targeted treatments.

1 Introduction

Alzheimer’s disease (AD) affects over 50 million people worldwide and represents the most common form of dementia, imposing a profound societal, economic, and personal burden [1]. Recent years have witnessed a landmark shift in the treatment landscape with the regulatory approval of disease-modifying therapies, specifically the anti-amyloid monoclonal antibodies lecanemab (Leqembi) and donanemab (Kisunla), which have been shown to slow cognitive decline in early-stage AD [2–4]. However, these treatments only modestly slow progression rather than halt or reverse the disease, and their use is associated with challenges including amyloid-related imaging abnormalities (ARIA), high costs, limited accessibility, and the requirement for early diagnosis [4,5]. Thus, the need to better understand the underlying mechanisms driving AD onset and progression remains urgent. AD is characterized by extracellular amyloid-beta ($A\beta$) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau, which disrupt synaptic function, promote neuronal loss, and manifest as progressive cognitive decline [6,7]. While the amyloid cascade hypothesis and related biomarker cascade frameworks have provided a foundational understanding of AD progression and are supported by substantial longitudinal imaging and clinical evidence [8,9], important questions remain regarding how these pathological processes propagate across interconnected brain regions and give rise to heterogeneous patient-specific trajectories. Addressing these challenges requires mechanistic models that integrate biomarker interactions with spatiotemporal disease dynamics.

Recent advances in biomarker imaging have transformed our ability to study AD in vivo. Positron emission tomography (PET) allows visualization of $A\beta$ and tau deposition, structural MRI quantifies cortical atrophy, and cerebrospinal fluid (CSF) assays provide complementary molecular insights [1,10–12]. Functional imaging further reveals network-level alterations linked to cognitive impairment [13], emphasizing that the critical questions are not only *what* changes occur in AD, but *how*, *where*, and *why* pathology propagates across the brain. These data create an unprecedented

opportunity to study AD as a spatiotemporally dynamic disease, but also highlight the limitations of conventional analytical approaches.

Mathematical and computational modeling [14–21] has emerged as an essential tool to integrate multi-modal data, formalize mechanistic hypotheses, and generate testable predictions and therapeutic interventions *in silico* [22–27]. Ordinary differential equation (ODE) models have been used to describe $A\beta$ production, aggregation, and clearance [22,23,28], as well as tau hyperphosphorylation [29,30]. Extensions incorporating neuroinflammation and other modulatory factors have provided additional mechanistic insights [31], and partial differential equation (PDE) frameworks capture the spatial propagation of pathology across brain regions [32–34]. Complementing these mechanistic approaches, statistical and machine learning, and deep learning approaches have become increasingly important for analyzing large-scale clinical datasets. Mixed-effects models are widely used to characterize longitudinal trajectories and population heterogeneity, while machine learning and deep learning approaches leverage multimodal biomarkers to predict disease onset, stratify patients, and infer biomarker relationships [35–40]. Although these methods often achieve strong predictive performance, they generally do not explicitly represent disease propagation over brain networks or provide a framework for evaluating competing biological hypotheses. As a result, they are generally less suited for testing mechanistic hypotheses or simulating intervention effects across interconnected brain regions within a unified disease-progression framework.

Despite these advances, critical gaps remain. Most models focus on individual pathways or global biomarkers, failing to capture the integrated spatiotemporal dynamics of amyloid, tau, and neuroinflammation [41–45]. Few frameworks provide personalized, spatially resolved predictions from longitudinal multi-modal imaging, limiting their translational relevance. Existing approaches often rely on MRI, regionally aggregated CSF or PET measures, lacking the spatial granularity needed to identify critical regions for targeted intervention [46,47]. Here, we present a novel, mechanistic, data-driven framework to model the spatiotemporal progression of AD biomarkers at the individual level. Our approach formulates a system of PDEs on the brain's functional connectivity network, capturing the regional propagation of three key AD biomarkers: $A\beta$, tau, cortical atrophy. The model incorporates subject-specific parameters inferred from PET and structural MRI data, enabling personalized predictions while preserving mechanistic interpretability. Comprehensive parameter inference and two-level sensitivity analyses identify critical disease drivers and brain regions. To our knowledge, this is the first mechanistic spatiotemporal model integrating multiple clinically validated biomarkers in a patient-specific framework. Beyond individualized prediction, the proposed framework serves as a mechanistic modeling platform that enables the incorporation and testing of competing biological hypotheses regarding disease propagation and therapeutic intervention effects.

This framework provides three key advances:

1. It unifies temporal biomarker progression with spatial propagation across brain networks.
2. It enables patient-specific modeling of AD progression using multi-modal imaging biomarkers.
3. It facilitates the prediction of region-specific therapeutic responses, advancing precision medicine in AD.

By bridging mechanistic modeling, graph-based brain networks, and longitudinal neuroimaging, our approach provides a comprehensive, personalized view of AD progression, with direct implications for early diagnosis, individualized prognosis, and targeted therapeutic strategies.

2 Results

We applied the spatiotemporal generalized AD Biomarker Cascade (generalized ADBC) model to characterize individualized dynamics of clinically validated AD biomarkers and evaluate its potential for personalized disease forecasting. The model, governed by 14 parameters (6 global and 8 region-specific), captures heterogeneity across the brain's functional network. Once estimated from neuroimaging data, it allows simulation of amyloid-beta ($A\beta$), tau, neurodegeneration

(N), and cognitive decline (C), while a two-level sensitivity analysis identifies region-specific vulnerabilities. The overall workflow is illustrated in Fig 1, highlighting the model's use for personalized biomarker prediction and sensitive-region identification.

2.1 Individual-level simulations and predictions

Fig 2 demonstrates the model's performance for three representative individuals. The model achieves prediction accuracies of 96.15%, 93.97%, and 93.35% for A β , tau, and N, respectively. Training fits (red rectangles), test evaluations (green), and future predictions (blue) are shown, with curves representing accumulated biomarker levels across 68 brain regions. By visualizing only two representative fitting points per biomarker, we simplify interpretation while preserving the spatial distribution of pathology. These results illustrate the model's capability to forecast individualized biomarker trajectories, providing actionable information for clinicians to anticipate disease progression and personalize interventions.

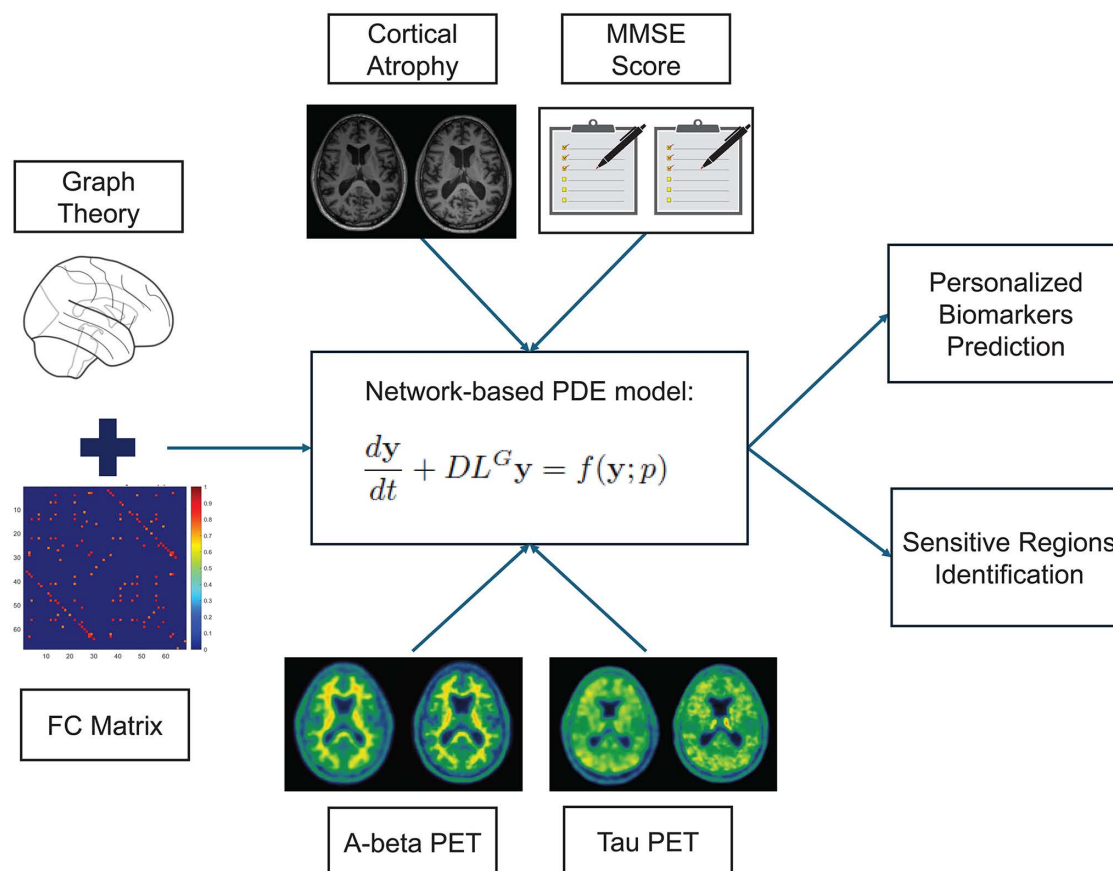


Fig 1. Workflow integrating graph theory, neuroimaging biomarkers (A β -PET, tau-PET, cortical atrophy, and MMSE score), AD pathophysiology, and mathematical modeling to construct a personalized digital twin of AD progression. The model, formulated as a spatiotemporal system of PDEs, captures biomarker diffusion and nonlinear interactions on the brain's functional connectivity network. Coupled with sensitivity analysis, the framework enables personalized forecasting and identification of region-specific vulnerabilities with sensitivity analysis.

<https://doi.org/10.1371/journal.pcbi.1014751.g001>

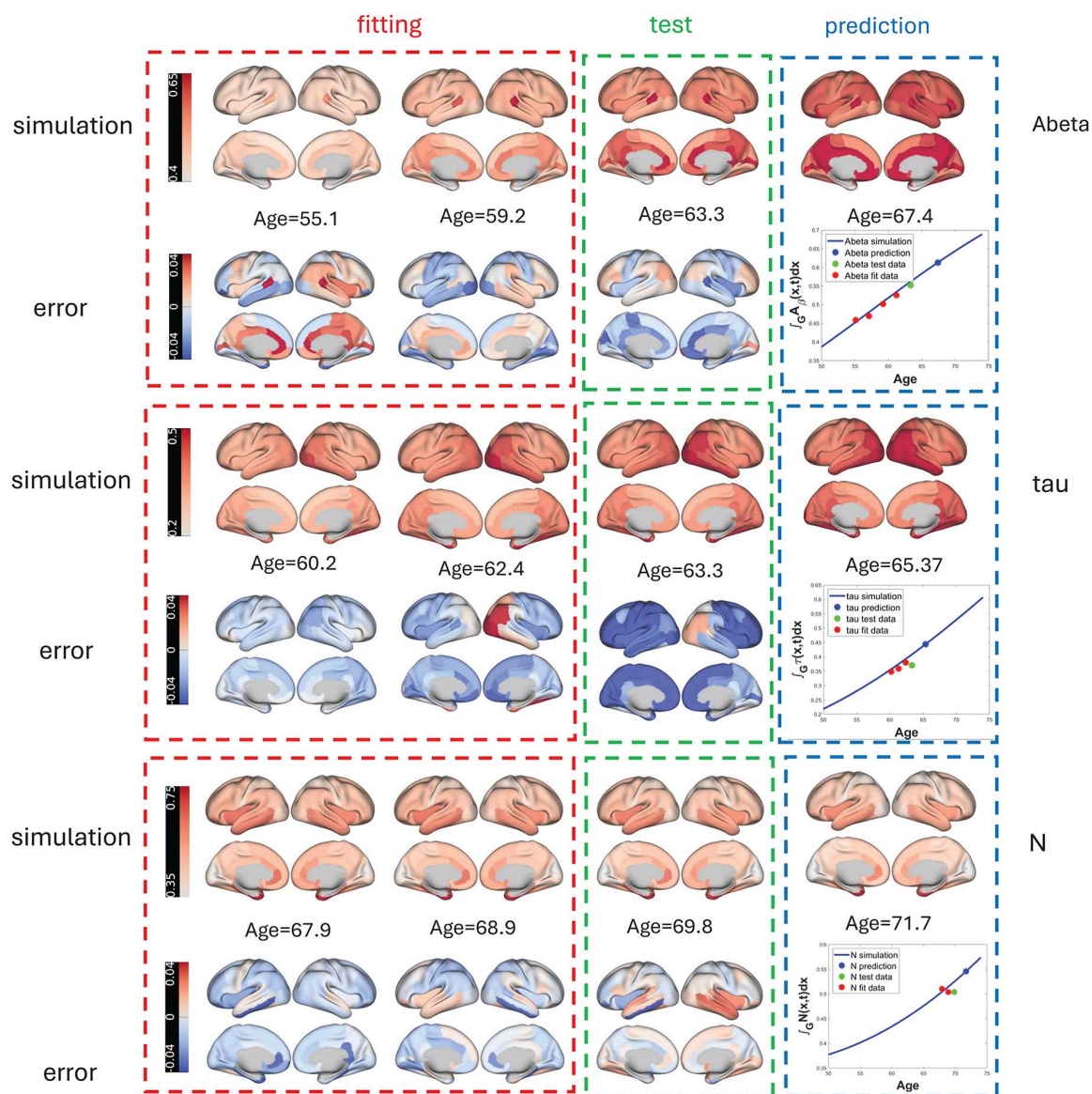


Fig 2. Model simulations of three spatially dependent biomarkers ($A\beta$, tau, N) for three individuals. Training fits, test evaluations, and future predictions are color-coded as red, green, and blue, respectively. Regional curves show accumulated biomarker levels across 68 brain regions.

<https://doi.org/10.1371/journal.pcbi.1014751.g002>

2.2 Population-level evaluation for one time point prediction

To assess generalizability, we evaluated performance across all subjects (Table 1). The proposed nonhomogeneous (NH) PDE model, which allows region-specific parameters to capture spatial heterogeneity, consistently outperforms the homogeneous (H) benchmark in both training and testing. On the test set, the NH model achieves higher mean accuracy for every outcome, with average gains of 1.87% ($A\beta$), 1.44% (tau), 4.40% (N), and 4.88% (C). In addition, the NH model shows smaller standard deviations, indicating more stable and robust predictions across subjects.

Table 1. Summary reported as (median, mean, std) for each biomarker for homogeneous (H) model and nonhomogeneous (NH) model for one-time-point prediction.

