Research Abstract

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1. Introduction

My research focuses on developing and applying advanced computational models to solve complex problems in science and medicine. By integrating techniques from applied mathematics, scientific computing, and machine learning, I aim to create models that are not only predictive but also interpretable, providing deeper insights into underlying dynamic systems. This document summarizes my three principal research endeavors.

2. Project 1: Personalized Neural ODE Modeling for Alzheimer's Disease Dynamics

This project introduces a sophisticated machine learning model for Alzheimer's Disease (AD) kinetics, moving beyond the limitations of existing methods to provide robust population-level and personalized predictions.

2.1. Motivation and Background

Research into AD often focuses on biomarkers like Amyloid-beta ($A\beta$) and tau (τ) proteins, neurodegeneration (N), and cognitive decline (C). While prior work by Zheng et al[1]. used sparse identification to create a quadratic

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polynomial ODE model suggesting a causal chain of $A\beta \rightarrow \tau \rightarrow N \rightarrow C$, this approach is inherently limited. Relying solely on quadratic polynomials can oversimplify the complex biological reality and offers limited interpretability. To address this, my work explores hybrid neural network architectures to strike a better balance between model performance, interpretability, and complexity.

2.2. Methodology

The core of this work is a hybrid ODE model that combines a traditional polynomial model with a Feedforward Neural Network (FNN) in a residual learning framework:

$$\frac{\mathrm{d}y}{\mathrm{d}s} = f(y) + P(y) \tag{1}$$

Here, y is the 4-dimensional state vector $(A\beta, \tau, N, C)$, $P(y)$ is the interpretable quadratic polynomial backbone, and $f(y)$ is the FNN correction term that captures more complex, non-linear dynamics.

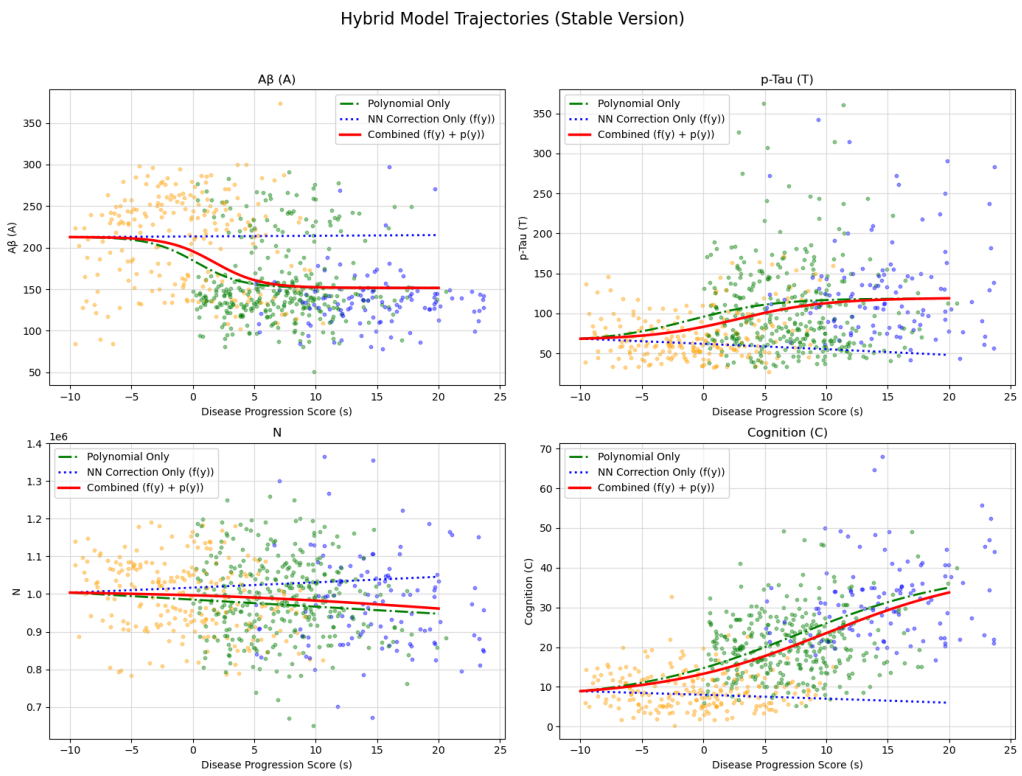
A critical component of the methodology is the **Disease Progression Score (DPS) Transformation**. To place all patients on a unified timeline, each patient's age $(t_i)_i$ is linearly transformed to a disease progression score $(s_i)_i$ via $s_i = a_i t_i + b_i$. To ensure numerical stability—a challenge when co-optimizing model and DPS parameters—I designed a robust three-step pre-training process:

1. **Initialization**: DPS parameters are initialized based on patients' clinical diagnoses (CN, LMCI, AD) to create a meaningful initial distribution.
2. **Sigmoid Fitting**: A four-parameter Sigmoid function is fitted to the population data to capture the macroscopic "S"-shaped trend of each biomarker.

