Doctoral School of Information and Biomedical Technologies Polish Academy of Sciences (TIB PAN)

SUBJECT*:* LEARNING IMPLICIT NEURAL REPRESENTATIONS FOR EARLY DETECTION OF NEURODEGENERATIVE DISEASES FROM MULTIMODAL CLINICAL SIGNALS

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Neurodegenerative diseases, including Alzheimer's, Parkinson's, and frontotemporal dementia pose a growing global health challenge, driven by aging populations **[1]**. Characterized by progressive and irreversible neuronal loss, these disorders manifest through diverse cognitive, motor, and behavioral impairments. Pathological changes begin years, often decades, before clinical symptoms emerge, offering a crucial window for early diagnosis and intervention to potentially slow disease progression. However, early detection remains challenging due to the heterogeneity of symptoms, the subtlety of early brain changes, and the complexity of the required multimodal data, spanning neuroimaging, fluid biomarkers, genetics, and cognitive assessments. While machine learning has shown promise, current methods often struggle with overfitting, poor generalization, and limited capacity to robustly integrate heterogeneous, longitudinal data in an interpretable manner. **[2-3]**.

This thesis proposes the use of Implicit Neural Networks (INNs) as a novel computational framework for the early diagnosis of neurodegenerative diseases. INNs are a class of models where outputs are defined as solutions to implicit equations—such as fixed-point iterations or differential operators—rather than explicit layer-by-layer transformations **[4]**. This architecture enables several key advantages: the ability to learn continuous-time and spatial representations, high parameter efficiency, theoretical expressiveness, and potential biological interpretability, as these models can approximate stable pathological states conditioned on patient-specific factors. Such capabilities are particularly well-suited for early diagnosis, where disease signals are subtle, nonlinear, and embedded in complex multimodal data. INNs can naturally fuse heterogeneous modalities—such as imaging, genomics, fluid biomarkers, and cognitive scores—while capturing nuanced biomarkers that may precede overt clinical symptoms. **This thesis introduces a novel INN-based framework that is both memory-efficient and adaptable, designed to detect early-stage neurodegenerative changes with improved robustness and interpretability.** The models will be trained and validated primarily using the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset, which offers rich, longitudinal multimodal data including MRI, PET, cerebrospinal fluid and blood biomarkers, APOE genotyping, and cognitive assessments. To assess generalizability across populations and acquisition protocols, additional datasets such as OASIS-3 and AIBL may be incorporated.

The main objectives of this work are:

- *To develop and implement novel INN architectures tailored for modeling complex, multimodal clinical data relevant to the early stages of neurodegenerative diseases.*
- *To design and implement implicit data fusion strategies that integrate heterogeneous modalities (e.g., neuroimaging, fluid biomarkers, genomics, cognitive scores) in a unified, interpretable latent space **[5]**.*
- *To evaluate the diagnostic performance of INN-based models in early-stage disease detection and progression prediction, benchmarking against conventional deep learning models (e.g., MLPs, CNNs, RNNs/LSTMs).*
- *To assess robustness, generalizability, and stability of the proposed models across cohorts, data acquisition protocols, and missing modality scenarios using datasets such as ADNI, OASIS-3, and AIBL.*
- *To investigate the biological and clinical interpretability of INNs by analyzing learned representations and their correspondence with known disease biomarkers and progression pathways.*
- *To contribute a scalable, clinically relevant framework for early and personalized diagnosis, with the potential for real-world integration in neurodegenerative disease screening and monitoring.*

The innovative contribution of this research lies in adapting implicit deep learning, i.e. a paradigm primarily explored in physics-informed modeling to the domain of complex clinical diagnostics **[6]**. This approach offers a flexible and scalable alternative to traditional deep learning, particularly effective in settings with irregular, incomplete, and multimodal data. By bridging theoretical advances with clinical relevance, this work aims to advance AI-driven tools for personalized, early detection of neurodegenerative diseases, with potential to reshape diagnostic workflows and disease monitoring in the future.

[1] Kharat et all. R. Navigating Neurodegenerative Disorders: A Comprehensive Review of Current and Emerging Therapies for Neurodegenerative Disorders. J Neurosci Neurol Disord. 2024; 8: 033-046 [2] Bazarbekov et all, A review of artificial intelligence methods for Alzheimer's disease diagnosis: Insights from neuroimaging to sensor data analysis. Biomedical Signal Processing and Control. 2024;92:106023 [3] Yang K, Mohammed EA. A review of artificial intelligence technologies for early prediction of Alzheimer's disease. arXiv preprint arXiv:2101.01781. 2020 [4] El Ghaoui ey all, Implicit deep learning. SIAM Journal on Mathematics of Data Science. 2021;3(3):930-58 [5] Sun et al,l,Medical Multimodal Foundation Models in Clinical Diagnosis and Treatment: Applications, Challenges, and Future Directions. arXiv preprint arXiv:2412.02621. 2024 [6] Chen et all, Neural ordinary differential equations. Advances in neural information processing systems. 2018;31