

Learning Disease Trajectories: A Disease Embedding Tree for Continuous Alzheimer’s and Lewy Body Dementia Progression Modeling

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This work introduces an interpretable prototype-based continuous disease progression framework that moves beyond conventional discrete dementia classification by modeling hierarchical disease trajectories, enabling both accurate diagnosis and patient -specific progression localization.

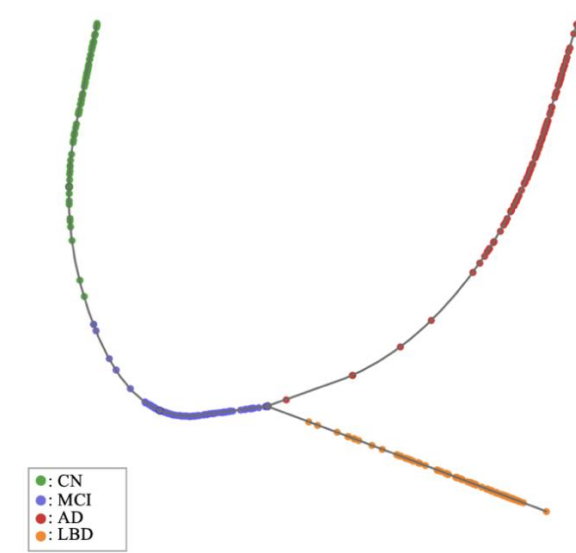
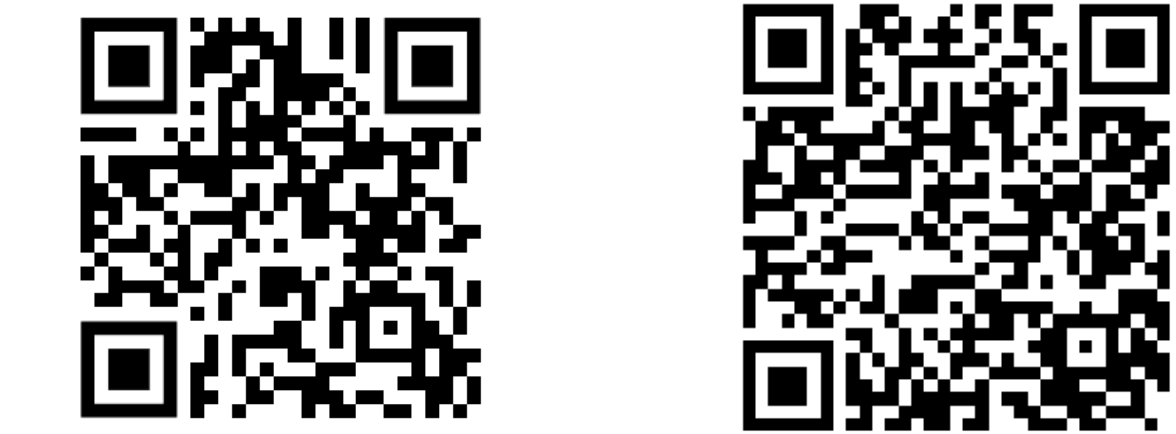
INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	METHODS & RESULTS																																										
Alzheimer's Disease (AD) and Lewy Body Dementia (LBD) are two of the most prevalent neurodegenerative disorders, yet their clinical diagnosis remains challenging due to overlapping neuropathological and symptomatic presentations. While numerous predictive approaches have demonstrated promise in early detection of such disorders, they predominantly employ discrete classification frameworks that fail to capture the continuous and gradual nature of disease progression. In this work, we develop a novel progression modeling framework that encodes the intrinsic relationships among clinical disease stages, yielding a Disease Embedding Tree (DETree) that hierarchically represents disease progression through a tree-structured trajectory. Individual clinical status can then be predicted by projecting patient embeddings onto this continuous trajectory space.	Our study utilized structural T1-weighted MRI (sMRI) from 375 subjects (77 CN, 100 MCI, 98 AD, 100 LBD). Images underwent standard preprocessing: DICOM-to-NIfTI conversion, N4 bias field correction, resampling to 1×1×1 mm³ isotropic voxels, MNI registration, and skull stripping, before feature extraction using a brain foundation model. We then project the extracted features into an embedding space through a prototype-based head containing four learnable prototypes (CN, MCI, AD, LBD) that construct the DETree. Training combines classification objectives with progression-aware constraints that enforce stage-specific clustering and hierarchical ordering. The overall framework is illustrated in Figure1.	The proposed framework achieved superior performance in dementia identification task. We performed 5-fold cross-validation, and the results are reported in Table 1. Figure illustrates how subjects across disease stages are projected onto the DETree using learned representations in the embedding space. 	