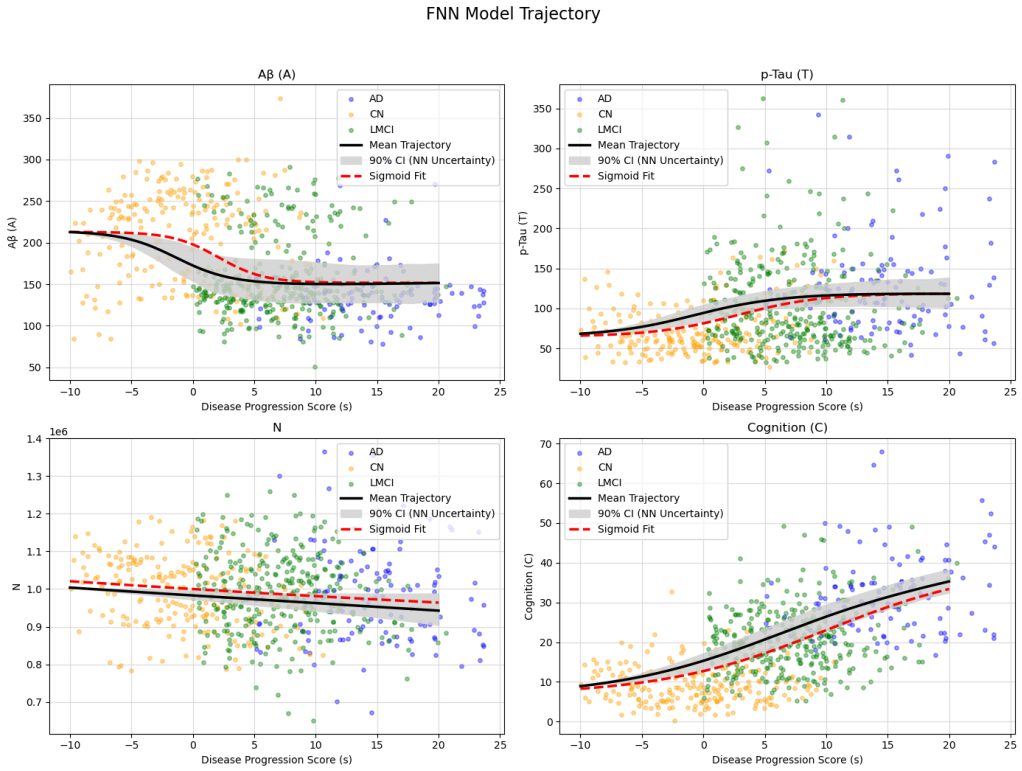
3. **Polynomial Pre-training**: The initial polynomial model is trained to approximate the analytical derivatives of the smooth Sigmoid curves, ensuring a stable and accurate starting point.

The final hybrid model is trained by solving the ODE system using a 4th-order Runge-Kutta (RK4) method and minimizing the Mean Squared Error (MSE) between the predicted trajectories and patient data points.

Below is the FNN+Polynomial Model's performance:



and below is the FNN-Only Model's performance:



2.3. Personalization and Uncertainty Quantification

Building on the population-level model, a personalized model is constructed for each patient. This is achieved through:

- **Sensitivity Analysis**: Identifying the most influential model parameters using gradient-based methods, as variance-based methods like Sobol are too computationally expensive for large neural networks.
- **Fine-Tuning**: For each patient, the most sensitive parameters are fine-tuned using their initial observations, with later data points reserved for validation. This approach has shown superior performance compared to the general population model.

Furthermore, to provide a measure of predictive confidence, I implemented uncertainty quantification. By sampling model parameters from a normal distribution around the trained values, we generate an ensemble of 100 models and plot the 2.5th and 97.5th percentiles to form a 95% confidence interval for the predicted trajectories.

3. Project 2: Tensor Neural Networks for High-Dimensional Problems

My second major research project focuses on Tensor Neural Networks (TNN/CTNN)[2], which are powerful mathematical tools for representing high-dimensional functions and solving complex problems that are intractable for conventional grid-based methods.

3.1. Core Concepts

TNNs are founded on tensor decomposition methods, primarily Canonical Polyadic (CP) decomposition. This mathematical framework allows a high-dimensional function to be represented as a sum of separable functions:

$$u(x) = \sum_k c_k \varphi_{k(x)} = \sum_k c_k \prod_{i=1}^{d} \varphi_{i(x_i)}, x \in \Omega \subset R^d \tag{2}$$