Homogeneous (H) model		
Biomarker	Fit (H) (%)	Test (H) (%)
Abeta	(89.15, 88.87, 1.98)	(87.95, 87.61, 2.87)
tau	(91.32, 89.48, 5.57)	(86.71, 85.07, 6.16)
N	(81.51, 80.03, 8.18)	(81.38, 79.30, 9.09)
C	(95.63, 91.33, 12.31)	(94.98, 88.26, 16.87)
Nonhomogeneous (NH) model		
Biomarker	Fit (NH) (%)	Test (NH) (%)
Abeta	(90.78, 91.33, 3.05)	(89.63, 89.48, 3.44)
tau	(92.49, 91.36, 5.01)	(88.06, 86.51, 5.62)
N	(85.16, 85.49, 5.80)	(83.92, 83.70, 5.82)
C	(96.58, 95.80, 3.52)	(95.81, 93.14, 7.59)

<https://doi.org/10.1371/journal.pcbi.1014751.t001>

Boxplots (Fig 3) and histograms (Fig 4) further confirm that most subjects achieve over 80% accuracy across biomarkers under the NH model. Together, these results support the utility of incorporating regional heterogeneity for reliable, personalized predictions at the population level.

2.3 Population-level evaluation for long term prediction

Based on the two-step prediction results summarized in Table 2, we further evaluated the model's multi-step forecasting ability by training on the first $N - 2$ time points and predicting the last two visits. This two-step-ahead validation provides a more stringent test of long-term predictive performance compared to the one-step-ahead setting. Consistent with the one-step results, the nonhomogeneous (NH) model consistently outperforms the homogeneous (H) benchmark across all biomarkers in both fitting and testing. On the test set, the NH model achieves higher mean accuracy for every biomarker, with average gains of 1.63% for $A\beta$, 15.46% for tau, 1.43% for N, and 2.11% for C. Notably, the improvement for tau is substantial, increasing from 72.20% (H) to 87.66% (NH), indicating that region-specific parameters are critical for capturing the heterogeneous progression of tau pathology. For N and C, the NH model also demonstrates more stable predictions,

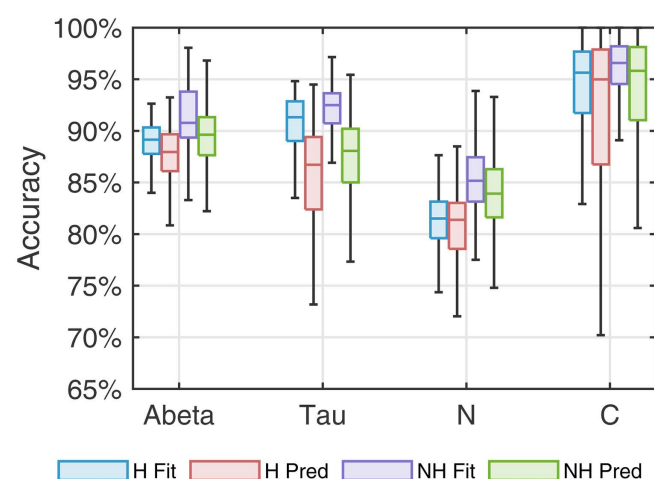


Fig 3. Boxplots of model accuracy across all subjects for H and NH models (interquartile range and median shown).

<https://doi.org/10.1371/journal.pcbi.1014751.g003>

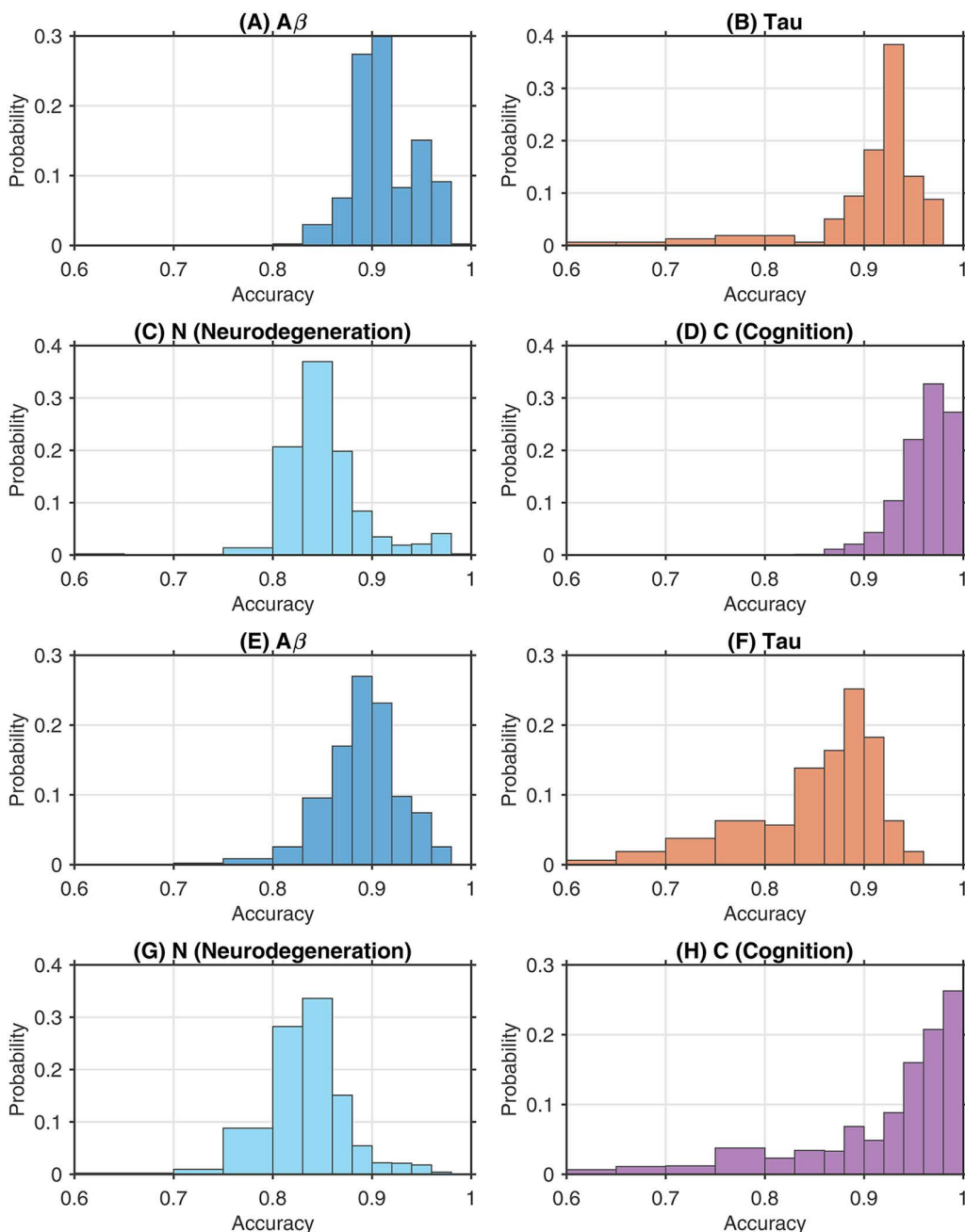


Fig 4. Distributions of fitting accuracies (top) and prediction accuracies (bottom) of the nonhomogeneous (NH) model across all subjects for the four biomarkers: A β , tau, neurodegeneration (N), and cognition (C). Each histogram shows the empirical distribution of subject-specific accuracies for the corresponding biomarker. The y-axis represents the probability (normalized frequency) of observations within each accuracy bin.

<https://doi.org/10.1371/journal.pcbi.1014751.g004>

as reflected by smaller standard deviations (2.30% vs. 2.63% for N; 5.99% vs. 8.87% for C on the test set). The two-step prediction results are consistent with the one-step findings, confirming that the NH model's superiority is not limited to short-term forecasting but generalizes to longer-term trajectory prediction. This multi-step validation directly addresses the concern regarding overestimation of predictive performance, demonstrating that the proposed model maintains robust

Table 2. Summary reported as (median, mean, std) for each biomarker for homogeneous (H) model and nonhomogeneous (NH) model for two-time-point prediction.

Homogeneous (H) model		
Biomarker	Fit (H) (%)	Test (H) (%)
Abeta	(89.25, 89.25, 1.98)	(88.37, 88.01, 2.05)
tau	(70.15, 71.44, 19.19)	(71.91, 72.20, 16.84)
N	(78.20, 77.84, 3.97)	(80.25, 79.94, 2.63)
C	(96.37, 96.74, 1.25)	(96.51, 93.01, 8.87)
Nonhomogeneous (NH) model		
Biomarker	Fit (NH) (%)	Test (NH) (%)
Abeta	(91.19, 91.30, 2.63)	(89.31, 89.64, 1.99)
tau	(93.53, 93.41, 1.82)	(87.57, 87.66, 4.34)
N	(80.45, 80.51, 1.42)	(81.31, 81.37, 2.30)
C	(96.37, 96.74, 1.26)	(97.38, 95.12, 5.99)

<https://doi.org/10.1371/journal.pcbi.1014751.t002>

accuracy even when tasked with predicting multiple future time points. The consistency across both evaluation settings (one-step and two-step) provides strong evidence for the model's ability to capture underlying disease progression dynamics and its potential utility for clinical trajectory forecasting.

2.4 Stability analysis of thresholds for creating functional connectivity network

We further assessed the sensitivity of the model to the choice of FC threshold used for network construction. As summarized in Table 3, the prediction accuracy remained consistently high across all thresholds, with median test accuracies ranging from 88.76% to 90.15%. Notably, the standard deviations of test accuracies decreased substantially at thresholds of 0.75 and 0.80 (from 7.51% to approximately 2%), indicating stable and reliable predictions. These findings demonstrate that the proposed nonhomogeneous model is highly robust to the specific FC threshold selection, maintaining strong predictive performance for A β deposition across a reasonable range of network configurations.

2.5 Impact of training strategies

We next evaluated the impact of the proposed hierarchical structured training strategy with homotopy regularization technique on parameter estimation and predictive performance. As shown in Fig 5, homotopy regularization consistently outperforms conventional training across a range of regularization weights. Compared with vanilla optimization, the proposed strategy improves both fitting and prediction accuracy, particularly in the intermediate regularization regime, while maintaining stable performance throughout the continuation process. These results suggest that homotopy regularization effectively stabilizes optimization of the nonlinear PDE-constrained inverse problem and reduces susceptibility to poor local minima. Besides, as demonstrated in Table 1 and Fig 3, the proposed hierarchical structured training strategy in Fig 9 consistently yields equal or improved fitting and prediction accuracy compared with the preceding stage. This

Table 3. Summary statistics of fit and prediction accuracy of nonhomogeneous model for predicting A β with different thresholds.

Threshold	Fit (%)			Test (%)		
	Median	Mean	Std	Median	Mean	Std
0.70	89.25	87.73	5.65	88.76	86.37	7.51
0.75	91.19	91.30	2.63	89.31	89.64	1.99
0.80	91.25	91.41	2.16	90.15	89.86	2.70

<https://doi.org/10.1371/journal.pcbi.1014751.t003>

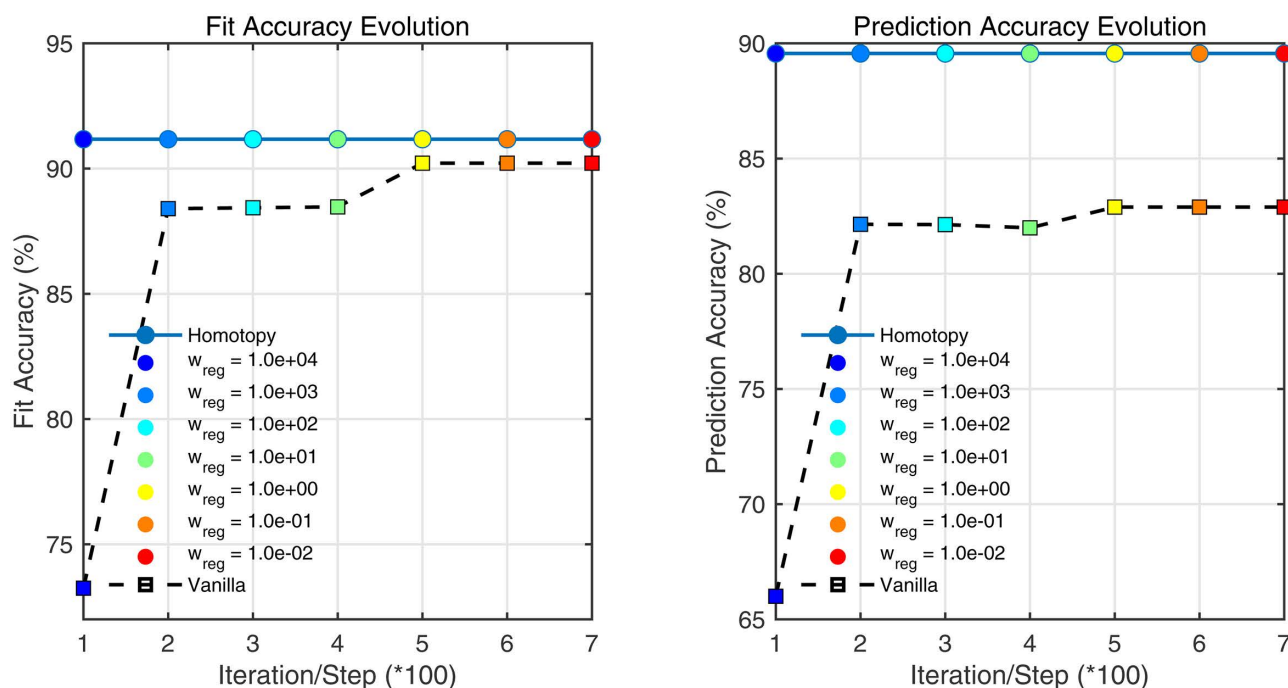


Fig 5. Comparison of homotopy regularization (solid lines with circles) and vanilla training (dashed lines with squares) across optimizer iterations. Homotopy training maintains consistently high fitting and prediction accuracy as the regularization weight is gradually reduced, whereas vanilla optimization exhibits substantially lower performance.

<https://doi.org/10.1371/journal.pcbi.1014751.g005>

coarse-to-fine strategy enables efficient exploration of the high-dimensional parameter space while preserving information learned at earlier stages.

2.6 Effectiveness of low-rank approximation for patient-specific functional connectivity network

We further evaluated the effectiveness of the proposed low-rank representation for personalized functional connectivity estimation. Fig 6 compares the approximation error of the learned patient-specific FC matrices with that of the optimal rank-2 SVD approximation. Despite being inferred indirectly from biomarker observations rather than FC measurements, the proposed representation achieves an error distribution comparable to the corresponding rank-2 SVD reconstruction. Since rank-2 SVD provides the optimal low-rank approximation in the least-squares sense, these results suggest that the learned representation captures the dominant subject-specific connectivity patterns relevant to disease progression.