The proposed disease progression framework effectively learned the continuous relationships between disease stages. By leveraging prototype-based deep learning with multi-objective progression constraints, our framework constructs a hierarchical embedding space that captures disease progression trajectories. Our approach not only offers a promising direction for modelling continuous disease evolution, but also facilitates early intervention through patient-specific trajectory localization.	(a) Data Preprocessing Pipeline DICOM Conversion N4 Correction Resampling MNI Registration Skull Stripping (b) Brain Foundation Model (Vision Transformer Backbone) Inputs Positional Embedding Feed Forward Network Add & Norm Multi-Head Self-Attention Add & Norm × L Input Embedding (c) Disease Embedding Tree (DETree) Learning Prototype-Based Projection Head DETree Embedding Space Learned Disease Progression Trajectories Disease Stage Prediction Classification Progression-Aware Constraints Joint Learning Table 1. Performance of the proposed framework for classifying CN, MCI, AD, and LBD across individual folds and the overall evaluation. F1-score, AUC, sensitivity, and specificity are all computed using a macro-averaging strategy, where each class is treated as positive against the remaining classes and the final score is obtained by averaging over all four classes. <table><tr><th>Split</th><th>Accuracy</th><th>F1-score</th><th>AUC</th><th>Sensitivity</th><th>Specificity</th></tr><tr><td>Fold 1</td><td>0.760</td><td>0.762</td><td>0.901</td><td>0.767</td><td>0.919</td></tr><tr><td>Fold 2</td><td>0.667</td><td>0.633</td><td>0.814</td><td>0.642</td><td>0.888</td></tr><tr><td>Fold 3</td><td>0.693</td><td>0.680</td><td>0.843</td><td>0.683</td><td>0.898</td></tr><tr><td>Fold 4</td><td>0.733</td><td>0.730</td><td>0.876</td><td>0.734</td><td>0.911</td></tr><tr><td>Fold 5</td><td>0.640</td><td>0.621</td><td>0.866</td><td>0.639</td><td>0.881</td></tr><tr><td>Overall (Mean ± Std)</td><td>0.699 ± 0.046</td><td>0.685 ± 0.063</td><td>0.860 ± 0.030</td><td>0.693 ± 0.048</td><td>0.899 ± 0.015</td></tr></table>	Split	Accuracy	F1-score	AUC	Sensitivity	Specificity	Fold 1	0.760	0.762	0.901	0.767	0.919	Fold 2	0.667	0.633	0.814	0.642	0.888	Fold 3	0.693	0.680	0.843	0.683	0.898	Fold 4	0.733	0.730	0.876	0.734	0.911	Fold 5	0.640	0.621	0.866	0.639	0.881	Overall (Mean ± Std)	0.699 ± 0.046	0.685 ± 0.063	0.860 ± 0.030	0.693 ± 0.048	0.899 ± 0.015
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Fig. 2. DETree generated from the best-performing fold, illustrating the continuous disease progression across stages. Each point represents an individual subject, colored by disease stage: CN (green), MCI (blue), AD (red), and LBD (orange).



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