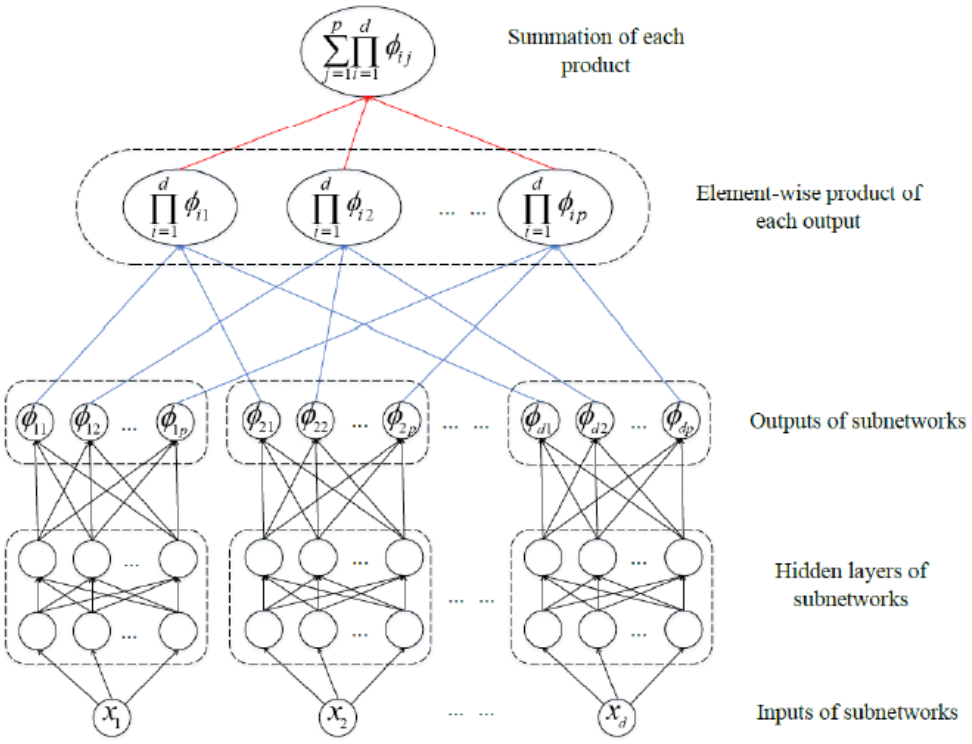
Using this property, we could decompose the high-dimensional integral of $u(x)$ into the product of 1-dimensional integrals:

$$\int_\Omega u(x)dx = \sum_k c_k \prod_{i=1}^{d} \int_{\Omega_i} \varphi_i(x_i)dx_i \tag{3}$$

in which we could use Gaussian integral which is precise and efficient.

This reduces the computational complexity from exponential to polynomial, enabling high-accuracy numerical integration and function approximation in high dimensional space. Specifically, when solving high-dimensional PDEs, we could utilize the integral characteristics of TNN to optimize the calculation of a large number of integrals in the loss function, significantly improving accuracy and speed.

The figure below shows the structure of TNNs:



3.2. Research Contributions

My work in this area has involved both theoretical and applied advancements:

- **Algorithm Development**: I mathematically derived and implemented novel algorithms for Convolutional Tensor Neural Networks (CTNNs), specifically designed to handle coupled input dimensions, which extends the applicability of the TNN framework.
- **Application to PDEs**: I have successfully applied these TNN and CTNN methods to solve high-dimensional Partial Differential Equation (PDE) boundary-value problems, utilizing a deep Galerkin method approach.
- **Performance Optimization**: I have explored and implemented techniques to accelerate the training of TNNs, including process decomposition and layer-wise training strategies. This also involved a comparative analysis of TNN performance against alternative architectures, such as weak adversarial networks, to benchmark their efficiency and accuracy.

4. Project 3: ODE-Based Multi-Omics Modeling for Autoimmune Diseases

Building on my foundational experience in ODE modeling and data mining, this emerging research project aims to tackle the complexity of autoimmune diseases[3], with an initial focus on IgG4-Related Disease (IgG4-RD). This research is mainly based on a unpublished paper.

4.1. Objective

The primary goal is to construct a dynamic, mechanistic model that can integrate multi-modal biological data to understand disease progression and predict the effect of therapeutic interventions[4]. This project bridges the gap between high-throughput data generation and actionable clinical insights.

4.2. Methodology

This research will leverage a diverse set of patient data, including:

- **Flow Cytometry Data**: To quantify immune cell populations.
- **Single-Cell Transcriptomics (scRNA-seq)**: To understand gene expression heterogeneity at the cellular level.
- **Proteomics Data**: To measure protein abundances, which are the functional actors in biological pathways.

My approach is to develop an ODE-based framework capable of assimilating these disparate data types into a single, cohesive model of the disease's cellular and molecular dynamics.

4.3. Anticipated Impact

Once validated, this dynamic model will serve as a powerful platform for large-scale **in silico** drug perturbation screening. By computationally simulating the effect of thousands of potential drug compounds on the system, the model can predict and prioritize drug targets most likely to reverse disease phenotypes. This work aims to establish a computational pipeline that significantly accelerates the discovery of effective treatments for complex autoimmune diseases.

References

[1] H. Zheng, J.R. Petrella, P.M. Doraiswamy, W. Hao, Data-driven causal model discovery and personalized prediction in Alzheimer's disease, Npj Digital Medicine 5 (2022). https://doi.org/10.1038/s41746-022-00632-7.

[2] Y. Wang, P. Jin, H. Xie, Tensor Neural Network and Its Numerical Integration, (2023). https://arxiv.org/abs/2207.02754.

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[4] L. Qian, R. Sun, R. Aebersold, P. Bühlmann, C. Sander, T. Guo, AI-empowered perturbation proteomics for complex biological systems, Cell Genomics 4 (2024). https://doi.org/10.1016/j.xgen.2024.100691.