To rigorously isolate and quantify the contribution of patient-specific functional connectivity (FC) to predictive performance, we conducted a controlled ablation study. Specifically, we held all learned nonhomogeneous model parameters and initial conditions fixed and compared two FC configurations: (i) population-average FC, implemented by setting $\mathbf{u} = \mathbf{v} = 0$, and (ii) patient-specific FC, in which $\mathbf{u}$ and $\mathbf{v}$ were optimized from individual neuroimaging data. By keeping all other model components identical, this design ensures that any difference in predictive performance can be attributed specifically to the incorporation of personalized connectivity information.

Using the biomarker $A\beta$ as a representative case, Table 4 reports the mean $\pm$ standard deviation of test accuracy and the maximum individual-level improvement achieved by incorporating patient-specific FC. At the population level, incorporating patient-specific FC results in only a modest improvement in predictive accuracy, with the mean test accuracy increasing from $89.25 \pm 3.51\%$ to $89.48 \pm 3.44\%$. This relatively small change indicates that population-average

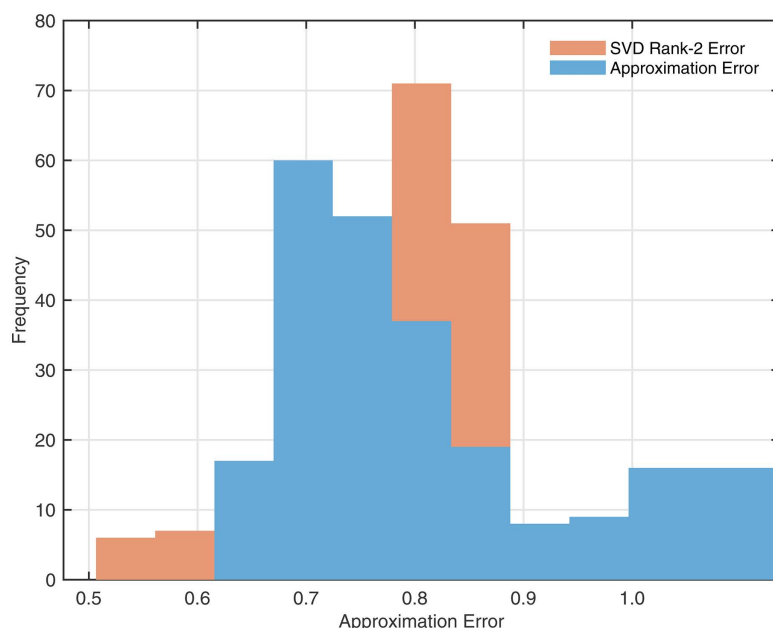


Fig 6. Distribution of relative approximation errors for patient-specific FC matrices. The proposed rank-2 latent representation achieves approximation accuracy comparable to the optimal rank-2 SVD reconstruction of the corresponding FC matrices, indicating that the dominant subject-specific connectivity structure can be captured using only a small number of latent parameters.

<https://doi.org/10.1371/journal.pcbi.1014751.g006>

Table 4. Comparison of prediction accuracy for $A\beta$ with and without patient-specific u, v in the non-homogeneous model. Accuracy is reported as mean $\pm$ std, together with the maximum individual-level improvement in accuracy.

Metric	Fit (%)	Test (%)
without u, v	91.08 $\pm$ 3.06, baseline	89.25 $\pm$ 3.51, baseline
with u, v	91.33 $\pm$ 3.05, 8.36	89.48 $\pm$ 3.44, 9.73

<https://doi.org/10.1371/journal.pcbi.1014751.t004>

FC provides a strong baseline for $A\beta$ prediction at the cohort level. Nevertheless, the individual-level analysis reveals substantially larger benefits for specific patients, with the maximum improvement in test accuracy reaching 9.73 percentage points. These results suggest that the predictive value of patient-specific FC is heterogeneous across individuals: while population-average connectivity may adequately represent patients whose functional connectivity patterns are close to the population norm, personalized FC can provide substantial additional predictive information for patients whose connectivity patterns deviate more substantially from the population average. Thus, although patient-specific FC does not substantially improve aggregate predictive performance, it can yield meaningful individualized gains for a subset of patients.

2.7 Two-level sensitivity analysis

We performed a two-level sensitivity analysis to identify critical model parameters and brain regions. First, assuming homogeneous parameters across all 68 DK regions, total sensitivity indices were calculated over age (Fig 7A), identifying six highly influential parameters: λ_{CN} , λ_T , $\lambda_{A\beta}$, K_T , λ_{TN} , and λ_N (Fig 7B). Second, we analyzed the top five region-specific

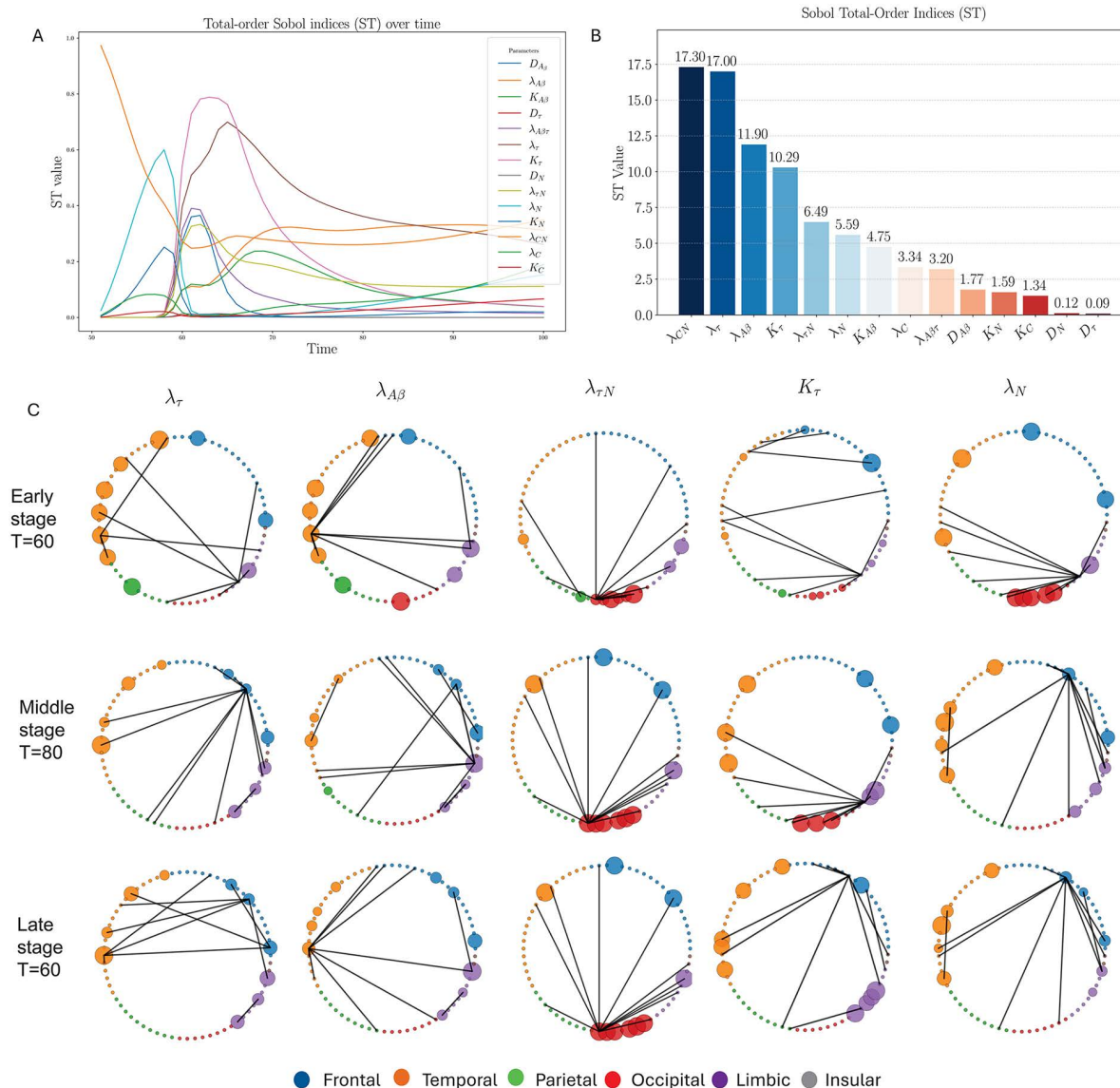


Fig 7. A: Dynamics of total sensitivity indices for 14 model parameters over age. B: Importance bar plot of sorted model parameters based on total sensitivity indices over age. C: The 68 Desikan–Killiany (DK) regions are grouped into six anatomical lobes. The second-level sensitivity analysis of key region-specific parameters is shown across three time stages ($t=60, 80$, and 100). The first-order Sobol index (S_1), represented by the circle radius, quantifies each lobe's direct contribution to the model variance, while the second-order index (S_2), encoded by edge width, captures the strength of pair-wise interactions between lobes. During computations, the model's initial condition is set to the population mean at $t=50$, and the parameter ranges are defined by the minimum and maximum values of each parameter across the 68 regions. Each second-level sensitivity analysis is performed for a single region-specific parameter, with all other parameters fixed at the mean of the optimized values across all subjects.

<https://doi.org/10.1371/journal.pcbi.1014751.g007>

parameters to pinpoint sensitive brain regions (Fig 7C), providing a quantitative basis for targeted monitoring and intervention.

Stage-wise sensitivity analysis reveals a dynamic network propagation mechanism: at early stages ($t=60$), first-order sensitivity indices (S_1) are relatively uniform, with modest cross-lobe interactions (S_2). By mid-stage ($t=80$), temporal–frontal, temporal–parietal, and temporal–limbic interactions dominate, while at late stage ($t=100$), inter-lobar

interactions drive model sensitivity, with frontal–temporal and frontal–limbic couplings particularly prominent. These findings quantitatively support a network-based mechanism of disease spread, consistent with connectome-driven hypotheses.

[Table 5](#) summarizes top DK regions for each biomarker and disease stage. The temporal and frontal lobes are most affected, with involvement intensifying over disease progression, whereas the insular lobe remains minimally affected. Aggregated across biomarkers, frontal and temporal lobes show increasing involvement from early to late stages, confirming that network hubs play a central role in AD progression [48].

Table 5. Top DK regions by biomarkers and three disease stages with lobe distribution. F: Frontal, T: Temporal, P: Parietal, O: Occipital, L: Limbic, I: Insular.

	Early Stage (t=60)	Middle Stage (t=80)	Late Stage (t=100)
A_{β}	LH Posteriorcingulate (L)	LH Medialorbitofrontal (P)	LH Temporalpole (T)
	RH Temporalpole (T)	LH Parahippocampal (T)	RH Bankssts (L)
	RH Postcentral (T)	RH Cuneus (T)	LH Parahippocampal (T)
	RH Insula (T)	RH Bankssts (L)	RH Cuneus (T)
	RH Parsorbitalis (F)	LH Caudalanteriorcingulate (L)	LH Caudalanteriorcingulate (L)
	LH Transversetemporal (P)	RH Precuneus (L)	RH Precuneus (L)
	RH Posteriorcingulate (L)	LH Frontalpole (F)	LH Frontalpole (F)
	LH Unknown (T)	RH Paracentral (T)	RH Paracentral (T)
	LH Postcentral (O)	RH Entorhinal (F)	RH Entorhinal (F)
	LH Bankssts (T)	LH Rostralanteriorcingulate (F)	LH Rostralanteriorcingulate (F)
Lobe	F:1, T:5, P:1, O:1, L:2	F:3, T:3, P:1, O:0, L:3	F:3, T:4, P:0, O:0, L:3
τ	LH Caudalmiddlefrontal (F)	LH Unknown (T)	RH Cuneus (T)
	RH Superiorfrontal (T)	RH Entorhinal (F)	LH Bankssts (T)
	LH Pericalcarine (T)	LH Bankssts (T)	RH Paracentral (T)
	RH Insula (T)	RH Paracentral (T)	LH Caudalanteriorcingulate (L)
	RH Posteriorcingulate (L)	LH Caudalanteriorcingulate (L)	RH Bankssts (L)
	LH Precuneus (L)	LH Rostralanteriorcingulate (F)	LH Rostralanteriorcingulate (F)
	LH Postcentral (O)	LH Parahippocampal (T)	LH Parahippocampal (T)
	LH Precentral (F)	RH Bankssts (L)	RH Entorhinal (F)
	RH Middletemporal (P)	LH Frontalpole (F)	LH Frontalpole (F)
	RH Precentral (F)	RH Precuneus (L)	RH Precuneus (L)
Lobe	F:3, T:3, P:1, O:1, L:2	F:3, T:4, P:0, O:0, L:3	F:3, T:4, P:0, O:0, L:3
N	RH Middletemporal (P)	RH Lateralorbitofrontal (O)	RH Superiorfrontal (T)
	RH Superiorfrontal (T)	RH Middletemporal (P)	LH Cuneus (O)
	RH Caudalmiddlefrontal (O)	LH Precuneus (L)	LH Pericalcarine (T)
	LH Pericalcarine (T)	LH Postcentral (O)	RH Caudalmiddlefrontal (O)
	LH Postcentral (O)	LH Lingual (O)	LH Frontalpole (F)
	LH Lingual (O)	RH Superiorfrontal (T)	LH Entorhinal (T)
	LH Cuneus (O)	LH Cuneus (O)	RH Entorhinal (F)
	RH Lateralorbitofrontal (O)	LH Paracentral (P)	RH Cuneus (T)
	LH Precuneus (L)	LH Pericalcarine (T)	RH Supramarginal (T)
	RH Posteriorcingulate (L)	RH Caudalmiddlefrontal (O)	LH Temporalpole (T)
Lobe	F:0, T:2, P:1, O:5, L:2	F:0, T:2, P:2, O:5, L:1	F:2, T:6, P:0, O:2, L:0
Total	F:4, T:10, P:3, O:7, L:6	F:6, T:9, P:3, O:5, L:7	F:8, T:14, P:0, O:2, L:6

<https://doi.org/10.1371/journal.pcbi.1014751.t005>

3 Discussion

We present a region-specific, spatiotemporal model of AD progression that integrates biomarker dynamics within the ATN framework. By coupling PDEs on the brain functional-connectivity network with a two-level sensitivity analysis, we identified both key parameters and spatiotemporal patterns that govern the cascade from amyloid- β ($A\beta$) deposition to tau (τ) aggregation and subsequent neurodegeneration (N). This framework provides a mechanistic, patient-specific approach to capture the dynamics of AD biomarkers and their propagation across the brain.

3.1 Model performance and predictive reliability

Leveraging multimodal neuroimaging data from the ADNI cohort, we parametrized the PDE model to construct individualized, region-specific biomarker trajectories. Unlike conventional AD criteria, which often overlook interindividual heterogeneity and focus on convergent phenotypes [49], our approach emphasizes personalized modeling as a pathway toward precision medicine.

The model demonstrated high accuracy in both fitting and prediction for $A\beta$, τ , N, and cognitive decline (Fig 3, Table 1), with consistently low variance between training and testing errors. Homotopy-regularized training improved convergence and optimization stability compared to standard training (Fig 5), mitigating overfitting in this high-dimensional parameter space. Furthermore, low-rank approximations of subject-specific FC matrices achieved comparable accuracy to SVD rank-2 approximations of true FC matrices, demonstrating that computational efficiency can be achieved without compromising predictive performance. These results also support the use of the rank-two parameterization in (7). The low-rank representation reflects a deliberate trade-off between model flexibility and parameter identifiability. While higher-rank parameterizations could potentially capture more complex subject-specific connectivity patterns, they would also introduce substantially more parameters relative to the limited amount of longitudinal rs-fMRI data available for each subject. The observed agreement between the learned FC matrices and the corresponding rank-two SVD approximations suggests that the proposed representation captures the dominant patient-specific connectivity variations while maintaining computational efficiency and robustness. The ablation study of $\mathbf{u}$, $\mathbf{v}$ further demonstrates that patient-specific FC provides a tangible, albeit modest, improvement over population-average FC. While the cohort-level gain is limited, the substantial individual-level improvements indicate that patient-specific $\mathbf{u}$ and $\mathbf{v}$ can provide meaningful additional predictive information for certain patients, particularly those whose connectivity patterns deviate from the population average. The modest aggregate improvement may partly reflect limitations in both the available neuroimaging data and the current low-rank parameterization, where the rank-two update may be too restrictive to fully capture the complexity of individual-specific FC patterns. With larger, higher-quality, and more longitudinally sampled datasets, together with more expressive personalized FC parameterizations, the benefits of patient-specific connectivity may become more pronounced. Collectively, these results validate both the robustness and the predictive reliability of the model, supporting its use for patient-specific forecasting.

3.2 Regional vulnerabilities and biological interpretation

The sensitivity analysis elucidated key parameters (λ_{CN} , λ_{τ} , $\lambda_{A\beta}$, K_{τ} , $\lambda_{\tau N}$, λ_N) that drive biomarker dynamics and highlighted spatiotemporal patterns of vulnerability [46]. Across disease stages, the temporal lobe consistently emerged as the earliest and most affected region, with frontal lobe involvement increasing in mid-to-late stages, whereas the insular lobe remained minimally affected and parietal/occipital lobes were relatively spared (Table 5). These patterns align with established neuropathological observations [50–52], wherein tau pathology initiates in the entorhinal and hippocampal cortices before propagating to temporal and frontal association areas. Imaging studies [53,54] similarly report cortical thinning beginning in medial temporal regions and progressing anteriorly with disease severity. Our findings reinforce the temporal lobe as a neurodegenerative epicenter and the frontal lobe as a late-stage amplifier.

3.3 Amyloid, tau, and neurodegeneration trajectories

The model recapitulates empirical biomarker propagation patterns observed in PET and MRI studies. Early A β accumulation was predicted in temporobasal and frontomedial cortices, followed by expansion to frontal and limbic regions [55–57]. Tau propagation persisted in temporal and frontal lobes across stages, consistent with functional-pathway-based stepwise spread [58,59]. Neurodegeneration, reflected in cortical thinning, intensified primarily in frontal and temporal lobes during late stages, in agreement with longitudinal MRI studies [60,61]. These trajectories capture the hallmark spatial hierarchy of AD progression: limbic–temporal initiation, frontal expansion, and relative parietal/occipital sparing.

3.4 Network interactions and clinical implications

Second-order sensitivity analysis revealed that inter-lobe interactions dominate over intra-lobe effects, suggesting that AD spreads as a coordinated network disruption rather than isolated regional atrophy. This observation supports connectome-driven propagation frameworks [45,48,62–64], highlighting the role of functional connectivity in mediating cross-lobe pathology. By leveraging functional rather than purely structural connectivity, our model captures dynamic interactions that may underlie symptom evolution: frontal–temporal interplay could correspond to transitions from memory to executive dysfunction, while late insular involvement may relate to emotional and interoceptive deficits. These insights emphasize the potential for network-targeted therapeutic strategies that aim to preserve functional resilience rather than focusing solely on single regions.

3.5 Limitations and future directions

Several limitations of the current framework should be acknowledged.

First, the proposed biomarker cascade model represents a simplified description of AD progression. The current formulation assumes a predominantly sequential pathway from amyloid-beta accumulation to tau pathology, neurodegeneration, and cognitive decline, consistent with the amyloid cascade hypothesis and ATN framework which has been adopted in numerous mathematical and computational models of disease progression [33,35,38]. However, accumulating evidence suggests bidirectional interactions and parallel pathological processes involving tau, neuroinflammation, vascular dysfunction, and metabolic alterations [65,66]. Direct amyloid-mediated neurotoxicity, biomarker feedback loops, and neuroinflammatory mechanisms are not explicitly represented in the current model. Future extensions will incorporate additional state variables and interaction pathways as richer longitudinal multimodal datasets become available.

Second, the model assumes a fixed patient-specific graph Laplacian throughout the observation period. Although functional connectivity evolves during aging and disease progression, reliable estimation of dynamic subject-specific connectivity requires denser longitudinal rs-fMRI data than are currently available. Consequently, the learned graph Laplacian should be interpreted as an individualized network substrate capturing dominant disease-relevant coupling patterns. Future work will investigate time-dependent graph Laplacians and dynamic network reorganization.

Third, another limitation concerns our incorporation of FC into the diffusion term. Our formulation is motivated by the graph Laplacian reaction–diffusion framework, in which FC naturally represents inter-regional coupling and governs the propagation of pathology through the diffusion process across brain regions. Nevertheless, alternative formulations are also possible. For example, FC may additionally influence local biological processes and could be incorporated into the reaction term to modulate regional disease dynamics. Although the current formulation is consistent with a large body of mathematical modeling studies on graph-based reaction–diffusion systems and is further supported by our robustness analyses, we acknowledge that it is not the only biologically plausible modeling strategy. Future work should systematically compare diffusion-driven and reaction-driven FC formulations to better understand their biological implications and improve the mechanistic interpretability of the resulting model parameters.

Fourth, uncertainty in model predictions was not quantified. The current framework provides point estimates of subject-specific parameters and future biomarker trajectories without corresponding confidence intervals or prediction

intervals, limiting our ability to assess the reliability of individualized forecasts. Future work will incorporate uncertainty quantification through Bayesian inference, probabilistic parameter estimation, and ensemble forecasting approaches, enabling more rigorous assessment of prediction confidence and improving the reliability of patient-specific forecasting.

Beyond these limitations, future work will integrate additional biological pathways, dynamic network evolution, uncertainty quantification, and richer multimodal datasets, including molecular, vascular, and neuroinflammatory biomarkers. Such extensions will further improve model personalization and provide a more comprehensive mechanistic framework for studying Alzheimer's disease progression and therapeutic interventions.

4 Conclusion

In this work, we developed a data-driven modeling framework to characterize the spatiotemporal progression of Alzheimer's disease (AD) biomarkers and cognitive decline by integrating mathematical modeling, AD pathophysiology, neuroimaging data, graph theory, and sensitivity analysis. Specifically, we proposed a novel spatiotemporal model formulated as a system of partial differential equations (PDEs) defined on the brain's functional connectivity network, capable of describing the regional propagation of the three key AD biomarkers and cognitive decline.

Using multimodal neuroimaging data from the ADNI cohort, we parametrized the PDE model to construct patient-specific and region-specific biomarker trajectories, enabling individualized characterization of disease dynamics. Recognizing that current AD criteria often overlook interindividual heterogeneity—thus limiting therapeutic efficacy as drug development targets convergent phenotypes rather than patient-specific mechanisms [49]—our approach emphasizes personalized modeling as a pathway toward precision medicine in AD.

To address the high-dimensional, non-convex optimization problem arising in parameter estimation, we implemented a hierarchical training strategy combined with a homotopy regularization scheme, which ensures robust and efficient calibration of the biomarker cascade model.

Overall, the proposed PDE-based network model successfully reproduces the hallmark spatial-temporal features of AD, including early temporal–limbic vulnerability, progressive frontal involvement, and relative parietal–occipital sparing. By bridging mathematical modeling with neurobiological evidence, this framework establishes a quantitative foundation for understanding region-specific disease progression and offers a principled platform for designing personalized, network-aware therapeutic interventions in Alzheimer's disease.

5 Methods

5.1 Data description

We accessed the multimodal data from the ADNI website following approval of our data use application (<http://adni.loni.usc.edu/>). The files titled “UC Berkeley - AV45 analysis [ADNI1,GO,2,3] (version:2020-05-12)” and “UC Berkeley - AV1451 analysis [ADNI1,GO,2,3] (version:2022-04-26)” compiled by ADNI were utilized to obtain A β -PET and tau-PET regional standardized uptake value ratios (SUVRs). Regional SUVRs were determined by dividing the standardized uptake values (SUVs) of the target regions by the SUV of the whole cerebellum, which served as the reference region because of its low specific binding and consistent uptake across the study population.

In this study, we quantify neurodegeneration using cortical thickness, a well-established MRI-based biomarker that reflects neuronal loss and structural atrophy in AD. This approach follows previous studies demonstrating that cortical thinning is strongly associated with AD pathology and predicts future cognitive decline [67–72]. Specifically, reduced cortical thickness in AD-signature regions such as the medial temporal, inferior parietal, and posterior cingulate cortices has been shown to correlate with amyloid and tau burden as well as with disease progression. Cortical thickness data was obtained from ADNI as part of the “UCSF-Cross-Sectional FreeSurfer (6.0) [ADNI3]” and “UCSF-Cross-Sectional FreeSurfer (5.1) [ADNI1, GO, 2]” datasets.

Resting-state fMRI data were acquired on 3 Tesla MR scanners across multiple ADNI sites using a standardized ADNI imaging protocol (<https://adni.loni.usc.edu/data-samples/adni-data/neuroimaging/mri/mri-scanner-protocols/>). Each session included a high-resolution 3D T1-weighted MPRAGE scan for anatomical segmentation and spatial registration. Acquisition parameters for the T1-weighted scan were: field of view = $208 \times 240 \times 256 \text{ mm}^3$, voxel size = $1 \times 1 \times 1 \text{ mm}^3$, TR = 2300 ms, TI = 900 ms, TE = minimum full echo, and scan duration of approximately 6 min 20 s. Resting-state functional images were obtained using the ADNI-3 Basic gradient-echo EPI-BOLD sequence with the following parameters: field of view = $220 \times 220 \times 163 \text{ mm}^3$, TR = 3000 ms, TE $\approx 30 \text{ ms}$, and flip angle = 90° . Each run lasted 10 min and produced approximately 200 volumes.

Preprocessing was performed using a standard resting-state pipeline consistent with prior ADNI studies (han2021reduced, han2024global, mao2026global). The preprocessing steps included motion correction, skull stripping, spatial smoothing with a 4 mm FWHM Gaussian kernel, temporal filtering in the 0.01–0.1 Hz range, and alignment of functional images to the individual T1-weighted scan followed by transformation into MNI-152 standard space. To minimize transient magnetization effects and filtering boundary artifacts, the first five and last five volumes of each run were removed prior to analysis. Parcel-wise resting-state time series were then derived using the Desikan–Killiany–Tourville 68-region atlas [73] by averaging the preprocessed BOLD signal within each cortical parcel. Functional connectivity (FC) data were derived by calculating Pearson’s correlation coefficients between time series extracted from regions defined by the DKT 68 atlas [73], based on rsfMRI data.

The Mini-Mental State Examination (MMSE) scores were obtained from “Mini-Mental State Examination (MMSE) [ADNI1,GO,2,3,4]”. In this study, we did not impose a strict requirement for each subject to have data available for all modalities mentioned. Instead, our inclusion criterion focused on ensuring that each subject had data from at least three separate visits for one of the key measurements: tau-PET, amyloid-beta ($A\beta$ -PET), or cortical thickness.

The study included 1,891 subjects from ADNI who were classified as cognitively normal (CN), mild cognitive impairment (MCI), AD, or of unknown status. The details are shown in Table 6 and the demographic details are shown in Table 7. Because the biomarker-cascade PDE system is sequentially driven ($A\beta \rightarrow \tau \rightarrow N \rightarrow C$), we estimate the model in a decoupled, stage-wise manner. Accordingly, the dataset is summarized in terms of *task-specific cohorts*: for each sub-equation, we include all participants who have at least three longitudinal time points for the modality/modalities required to fit that sub-equation. Importantly, the resulting cohorts are *not mutually exclusive*. For example, the “ $A\beta$ cohort”

Table 6. Task-specific cohorts used in the sequential (decoupled) estimation of the biomarker-cascade PDE system. For each sub-equation, we report the number of ADNI participants with at least three longitudinal time points for the required modality/modalities. Rows correspond to effective sample sizes for fitting each sub-equation and are not mutually exclusive (e.g., the $A\beta$ cohort is the union of all participants with $A\beta$ available, regardless of whether τ , N , and/or C are also observed). CN: cognitively normal; MCI: mild cognitive impairment; AD: Alzheimer’s disease.

Sub-equation	Required observed modalities	CN	MCI	AD	Unknown	Total
$A\beta$ dynamics ($A\beta$)	$A\beta$	142	140	3	186	471
τ dynamics (τ)	τ and $A\beta$	30	36	1	17	84
	τ only ($A\beta$ not available)	30	26	16	3	75
Neurodegeneration (N)	$A\beta + \tau + N$	40	53	0	14	107
	$\tau + N$ only ($A\beta$ not available)	19	9	4	0	32
	$A\beta + N$ only (τ not available)	121	192	1	21	335
	N only (neither $A\beta$ nor τ available)	87	264	109	20	480
Cognition (C)	$A\beta + \tau + N + C$	40	53	0	14	107
	$\tau + N + C$ only ($A\beta$ not available)	19	9	4	0	32
	$A\beta + N + C$ only (τ not available)	121	192	1	21	335
	$N + C$ only (neither $A\beta$ nor τ available)	83	254	100	20	457

<https://doi.org/10.1371/journal.pcbi.1014751.t006>

Table 7. Subject characteristics after keeping participants with at least 3 longitudinal records for each modality. Values are counts unless stated otherwise.

	MMSE	A β	τ	N (12GO)	N (ADNI3)
Unique subjects (N)	1889	471	159	806	148
Gender (M/F/Missing)	1027 / 862 / 0	236 / 235 / 0	73 / 86 / 0	436 / 370 / 0	69 / 79 / 0
APOE genotype counts	2/2: 3 2/3: 140 2/4: 39 3/3: 873 3/4: 651 4/4: 181 Missing: 2	2/2: 1 2/3: 47 2/4: 8 3/3: 260 3/4: 129 4/4: 26	2/3: 9 2/4: 2 3/3: 77 3/4: 56 4/4: 15	2/2: 1 2/3: 66 2/4: 14 3/3: 369 3/4: 279 4/4: 77	2/3: 15 2/4: 4 3/3: 79 3/4: 42 4/4: 8
Age, mean (SD)	73.35 (7.50)	72.76 (7.20)	73.59 (7.60)	73.42 (7.32)	74.82 (7.03)
Age missing	0	0	0	0	0

<https://doi.org/10.1371/journal.pcbi.1014751.t007>

is the union of all participants with longitudinal A β PET data, regardless of whether τ , N, and/or cognition (C, derived from MMSE) are also available. Table 6 reports the effective sample sizes by diagnosis group for fitting each stage.

5.2 Data preparation

We normalize data measurements across all subjects and brain subregions using:

$$\mathbf{y}_j^i = \frac{\mathbf{y}_j^i}{\mathbf{y}_j^{ref}} \quad (1)$$

where $i = 1, 2, \dots, N$ indexes the i -th subject, $j = 1, 2, \dots, 68$ denotes the j -th brain subregion. And $\mathbf{y}_j^{ref}$ is the reference value for $\mathbf{y}_j$ in the j -th region. $\mathbf{y}$ include amyloid-beta (A β), tau (τ_p), neurodegeneration (N) and cognitive impairment C.

To ensure uniform biomarker trajectories and cognitive decline trajectory aligned with disease progression (all increasing with severity), we define linear transformations on the normalized biomarkers and cognitive decline as follows:

- Amyloid β and tau proteins: both A β and τ_p increase with disease progression, as measured in PET imaging.
- Neurodegeneration: N_{ct} quantified by cortical thickness which decreases as AD advances. We invert this trend by defining $N = 1 - N_{ct}$.
- Cognitive decline: Measured via the Mini-Mental State Examination (MMSE) score S, which declines with worsening pathology. We reverse its directionality using $C = 1 - S$.

This normalization and transformation framework ensures consistent biomarker and cognitive decline behavior between subjects and subregions, simplifying the interpretation of the model.

5.3 Patient-specific spatiotemporal partial differential equations model

We propose a spatiotemporal generalized Alzheimer's Disease Biomarker Cascade (ADBC) model that incorporates neuroimaging data and regional dynamics using graph theory and network science. This model can be used to capture the spatiotemporal progression of pathology in amyloid and taupathy, neurodegeneration, as well as cognitive decline. As illustrated in Fig 8A, we represent the brain's geometry as an undirected weighted graph $\mathcal{G} = (\mathcal{V}, \mathcal{E})$. Here, 68 nodes (vertices) correspond to DKT 68 atlas, while edges encode functional connectivity between regions. Edge weights, proportional to connectivity strength, are visualized as varying widths. This graph-based topology provides the foundation for

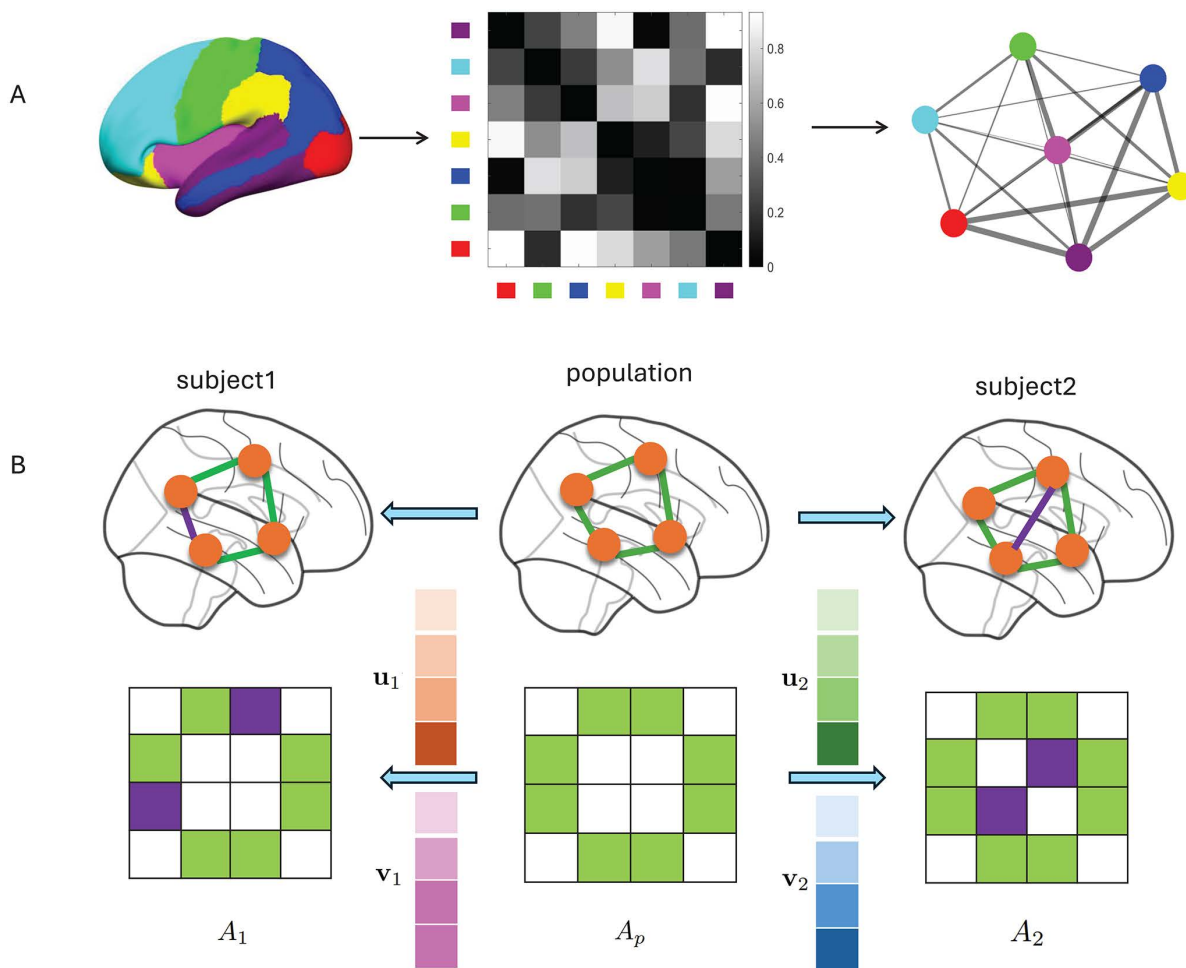


Fig 8. A: Topological representation of the human brain as a graph $\mathcal{G} = (\mathcal{V}, \mathcal{E})$. Node set $\mathcal{V}$ comprises 7 functionally defined brain regions (Left). Edge set $\mathcal{E}$ is derived from a functional connectivity matrix, where connections between regions are thresholded for denoising (Middle). The undirected weighted graph $\mathcal{G}$ visualizes connectivity strengths, with edge widths proportional to the magnitude of entries in the functional connectivity matrix (Right). This graph structure enables spatially resolved modeling of Alzheimer's disease progression. B: A schematic representation of a simplified brain network as a graph, illustrating possible ways to derive a patient-specific adjacency matrix from the population-level adjacency matrix. The left arrow indicates that the topology remains unchanged, but the weights (FC values) on the edges differ, representing variations in the strength of functional connectivity between nodes. The right arrow illustrates a topology change, where a new edge is added to the graph, representing a functional connection strong enough to be included in the patient's network.

<https://doi.org/10.1371/journal.pcbi.1014751.g008>

our extended mathematical model, enabling spatially resolved modeling of disease progression while retaining the core dynamics of the ADBC framework.

Now we are ready to extend the ADBC model to be a spatial discretized partial differential equation (PDE) of A_β , τ_ρ , N and the ordinary differential equation (ODE) of C defined on the brain $\mathcal{G}$ as follows:

$$\begin{aligned} \frac{dA_\beta}{dt} + D_{A_\beta} L^G A_\beta &= \lambda_{A_\beta} A_\beta (K_{A_\beta} - A_\beta), \\ \frac{d\tau_\rho}{dt} + D_{\tau_\rho} L^G \tau_\rho &= \lambda_{\tau_\rho A_\beta} A_\beta + \lambda_{\tau_\rho} \tau_\rho (K_{\tau_\rho} - \tau_\rho), \\ \frac{dN}{dt} + D_N L^G N &= \lambda_{N\tau_\rho} \tau_\rho + \lambda_N N (K_N - N), \end{aligned} \quad (2)$$

and

$$\frac{dC}{dt} = \lambda_{CN} \int_G N dv + \lambda_C C (K_C - C), \quad (3)$$

where the integration in last equation is defined as:

$$\int_G N(v) dv = \frac{\sum_{v \in \mathcal{V}} d_v N(v)}{\sum_{v \in \mathcal{V}} d_v}, \quad (4)$$

where d_v is the degree of vertices $v \in \mathcal{V}$. This term is a global burden summary of neurodegeneration. λ_{CN} represents how strongly degeneration burden translates into cognitive decline rate.

In the model, A_β represents amyloid pathology, τ_ρ represents amyloid-related tau pathology (measured by tau-PET), N represents neuronal dysfunction/loss, and C represents cognitive impairment. D_{A_β} , D_τ , D_N , λ_{CN} , λ_C and K_C are 6 scalar parameters and λ_{A_β} , λ_{τ_ρ} , λ_N , $\lambda_{\tau_\rho A_\beta}$, $\lambda_{N\tau_\rho}$, K_{A_β} , K_{τ_ρ} and K_N are 8 region-specific parameters which are graph functions $\mathcal{V} \rightarrow \mathbb{R}$ defined on 68 vertices. D_{A_β} , D_τ and D_N characterize the diffusion properties for A_β , τ and N , respectively. λ_{A_β} , λ_{τ_ρ} , λ_N and λ_C reflect the logistic growth rates of the various biomarker cascades. $\lambda_{\tau_\rho A_\beta}$, $\lambda_{N\tau_\rho}$ and λ_{CN} reflect linear growth rates of the biomarkers and determine the influence of various factors on the time-of-onset of the subsequent biomarker cascades. K_{A_β} , K_{τ_ρ} , K_N and K_C , represent the biomarker carrying capacities respectively. We would like to estimate these model parameters using the longitudinal neuroimaging data. L^G is the patient-specific graph Laplacian corresponding to the patient's specific brain functional connectivity network. Note that the graph Laplacian matrix is symmetric positive semi-definite, which can be treated as the discretized version of $-\Delta$ using a finite difference method with Neumann or periodic boundary conditions. We will discuss how to learn patient-specific graph Laplacian L^G from limited functional connectivity data below.

5.4 Learning patient-specific functional connectivity matrix

The graph Laplacian L^G of a undirected weighted graph $\mathcal{G} = (\mathcal{V}, \mathcal{E})$ is defined as the difference between the corresponding degree matrix D and adjacency matrix A

$$L^G = D - A, \quad (5)$$

where $A = (a_{ij}) \in \mathbb{R}^{68 \times 68}$, the adjacency matrix, which is symmetric, is a collection of weights a_{ij} assigned for connected node pairs $(n_i, n_j) \in \mathcal{E}$.

The corresponding degree matrix D , that is, the number of edges attached to each node defined as follow:

$$D_{ij} = \begin{cases} \sum_{k=1}^{68} a_{ik}, & \text{if } i = j, \\ 0 & \text{if } i \neq j. \end{cases} \quad (6)$$

We use the functional connectivity (FC) matrix of 68 regions to compute the adjacency matrix A of brain graph $\mathcal{G}$ after statistical truncation for denoising purpose [74]. More precisely, we treat the two subregions are connected where the corresponding Pearson correlation coefficient value in FC matrix exceed 0.75 and the corresponding p value is less than $1e-5$. Consequently, an edge is established between such pairs of nodes in the graph representation of $\mathcal{G}$. The corresponding adjacency matrix is weighted by the functional connectivity values after removing self-connections.

FC data were derived by calculating Pearson's correlation coefficients between time series extracted from regions defined by the DKT 68 atlas [73], based on resting-state fMRI data. fMRI scans require expensive equipment and technical expertise. Conducting repeated scans over time (longitudinal studies) adds significantly to the cost. fMRI generates

large datasets, especially when acquired longitudinally. Processing these datasets to extract meaningful information requires substantial computational resources. The size of fMRI datasets necessitates significant storage capacity. Patient data must be handled in compliance with strict privacy regulations, adding to the cost and complexity. Hence, a novel mathematical model/method for learning a patient-specific FC matrix (therefore graph Laplacian) from limited FC data collected from a public dataset is necessary.

We propose a qualitative method to learn a patient-specific adjacency matrix (FC matrix), defined as:

$$A = A_p + \frac{1}{2}(\mathbf{u}\mathbf{v}^T + \mathbf{v}\mathbf{u}^T) - \text{diag}\{\mathbf{u}.\mathbf{v}\}, \quad (7)$$

where $\mathbf{u}.\mathbf{v}$ represents the elementwise product of $\mathbf{u}$ and $\mathbf{v}$, resulting in a vector. The term $A_p = \frac{1}{K} \sum_{k=1}^K A^{(k)}$ denotes the population-level adjacency matrix derived from a limited population group. The rank-two matrix $\frac{1}{2}(\mathbf{u}\mathbf{v}^T + \mathbf{v}\mathbf{u}^T)$ approximates the difference between a specific patient's connectivity and the population mean, while the diagonal term $-\text{diag}\{\mathbf{u}.\mathbf{v}\}$ ensures self-connections are removed. The parameters $\mathbf{u}$ and $\mathbf{v}$, which are unit column vectors in $\mathbb{R}^{68}$, quantify the patient-specific functional connectivity variation between different node pairs. The latent vectors $\mathbf{u}$ and $\mathbf{v}$ are introduced as a parsimonious parameterization of patient-specific deviations from the population-level connectivity network. They should not be interpreted as directly measurable biological quantities or clinical biomarkers. Instead, their role is analogous to latent factors in low-rank matrix factorization, providing a compact representation of individualized functional connectivity variations while maintaining model identifiability and computational tractability. In this framework, $\mathbf{u}$ and $\mathbf{v}$ generate subject-specific perturbations of the population adjacency matrix and consequently define personalized graph Laplacians for disease progression modeling.

If $\mathbf{u} = \mathbf{v}$, then (7) degenerates to the case with rank one approximation as follows:

$$A = A_p + \mathbf{u}\mathbf{u}^T - \text{diag}\{\mathbf{u}^2\}. \quad (8)$$

We propose using a rank-two matrix instead of a rank-one matrix to improve expressive capability and to address limitations associated with rank-one representations. A rank-one matrix, such as $\mathbf{u}\mathbf{u}^T$ with the constraint $\|\mathbf{u}\|_2 = 1$, introduces unnecessary coupling between weights corresponding to different node pairs (n_i, n_j) and (n_k, n_l) . For example:

$$\mathbf{u}\mathbf{u}^T = \begin{bmatrix} u_1^2 & u_1u_2 & u_1u_3 & \cdots & u_1u_n \\ u_2u_1 & u_2^2 & u_2u_3 & \cdots & u_2u_n \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ u_nu_1 & u_nu_2 & u_nu_3 & \cdots & u_n^2 \end{bmatrix}, \quad (9)$$

with the constraint $\sum_{i=1}^n u_i^2 = 1$.

In contrast, the rank-two representation $\mathbf{u}\mathbf{v}^T + \mathbf{v}\mathbf{u}^T$ provides greater flexibility:

$$\begin{bmatrix} 2u_1v_1 & u_1v_2 + v_1u_2 & \cdots & u_1v_n + v_1u_n \\ u_2v_1 + v_2u_1 & 2u_2v_2 & \cdots & u_2v_n + v_2u_n \\ \vdots & \vdots & \ddots & \vdots \\ u_nv_1 + v_nu_1 & u_nv_2 + v_nu_2 & \cdots & 2u_nv_n \end{bmatrix}, \quad (10)$$

where the unit constraints $\|\mathbf{u}\|_2 = \|\mathbf{v}\|_2 = 1$ are imposed to enhance numerical stability and prevent stiffness in solving ODE problems.

This representation offers significantly enhanced expressive capability compared to $\mathbf{u}\mathbf{u}^T$. For instance, in the rank-one matrix $\mathbf{u}\mathbf{u}^T$, the weight for the connection between nodes n_1 and n_2 (u_1u_2) is tightly constrained by the weight for the

connection between n_5 and n_6 (u_5u_6) due to the unit norm constraint $\|\mathbf{u}\|_2 = 1$. In reality, the strength of the connection between n_1 and n_2 should not inherently depend on the strength of the connection between n_5 and n_6 . The rank-two representation $\mathbf{uv}^T + \mathbf{vu}^T$ overcomes this limitation, enabling a more accurate and flexible modeling of patient-specific FC.

As illustrated in Fig 8B, the brain network is represented as a graph with four nodes. The middle panel represents the population-level brain network, while individual deviations from this representation can be categorized into two fundamental cases:

- (a) *edge weight changes*: The topology remains unchanged, but the weights on the existing edges differ from the population adjacency matrix. There exists an edge e_i between nodes n_k and n_h , and the weight is modified as $a_{kh} + \frac{1}{2}(u_kv_h + v_ku_h) - \delta_{kh}u_kv_h$ with constraint $-a_{kh} \leq \frac{1}{2}(u_kv_h + v_ku_h) - \delta_{kh}u_kv_h \leq 1 - a_{kh}$. Note that the entries of $\mathbf{u}, \mathbf{v}$ can be negative values as long as they satisfy the constraints so that the weight values could be increased or decreased.
- (b) *topology changes*: New edges are added, representing additional functional connectivity between regions. A new edge e_i^{new} is lighted up between nodes n_l and n_m with the associated weight $a_{lm} = \frac{1}{2}(u_lv_h + v_lu_h) - \delta_{lh}u_lv_h$ with constraint $0 \leq \frac{1}{2}(u_lv_h + v_lu_h) - \delta_{lh}u_lv_h \leq 1$.

Luckily, the expression (7) can cover both cases. As shown in Fig 8B: (a) The left arrow indicates that the topology is identical to the population network, but the strength of functional connectivity (edge weights) varies, indicated by a purple color of the edge. (b) The right arrow illustrates a change in topology, where a new edge appears, representing functional connectivity between two regions strong enough to warrant inclusion. With this model, we address the challenges of data collection and computational expense, enabling efficient analysis of patient-specific brain networks. With the graph Laplacian definition (5) and the patient-specific adjacency matrix formulation (7), the corresponding patient-specific graph Laplacian is defined as

$$L^G = L_p^G + \frac{1}{2} \text{diag}(\mathbf{u} \cdot (\mathbf{v}^T \mathbf{1}) + \mathbf{v} \cdot (\mathbf{u}^T \mathbf{1})) - \frac{1}{2}(\mathbf{uv}^T + \mathbf{vu}^T), \quad (11)$$

where L_p^G denotes the population-level graph Laplacian given by

$$L_p^G = \frac{1}{K} \sum_{k=1}^K (D^{(k)} - A^{(k)}) - \frac{1}{K} \sum_{k=1}^K D^{(k)} - A_p \quad (12)$$

To ensure symmetry of the connectivity network, we replace each measured adjacency matrix by its symmetrized form $A^{(k)} = \frac{A^{(k)T} + A^{(k)}}{2}$ which mitigates asymmetries introduced by the measurement noise. For computational tractability and parameter identifiability, we assume that the patient-specific graph Laplacian L^G remains fixed throughout the observation period.

5.5 Parameters inference by novel hierarchical structured training strategy

Let $\mathbf{y} = (A_\beta, \tau_\rho, N, C)^T$ represent the solution vector obtained by solving model (2), where θ denotes the collection of all model parameters, and $\mathbf{y}_0$ is the initial values of this model. $\hat{\mathbf{y}}(t_i)$ is the clinical data of a specific subject for given age t_i , and $\mathbf{y}(t_i; \theta)$ is the solution of the generalized ADBC model. The model parameters for each patient can be inferred by solving the constrained optimization problem:

$$\begin{aligned} & \min_{\theta, \mathbf{y}_0, \mathbf{u}, \mathbf{v}} \mathcal{L}(\theta, \mathbf{y}_0, \mathbf{u}, \mathbf{v}), \\ \text{subject to: } & a_{kh} + \frac{1}{2}(u_kv_h + v_ku_h) - \delta_{kh}u_kv_h \geq 0, \\ & a_{kh} + \frac{1}{2}(u_kv_h + v_ku_h) - \delta_{kh}u_kv_h \leq 1, \\ & \forall k, h = 1, \dots, 68, \end{aligned} \quad (13)$$

where the objective function is defined as

$$\mathcal{L}(\theta, \mathbf{y}_0, \mathbf{u}, \mathbf{v}) := \sum_{i=1}^M \frac{\|\mathbf{y}(t_i; \theta) - \tilde{\mathbf{y}}(t_i)\|_2^2}{\|\tilde{\mathbf{y}}(t_i)\|_2^2} + w \|\mathbf{y}(100; \theta) - \mathbf{1}\|_2^2, \quad (14)$$

where $\mathbf{u} = (u_1, \dots, u_{68})$ and $\mathbf{v} = (v_1, \dots, v_{68})$ are two unit vectors to learn patient-specific graph Laplacian, a_{kh} is the (k, h) element of adjacency matrix A_p . $\mathbf{y}_0$ is imposed as an optimized variable to avoid the overfitting of the measurement noise in $\tilde{\mathbf{y}}_0$.

This optimization problem is to minimize the L^2 loss on given clinical patient data points and constraint on $\mathbf{y}(100; \theta) = \mathbf{1}$ as the penalty term which is used to ensure the biomarkers and cognitive decline increasing with severity. This optimization problem was solved for each subject in the cohort using all available biomarker and cognitive decline time points $t_i, i = 1, \dots, M$.

To address this challenging high-dimensional problem, we introduce a novel hierarchical structured training strategy incorporating a homotopy regularization technique to enhance the stability and efficiency of parameter learning, as shown in Fig 9. This hierarchical strategy consists of four sequential stages, where the solution obtained at each stage serves as the initial condition for the next, enabling a progressively refined learning of the extended ADBC model from neuroimaging data. By initializing each stage with the optimized solution from the previous stage, the framework progressively enlarges the parameter space while preserving previously learned information, thereby providing a monotonic refinement strategy in which additional model flexibility is introduced progressively, allowing the optimization to maintain or improve upon the fitting performance achieved at earlier stages. To illustrate this procedure concretely, we take the $A\beta$ equation as an example and describe the hierarchical approach in detail below. The equations for other biomarkers can be solved in an equation-by-equation manner [75].

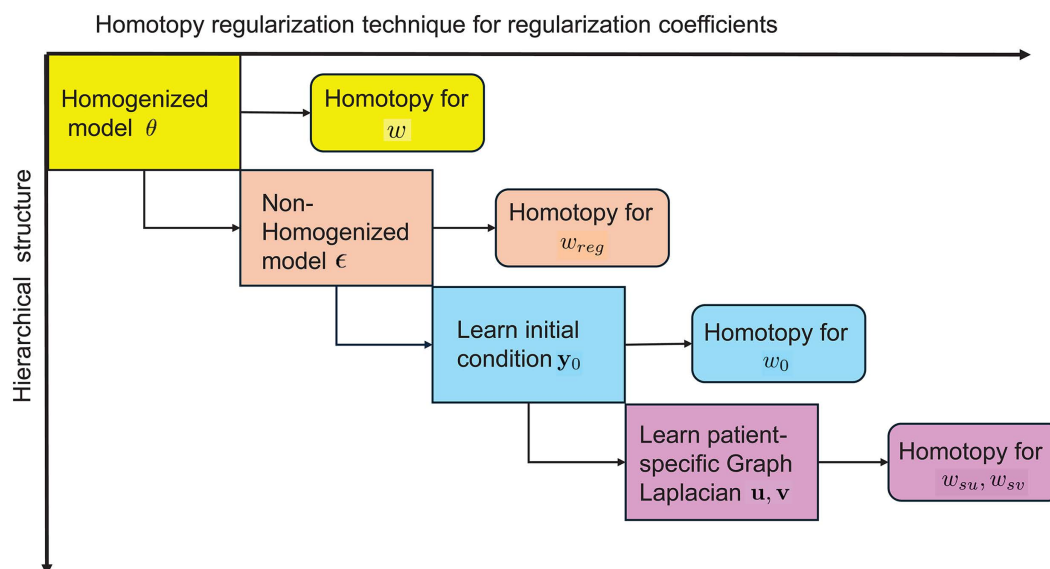


Fig 9. Diagram of the strategies for solving the complex original constrained optimization problem. The original optimization problem is split into 4 optimization steps with a hierarchical structure as shown vertically. The homotopy regularization technique is applied to every regularization coefficient w, w_{reg}, w_0, w_{sv} , and w_{su} for every optimization step accordingly, as shown horizontally.

<https://doi.org/10.1371/journal.pcbi.1014751.g009>

1. Homogenized Model (benchmark): To get a good initial guess for model parameters θ , we homogenize the model by homogenizing the regional variability. Namely, let $(D_{A_\beta}^s, \lambda_{A_\beta}^s, K_{A_\beta}^s)$ and $A_{\beta 0}^s$ be scalars. Then, the model parameters of this homogenized model is $\theta_{A_\beta}^s = (\mathbf{I}^{68} D_{A_\beta}^s, \mathbf{I}^{68} \lambda_{A_\beta}^s, \mathbf{I}^{68} K_{A_\beta}^s)$. Because different patients have different onset times, in order to give the initial conditions, we assume that the initial time for all people is 50 years old, and the corresponding initial value $\mathbf{I}^{68} A_{\beta 0}^s$ is a parameter that needs to be inferred. The optimization problem is formulated as:

$$\min_{\theta_{A_\beta}, A_{\beta 0}} \mathcal{L}(\theta_{A_\beta}, A_{\beta 0}) = \sum_{i=1}^{M_{A_\beta}} \frac{\|A_\beta(t_i; \theta_{A_\beta}) - \tilde{A}_{\beta i}\|_2^2}{\|\tilde{A}_{\beta i}\|_2^2} + w \|A_\beta(100; \theta_{A_\beta}) - 1\|_2^2, \quad (15)$$

where the coefficient w for the penalty term enforce a sigmoid-like solution. The parameters $\theta_{A_\beta}^s$ and $A_{\beta 0}^s$ are optimized using MATLAB's `fmincon` iteratively with randomly generated initial guess with bounds $D_{A_\beta} \in [0, 2]$, $\lambda_{A_\beta} \in [0, 2]$, $K_{A_\beta} \in [1, 2]$, and $A_{\beta 0}^s \in [0, 1]$. And the initial condition of this equation is $\mathbf{I}^{68} A_{\beta 0}^s := A_\beta(t_0 = 50)$ with $\mathbf{I}^{68} = \text{ones}(68, 1)$. The spatial discretized PDE model is solved by `ode45`.

2. Non-homogenized model: Extend homogenized parameters $\theta_{A_\beta}^s$ to non-homogenized parameters, denoted as $\theta_{A_\beta}^{68D}$ to account for regional variability. Let the sparse deviations from the scalar parameters denoted as $\epsilon_{A_\beta} = \theta_{A_\beta}^{68D} - \theta_{A_\beta}^s$, the optimization problem is formulated as:

$$\min_{\epsilon_{A_\beta}} \mathcal{L}(\epsilon_{A_\beta}) = \sum_i \frac{\|A_\beta(t_i; \epsilon_{A_\beta} + \theta_{A_\beta}^s) - A_\beta(t_i)\|_2^2}{\|A_\beta(t_i)\|_2^2} + w \|A_\beta(100; \epsilon_{A_\beta} + \theta_{A_\beta}^s) - 1\|_2^2 + w_{reg} \|\epsilon_{A_\beta}\|_1, \quad (16)$$

where $\theta_{A_\beta}^s = (\mathbf{I}^{68} D_{A_\beta}^s, \mathbf{I}^{68} \lambda_{A_\beta}^s, \mathbf{I}^{68} K_{A_\beta}^s)$ and $A_{\beta 0}^s$ are the solution of homogenized model of step 1. To avoid overfitting issue, an L^1 regularization term is imposed for the model parameters. Regularization weight w_{reg} is tuned to balance fit and sparsity so that to avoid potential overfitting. This optimization problem is solved using MATLAB's `fmincon` starting with $\theta_{A_\beta}^s$ as the initial of the model parameters.

3. Learnable Initial Conditions: Extend the homogenized initial condition $A_{\beta 0}^s$ to a non-homogenized vector to account for regional variability, denoted as $A_{\beta 0}^{68D}$. To avoid overfitting issues, an L^1 regularization term is imposed for initial condition parameters. Let the sparse deviation from the scalar initial condition be denoted as $\epsilon_{A_{\beta 0}} = A_{\beta 0}^{68D} - \mathbf{I}^{68} A_{\beta 0}^s$. The optimization problem is formulated as:

$$\min_{\epsilon_{A_{\beta 0}}} \sum_i \mathcal{L}(\epsilon_{A_{\beta 0}}) = \frac{\|A_\beta(t_i; \theta_{A_\beta}^{68D}) - A_\beta(t_i)\|_2^2}{\|A_\beta(t_i)\|_2^2} + w \|A_\beta(100; \theta_{A_\beta}^{68D}) - 1\|_2^2 + w_0 \|\epsilon_{A_{\beta 0}}\|_1, \quad (17)$$

where $\theta_{A_\beta}^{68D}$ is the solution obtained from the previous step and keep fixed during the optimization in this step.

4. Patient-Specific FC matrix: For previous 3 steps, the population FC matrix is keep fixed. Now, we learn a patient-specific FC matrix from PET scan data by incorporating a low-rank variation of L_p , modeled as (11). The constrained optimization problem is formulated as:

$$\begin{aligned} \min_{\mathbf{u}, \mathbf{v}} \mathcal{L}(\mathbf{u}, \mathbf{v}) = & \sum_i \frac{\|A_\beta(t_i; \theta_{A_\beta}^{68D}) - A_\beta(t_i)\|_2^2}{\|A_\beta(t_i)\|_2^2} \\ & + w \|A_\beta(100; \theta_{A_\beta}^{68D}) - 1\|_2^2 \\ & + w_u (\|\mathbf{u}\|_2 - 1)^2 + w_v (\|\mathbf{v}\|_2 - 1)^2 \\ & + w_{su} \|\mathbf{u}\|_1 + w_{sv} \|\mathbf{v}\|_1, \\ \text{subject to: } & a_{kh} + \frac{1}{2}(u_k v_h + v_k u_h) - \delta_{kh} u_k v_h \geq 0, \\ & a_{kh} + \frac{1}{2}(u_k v_h + v_k u_h) - \delta_{kh} u_k v_h \leq 1, \\ & \forall k, h = 1, \dots, 68, \end{aligned} \quad (18)$$

where a_{kh} is the kh -th element of FC matrix A_p , $\mathbf{u} = (u_1, \dots, u_{68})$, $\mathbf{v} = (v_1, \dots, v_{68})$ are imposed to ensure stability and interpret ability of the model and optimized by MATLAB `fmincon` function.

5.6 Homotopy regularization technique for optimization stability

At each optimization step, a regularization term with a corresponding coefficient is introduced to prevent overfitting – a critical requirement for ensuring the learned model's generalizability. However, directly setting the regularization coefficient to a small target value (often necessary for high model fidelity) leads to training instability due to the complex, non-convex loss landscape. To address this, we propose a homotopy regularization technique inspired by numerical homotopy continuation – a method in computational mathematics that solves hard problems by gradually transforming them from simpler, related problems [76].

The core idea involves solving a sequence of progressively harder optimization problems through a continuous deformation of the regularization coefficient. Specifically:

1. Initialization: Begin with a large regularization coefficient (e.g., $w_{reg}^0 = 1000$), which simplifies the loss landscape by dominating the objective function, ensuring stable convergence.
2. Progressive Refinement: For each stage, w_{reg}^k , $k = 0, \dots, n$ is fixed, and after certain iteration steps of optimization, one can reduce the regularization coefficient by a decay factor (e.g., $w_{reg}^{k+1} = w_{reg}^k / 10$). Namely, gradually reduce the regularization coefficient by a decay factor at each stage.
3. Warm-Start Propagation: Use the solution from the previous stage (larger λ) as the initial guess for the next stage (smaller λ), leveraging the continuity of the homotopy path.

This approach effectively navigates the loss landscape by iteratively transitioning from a heavily regularized, convex-like regime to the target low-regularization regime, mitigating the risk of poor local minima or divergence.

5.7 Training, testing, and prediction evaluation protocol

To evaluate our model's predictive capability on a per-patient basis, we employ a time-series split strategy using each patient's individual longitudinal data.

For a given patient with biomarker and cognitive decline measurements at N time points $t_1, t_2, \dots, t_N$, we implement the following protocol:

Training (Parameter Inference): We use the first $N - 1$ time points $t_1, \dots, t_{N-1}$ as the training set. The model parameters are inferred by fitting the PDE dynamics to these historical data points.

Testing (One-Step-Ahead Prediction): Using the parameters learned in the training step, we solve the PDE to simulate the biomarker dynamics and cognitive decline dynamics forward in time. We then evaluate the model's prediction at time t_N (the last observed time point, which was held out during training). The testing accuracy is calculated by comparing this predicted value against the actual observed measurement at t_N . The accuracy (%) is defined as a normalized error-based similarity measure

$$100 \times (1 - \frac{\|\mathbf{y} - \hat{\mathbf{y}}\|}{\|\mathbf{y}\|}), \quad (19)$$

where $\mathbf{y} \in \mathbb{R}^{68}$ is the vector of quantities of interest and $\hat{\mathbf{y}}$ is the corresponding model prediction.

Prediction (Future Forecasting): Once the model's short-term accuracy is validated on the test point, we use the same inferred parameters to solve the PDE for future times. Specifically, we predict the biomarker value at $t_N + \delta t$ (e.g., δt years into the future).

This protocol ensures that the model's predictive performance is evaluated on data not used during training, providing a robust assessment of its generalization capability for individual patients.

5.8 Sensitivity analysis of model parameters

In this part, we introduce the sensitivity analysis of the model parameters, which provides a better understanding of how the changes in the output of a model can be apportioned to different changes in the model parameters [77]. Sobol method [78], a variance-based sensitivity estimate for nonlinear mathematical models, is employed. It obtains the contribution of each parameter to the variance of the quantities of interest (i.e., the model output $C(100)$ in our case). The sensitivity index quantifies a parameter's influence on the model output—the larger the index, the greater the parameter's impact, and thus the higher its importance in the model.

Consider a model in the form $Y = f(X_1, \dots, X_k)$ with Y a scalar output of the model, X_i is the i -th parameter and $\mathbf{X}_{\sim i}$ denotes all parameters but X_i . The effect on the model output by varying X_i alone, called the first-order index of X_i , is defined as the normalized variance given below

$$S_1^{(i)} = \frac{\text{Var}_{X_i}(E_{\mathbf{X}_{\sim i}}(Y|X_i))}{\text{Var}(Y)}. \quad (20)$$

The effect on the model output by varying X_i and X_j simultaneously and removing the effect of their individual first-order indexes is called the second-order index and is defined as

$$S_2^{(ij)} = \frac{\text{Var}_{X_i, X_j}(E_{\mathbf{X}_{\sim ij}}(Y|X_i, X_j))}{\text{Var}(Y)} - S_1^{(i)} - S_1^{(j)}. \quad (21)$$

The total index of parameter X_i measures the contribution to the output variance of X_i including all variance caused by its interactions, of any order, with any other model parameters, and it is defined as

$$S_T^{(i)} = \frac{E_{\mathbf{X}_{\sim i}}[\text{Var}_{X_i}(Y|\mathbf{X}_{\sim i})]}{\text{Var}(Y)} = 1 - \frac{\text{Var}_{\mathbf{X}_{\sim i}}[E_{X_i}(Y|\mathbf{X}_{\sim i})]}{\text{Var}(Y)}. \quad (22)$$

The total index $S_T^{(i)}$ measures the total effects, i.e., first- and higher-order effects (interactions) of parameter X_i .

Author contributions

Conceptualization: Chunyan Li, Xiao Liu, Wenrui Hao.

Formal analysis: Chunyan Li.

Funding acquisition: Xiao Liu, Wenrui Hao.

Investigation: Yutong Mao.

Methodology: Chunyan Li, Wenrui Hao.

Project administration: Wenrui Hao.

Resources: Yutong Mao.

Software: Chunyan Li.

Supervision: Xiao Liu, Wenrui Hao.

Visualization: Chunyan Li, Yutong Mao.

Writing – original draft: Chunyan Li.

Writing – review & editing: Yutong Mao, Xiao Liu, Wenrui Hao.

References

- Scheltens P, De Strooper B, Kivipelto M, Holstege H, Ch  telat G, Teunissen CE, et al. Alzheimer's disease. *Lancet*. 2021;397(10284):1577–90. [https://doi.org/10.1016/S0140-6736\(20\)32205-4](https://doi.org/10.1016/S0140-6736(20)32205-4) PMID: 33667416
- van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in Early Alzheimer's Disease. *N Engl J Med*. 2023;388(1):9–21. <https://doi.org/10.1056/NEJMoa2212948> PMID: 36449413
- Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA*. 2023;330(6):512–27. <https://doi.org/10.1001/jama.2023.13239> PMID: 37459141
- Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F. Alzheimer's disease drug development pipeline: 2023. *Alzheimers Dement (N Y)*. 2023;9(2):e12385. <https://doi.org/10.1002/trc2.12385> PMID: 37251912
- Honig LS, Barakos J, Dhadda S, Kanekiyo M, Reyderman L, Irizarry M, et al. ARIA in patients treated with lecanemab in the phase 3 Clarity AD study. *Alzheimer's & Dementia*. 2023;19:e076105.
- Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science*. 1992;256(5054):184–5. <https://doi.org/10.1126/science.1566067> PMID: 1566067
- Arezoumandan S, Xie SX, Cousins K, Mechanic-Hamilton DJ, Peterson CS, Huang CY, et al. Regional distribution and maturation of tau pathology among phenotypic variants of Alzheimer's disease. *Acta Neuropathol*. 2022;144(6):1103–16. <https://doi.org/10.1007/s00401-022-02472-x> PMID: 35871112
- Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Molecular Medicine*. 2016;8(6):595–608.
- Tolar M, Abushakra S, Sabbagh M. The path forward in Alzheimer's disease therapeutics: A new generation of amyloid-targeting agents. *Journal of Alzheimer's Disease*. 2020;78(1):1–8.
- de Leon MJ, DeSanti S, Zinkowski R, Mehta PD, Pratico D, Segal S, et al. MRI and CSF studies in the early diagnosis of Alzheimer's disease. *J Intern Med*. 2004;256(3):205–23. <https://doi.org/10.1111/j.1365-2796.2004.01381.x> PMID: 15324364
- Raj A, Sipes BS, Verma P, Mathalon DH, Biswal B, Nagarajan S. Spectral graph model for fMRI: A biophysical, connectivity-based generative model for the analysis of frequency-resolved resting-state fMRI. *Imaging Neurosci (Camb)*. 2024;2:imag–2–00381. https://doi.org/10.1162/imag_a_00381 PMID: 40800294
- Jack CR Jr, Wiste HJ, Weigand SD, Therneau TM, Lowe VJ, Knopman DS, et al. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. *Alzheimers Dement*. 2017;13(3):205–16. <https://doi.org/10.1016/j.jalz.2016.08.005> PMID: 27697430

13. Wiesman AI, Murman DL, May PE, Schantell M, Losh RA, Johnson HJ, et al. Spatio-spectral relationships between pathological neural dynamics and cognitive impairment along the Alzheimer's disease spectrum. *Alzheimers Dement (Amst)*. 2021;13(1):e12200. <https://doi.org/10.1002/dad2.12200> PMID: 34095434
14. Mohammad Mirzaei N, Tatarova Z, Hao W, Changizi N, Asadpoure A, Zervantonakis IK, et al. A PDE Model of Breast Tumor Progression in MMTV-PyMT Mice. *J Pers Med*. 2022;12(5):807. <https://doi.org/10.3390/jpm12050807> PMID: 35629230
15. Kirshtein A, Akbarinejad S, Hao W, Le T, Su S, Aronow RA, et al. Data Driven Mathematical Model of Colon Cancer Progression. *J Clin Med*. 2020;9(12):3947. <https://doi.org/10.3390/jcm9123947> PMID: 33291412
16. Le T, Su S, Shahriyari L. Investigating Optimal Chemotherapy Options for Osteosarcoma Patients through a Mathematical Model. *Cells*. 2021;10(8):2009. <https://doi.org/10.3390/cells10082009> PMID: 34440778
17. Cang Z, Mu L, Wei G-W. Representability of algebraic topology for biomolecules in machine learning based scoring and virtual screening. *PLoS Comput Biol*. 2018;14(1):e1005929. <https://doi.org/10.1371/journal.pcbi.1005929> PMID: 29309403
18. Kostelich EJ, Xu Y, Calderón-Valero C, Harris DC, Alcantar-Garibay O, Gomez-Castro G, et al. Mathematical modeling for glioblastoma treatment: scenario generation and validation for clinical patient counseling. *Front Oncol*. 2025;15:1647144. <https://doi.org/10.3389/fonc.2025.1647144> PMID: 41089515
19. Tursynkozha A, Harris DC, Kuang Y, Kashkynbayev A. Go-or-grow-or-die as a framework for the mathematical modeling of glioblastoma dynamics. *Math Biosci*. 2025;388:109520. <https://doi.org/10.1016/j.mbs.2025.109520> PMID: 40850592
20. Baez J, Kuang Y. Mathematical Models of Androgen Resistance in Prostate Cancer Patients under Intermittent Androgen Suppression Therapy. *Applied Sciences*. 2016;6(11):352. <https://doi.org/10.3390/app6110352>
21. Huo Z, Huang J, Kuang Y, Ruan S, Zhang Y. Oscillations in a tumor-immune system interaction model with immune response delay. *Math Med Biol*. 2025;42(2):131–58. <https://doi.org/10.1093/imammb/dqae016> PMID: 39287223
22. Hao W, Friedman A. Mathematical model on Alzheimer's disease. *BMC Syst Biol*. 2016;10(1):108. <https://doi.org/10.1186/s12918-016-0348-2> PMID: 27863488
23. Bertsch M, Franchi B, Meacci L, Primicerio M, Tesi MC. The amyloid cascade hypothesis and Alzheimer's disease: A mathematical model. *Eur J Appl Math*. 2020;32(5):749–68. <https://doi.org/10.1017/s0956792520000339>
24. Rabiei K, Petrella JR, Lenhart S, Liu C, Doraiswamy PM, Hao W. Data-Driven Modeling of Amyloid-beta Targeted Antibodies for Alzheimer's Disease. *arXiv preprint arXiv:250308938*. 2025.
25. Thompson TB, Vigil BZ, Young RS. Alzheimer's disease and the mathematical mind. *Brain Multiphysics*. 2024;6:100094. <https://doi.org/10.1016/j.brain.2024.100094>
26. Cottrell S, Yoon S, Wei X, Dickson A, Wei GW. Computational Drug Repurposing for Alzheimer's Disease via Sheaf Theoretic Population-Scale Analysis of snRNA-seq Data. *arXiv preprint arXiv:250925417*. 2025.
27. Hao W, Lenhart S, Petrella JR. Optimal anti-amyloid-beta therapy for Alzheimer's disease via a personalized mathematical model. *PLoS Comput Biol*. 2022;18(9):e1010481. <https://doi.org/10.1371/journal.pcbi.1010481> PMID: 36054214
28. Bossa MN, Sahli H. A multidimensional ODE-based model of Alzheimer's disease progression. *Sci Rep*. 2023;13(1):3162. <https://doi.org/10.1038/s41598-023-29383-5> PMID: 36823416
29. Vosoughi A, Sadigh-Eteghad S, Ghorbani M, Shahmorad S, Farhoudi M, Rafi MA, et al. Mathematical Models to Shed Light on Amyloid-Beta and Tau Protein Dependent Pathologies in Alzheimer's Disease. *Neuroscience*. 2020;424:45–57. <https://doi.org/10.1016/j.neuroscience.2019.09.017> PMID: 31682825
30. Bertsch M, Franchi B, Tesi MC, Tora V. The role of A β and Tau proteins in Alzheimer's disease: a mathematical model on graphs. *J Math Biol*. 2023;87(3):49. <https://doi.org/10.1007/s00285-023-01985-7> PMID: 37646953
31. Patel H, Solanki N, Solanki A, Patel M, Patel S, Shah U. Mathematical modelling of Alzheimer's disease biomarkers: Targeting Amyloid beta, Tau protein, Apolipoprotein E and Apoptotic pathways. *Am J Transl Res*. 2024;16(7):2777–92. <https://doi.org/10.62347/UJQF5204> PMID: 39114703
32. Xu C, Xu E, Xiao Y, Yang D, Wu G, Chen M. A multiscale model to explain the spatiotemporal progression of amyloid beta and tau pathology in Alzheimer's disease. *Int J Biol Macromol*. 2025;310(Pt 2):142887. <https://doi.org/10.1016/j.ijbiomac.2025.142887> PMID: 40220824
33. Hao W, Kao CY, Lee S, Li Z. Optimal Control For Anti-Abeta Treatment in Alzheimer's Disease using a Reaction-Diffusion Model. *arXiv preprint arXiv:250407913*. 2025.
34. Raj A, Torok J, Ranasinghe K. Understanding the complex interplay between tau, amyloid and the network in the spatiotemporal progression of Alzheimer's Disease. *Progress in Neurobiology*. 2025:102750.
35. Zheng H, Petrella JR, Doraiswamy PM, Lin G, Hao W, Alzheimer's Disease Neuroimaging Initiative. Data-driven causal model discovery and personalized prediction in Alzheimer's disease. *NPJ Digit Med*. 2022;5(1):137. <https://doi.org/10.1038/s41746-022-00632-7> PMID: 36076010
36. Zhang Z, Zou Z, Kuhl E, Karniadakis GE. Discovering a reaction-diffusion model for Alzheimer's disease by combining PINNs with symbolic regression. *Computer Methods in Applied Mechanics and Engineering*. 2024;419:116647. <https://doi.org/10.1016/j.cma.2023.116647>
37. Wang J, Mao Y, Liu X, Hao W. Learning Patient-Specific Spatial Biomarker Dynamics via Operator Learning for Alzheimer's Disease Progression. *arXiv preprint arXiv:250716148*. 2025.

38. Petrella JR, Jiang J, Sreeram K, Dalziel S, Doraiswamy PM, Hao W. Personalized Computational Causal Modeling of the Alzheimer Disease Biomarker Cascade. *J Prev Alzheimers Dis*. 2024;11(2):435–44. <https://doi.org/10.14283/jpad.2023.134> PMID: 38374750
39. Davodabadi A, Daneshian B, Saati S, Razavyan S. Mathematical model and artificial intelligence for diagnosis of Alzheimer's disease. *Eur Phys J Plus*. 2023;138(5):474. <https://doi.org/10.1140/epjp/s13360-023-04128-5> PMID: 37274456
40. Petrella JR, Hao W, Rao A, Doraiswamy PM. Computational Causal Modeling of the Dynamic Biomarker Cascade in Alzheimer's Disease. *Comput Math Methods Med*. 2019;2019:6216530. <https://doi.org/10.1155/2019/6216530> PMID: 30863455
41. Sandell R, Torok J, Nagaragan S, Ranasinghe KG, Ma D, Raj A. Integrating Event-Based and Network Diffusion Models to Predict Individual Tau Progression in Alzheimer's Disease. In: *Alzheimer's Association International Conference. ALZ*. 2025.
42. Sandell R, Torok J, Ranasinghe KG, Nagarajan SS, Raj A. Back to the Future: Predicting Individual Tau Progression in Alzheimer's Disease. *Research Square*. 2025:3.
43. Tora V, Torok J, Bertsch M, Raj A. A network-level transport model of tau progression in the Alzheimer's brain. *Math Med Biol*. 2025;42(2):212–38. <https://doi.org/10.1093/imammb/dqaf003> PMID: 40080630
44. Butler T, Wang XH, Chiang GC, Li Y, Zhou L, Xi K, et al. Choroid Plexus Calcification Correlates with Cortical Microglial Activation in Humans: A Multimodal PET, CT, MRI Study. *AJNR Am J Neuroradiol*. 2023;44(7):776–82. <https://doi.org/10.3174/ajnr.A7903> PMID: 37321857
45. Torok J, Mezas C, Raj A. Directionality bias underpins divergent spatiotemporal progression of Alzheimer-related tauopathy in mouse models. *Alzheimers Dement*. 2025;21(5):e70092. <https://doi.org/10.1002/alz.70092> PMID: 40396482
46. Vogel JW, Young AL, Oxtoby NP, Smith R, Ossenkoppele R, Strandberg OT, et al. Characterizing the spatiotemporal variability of Alzheimer's disease pathology. *MedRxiv*. 2020:2020–08.
47. Sanami S, Intzandt B, Huck J, Villeneuve S, Iturria-Medina Y, Gauthier CJ, et al. Longitudinal relationships among cerebrospinal fluid biomarkers, cerebral blood flow, and grey matter volume in individuals with a familial history of Alzheimer's disease. *Neurobiol Aging*. 2025;152:43–53. <https://doi.org/10.1016/j.neurobiolaging.2025.04.011> PMID: 40347524
48. Murray ME, Graff-Radford NR, Ross OA, et al. Clinicopathologic and ¹¹C-PiB PET correlates of three Alzheimer's disease subtypes: typical, limbic-predominant, and hippocampal-sparing. *Brain*. 2015;138(5):1370–81. <https://doi.org/10.1093/brain/awv050>
49. Korczyn AD, Grinberg LT. Is Alzheimer disease a disease? *Nature Reviews Neurology*. 2024;20(4):245–51.
50. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol*. 1991;82(4):239–59. <https://doi.org/10.1007/BF00308809> PMID: 1759558
51. Thal DR, Rüb U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology*. 2002;58(12):1791–800. <https://doi.org/10.1212/wnl.58.12.1791> PMID: 12084879
52. Planche V, Manjon JV, Mansencal B, Lanuza E, Tournier T, Catheline G, et al. Structural progression of Alzheimer's disease over decades: the MRI staging scheme. *Brain Commun*. 2022;4(3):fcac109. <https://doi.org/10.1093/braincomms/fcac109> PMID: 35592489
53. Singh V, Chertkow H, Lerch JP, Evans AC, Dorr AE, Kabani NJ. Spatial patterns of cortical thinning in mild cognitive impairment and Alzheimer's disease. *Brain*. 2006;129(Pt 11):2885–93. <https://doi.org/10.1093/brain/awl256> PMID: 17008332
54. Du A-T, Schuff N, Kramer JH, Rosen HJ, Gorno-Tempini ML, Rankin K, et al. Different regional patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia. *Brain*. 2007;130(Pt 4):1159–66. <https://doi.org/10.1093/brain/awm016> PMID: 17353226
55. Johnson K, Schultz A, Betensky R, et al. Tau PET imaging in aging and early Alzheimer's disease. *Annals of Neurology*. 2016;79(1):110–9. <https://doi.org/10.1002/ana.24546>
56. Collij LE, Salvadó G, Wottschel V, Mastenbroek SE, Schoenmakers P, Heeman F, et al. Spatial-Temporal Patterns of β -Amyloid Accumulation: A Subtype and Stage Inference Model Analysis. *Neurology*. 2022;98(17):e1692–703. <https://doi.org/10.1212/WNL.000000000000148> PMID: 35292558
57. Nestor PJ, Fryer TD, Hodges JR. Declarative memory impairments in Alzheimer's disease and semantic dementia. *Neuroimage*. 2006;30(3):1010–20. <https://doi.org/10.1016/j.neuroimage.2005.10.008> PMID: 16300967
58. Ossenkoppele R, Schonhaut DR, Schöll M, Lockhart SN, Ayakta N, Baker SL, et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. *Brain*. 2016;139(Pt 5):1551–67. <https://doi.org/10.1093/brain/aww027> PMID: 26962052
59. Berron D, Vogel JW, Insel PS, Pereira JB, Xie L, Wisse LEM, et al. Early stages of tau pathology and its associations with functional connectivity, atrophy and memory. *Brain*. 2021;144(9):2771–83. <https://doi.org/10.1093/brain/awab114> PMID: 33725124
60. Scallan RI, Schott JM, Stevens JM, Rostor MN, Fox NC. Mapping the evolution of regional atrophy in Alzheimer's disease: unbiased analysis of fluid-registered serial MRI. *Proc Natl Acad Sci U S A*. 2002;99(7):4703–7. <https://doi.org/10.1073/pnas.052587399> PMID: 11930016
61. Desikan RS, Fischl B, Cabral HJ, Kemper TL, Guttman CRG, Blacker D, et al. MRI measures of temporoparietal regions show differential rates of atrophy during prodromal AD. *Neurology*. 2008;71(11):819–25. <https://doi.org/10.1212/01.wnl.0000320055.57329.34> PMID: 18672473
62. Bougacha S, Roquet D, Landeau B, Saul E, Naveau M, Sherif S, et al. Contributions of connective pathways to shaping Alzheimer's disease pathologies. *Brain Commun*. 2025;7(1):fcae459. <https://doi.org/10.1093/braincomms/fcae459> PMID: 39763634
63. Torok J, Anand C, Verma P, Raj A. Connectome-based biophysics models of Alzheimer's disease diagnosis and prognosis. *Transl Res*. 2023;254:13–23. <https://doi.org/10.1016/j.trsl.2022.08.008> PMID: 36031051

64. Abdelnour F, Kuceyeski A, Raj A, Iturria-Medina Y, Deslauriers-Gauthier S. Editorial: Advances in brain functional and structural networks modeling via graph theory. *Front Neurosci*. 2022;16:1031280. <https://doi.org/10.3389/fnins.2022.1031280> PMID: [36408385](#)
65. Zhou X, Huang L, Cheng P, Yin W, Zhang R, Hao W, et al. Accelerating Causal Network Discovery of Alzheimer Disease Biomarkers via Scientific Literature-based Retrieval Augmented Generation. *arXiv preprint arXiv:250408768*. 2025.
66. Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, Smith I, et al. Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nat Med*. 2008;14(8):837–42. <https://doi.org/10.1038/nm1782> PMID: [18568035](#)
67. Dickerson BC, Wolk DA, Alzheimer's Disease Neuroimaging Initiative. MRI cortical thickness biomarker predicts AD-like CSF and cognitive decline in normal adults. *Neurology*. 2012;78(2):84–90. <https://doi.org/10.1212/WNL.0b013e31823efc6c> PMID: [22189451](#)
68. Dickerson BC, Bakkour A, Salat DH, Feczko E, Pacheco J, Greve DN, et al. Alzheimer-signature MRI biomarker predicts AD dementia: Regional cortical thinning in relation to future AD dementia. *Neurology*. 2011;76(2):139–48. <https://doi.org/10.1212/WNL.0b013e3182166e96>
69. Harrison TM, Du R, Klencklen G, Baker SL, Jagust WJ. Distinct effects of beta-amyloid and tau on cortical thickness in cognitively healthy older adults. *Alzheimers Dement*. 2021;17(7):1085–96. <https://doi.org/10.1002/alz.12249> PMID: [33325068](#)
70. Mehta RI, Wolf A, Price L, Kelly L, Yousuf M, van Westen D, et al. Early-onset Alzheimer's disease MRI signature: a replication and extension. *Cerebral Cortex*. 2024;34(12):bhae475. <https://doi.org/10.1093/cercor/bhae475>
71. Racine AM, Clark LR, Berman SE, Kosciak RL, Mueller KD, Norton D, et al. The personalized Alzheimer's disease cortical thickness index: characterization and replication in independent cohorts. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*. 2018;10:400–10. <https://doi.org/10.1016/j.dadm.2018.02.003>
72. Keuss SE, Lane CA, Lungu O, Parker TD, Coath W, Murray-Smith H, et al. Rates of cortical thinning in Alzheimer's disease signature regions predict disease progression. *Journal of Neurology, Neurosurgery & Psychiatry*. 2024;95(8):748–55. <https://doi.org/10.1136/jnnp-2023-333288>
73. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006;31(3):968–80. <https://doi.org/10.1016/j.neuroimage.2006.01.021> PMID: [16530430](#)
74. Ottroy J, Kang MS, Tan JXM, Boone L, Vos de Wael R, Park B-Y, et al. Tau follows principal axes of functional and structural brain organization in Alzheimer's disease. *Nat Commun*. 2024;15(1):5031. <https://doi.org/10.1038/s41467-024-49300-2> PMID: [38866759](#)
75. Hao W, Harlim J. An equation-by-equation method for solving the multidimensional moment constrained maximum entropy problem. *Commun Appl Math Comput Sci*. 2018;13(2):189–214. <https://doi.org/10.2140/camcos.2018.13.189>
76. Hao W. A Homotopy Method for Parameter Estimation of Nonlinear Differential Equations with Multiple Optima. *J Sci Comput*. 2017;74(3):1314–24. <https://doi.org/10.1007/s10915-017-0518-4>
77. Saltelli A, Sobol' IM. About the use of rank transformation in sensitivity analysis of model output. *Reliability Engineering & System Safety*. 1995;50(3):225–39. [https://doi.org/10.1016/0951-8320\(95\)00099-2](https://doi.org/10.1016/0951-8320(95)00099-2)
78. Sobol' IM. Global sensitivity indices for nonlinear mathematical models and their Monte Carlo estimates. *Mathematics and Computers in Simulation*. 2001;55(1–3):271–80. [https://doi.org/10.1016/s0378-4754\(00\)00270-6](https://doi.org/10.1016/s0378-4754(00)00270-6)