PINN for solving PDE and Its application in Alzheimer's disease

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Abstract. Understanding complex biological processes often requires modeling using partial differential equations (PDEs) with unknown terms that are difficult to determine experimentally. This study introduces a novel mechanism combining Physics-Informed Neural Networks (PINNs) and symbolic regression to predict such terms. To illustrate the approach, we focus on Alzheimer's disease and model the diffusion-reaction dynamics of tau protein in the brain. Misfolded tau proteins are pivotal to the progression and pathology of Alzheimer's disease. Recent research indicates that the spatiotemporal behavior of these proteins can be effectively modeled using diffusion-reaction equations. So, using our mechanism, we can predict the reaction term $f(c)$ in the diffusion-reaction equation for the two groups, revealing the dynamics of tau protein in Alzheimer's brain.

Keywords: PINN · Symbolic Regression · Solving PDEs · Prediction of unknown Mathematical Terms.

1 Introduction

The progression of neurodegenerative diseases like Alzheimer's disease involves intricate biological mechanisms that are not yet fully understood. Among these, the aggregation and diffusion of tau protein in the brain have been identified as key processes contributing to disease development. Mathematical modeling, particularly using partial differential equations (PDEs), has emerged as a powerful tool for studying such phenomena. However, the complexity of these systems often involves unknown terms, such as reaction dynamics, that are difficult to deduce experimentally or theoretically.

Recent advances in machine learning, especially Physics-Informed Neural Networks (PINNs)[12], offer a promising avenue for integrating domain knowledge from physics and data-driven approaches. When coupled with symbolic regression[13,14], the increasing adoption of PINNs, as seen in our project and that of others [24,6,15], highlights the method's potential in extracting meaningful parameters from real-world data to enhance our understanding of various phenomena

In this work, we introduce a novel mechanism to predict unknown terms in PDEs and demonstrate its application to Alzheimer's disease. Specifically, we focus on the reaction-diffusion equation governing tau protein dynamics[19]. Our approach involves training PINNs on synthetic data generated from known reaction equations and using symbolic regression to derive interpretable expressions for the reaction term. This mechanism is then validated through numerical simulations and visualization, offering insights into the potential spatial progression of tau protein in the brain.

This study not only provides a framework for exploring tau protein dynamics in Alzheimer's disease but also establishes a broader methodology for addressing unknowns in complex biological models. By integrating machine learning and physics-based modeling, our work paves the way for innovative solutions to challenging problems in neurodegenerative disease research.

The rest of this paper is organized as follows: In Section 2, 3, we present the definition of the problem and the methodology developed for the discovery of the model and then we preview our results in section 4.

2 Problem Definition

Understanding and predicting the progression of Alzheimer's disease remains a significant challenge due to the complexity of the underlying biological processes. The dynamics of tau protein, a hallmark of the disease, are governed by reaction-diffusion equations that include terms describing both diffusion and reaction mechanisms. While the diffusion term can often be estimated or assumed, the reaction term—representing biochemical interactions and aggregation processes—is typically unknown and difficult to measure directly.

Now we focus on Alzheimer diffusion-reaction model where we describe the problem in more detailed approach.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the abnormal accumulation and propagation of misfolded tau proteins in the brain. A key challenge in understanding AD lies in modeling the spatio-temporal dynamics of tau protein aggregation and propagation across interconnected brain regions. This process can be mathematically described by the reaction-diffusion partial differential equation (KPP Equation)[3]. This equation describes how the concentration of misfolded protein c changes w.r.t time and space based on the assumption that tau pathology develops in a prion-like fashion[9] :

$$\frac{\partial c}{\partial t} = \nabla \cdot (D \cdot \nabla c) + f(c), \tag{1}$$

- $c(t, x)$*:* Concentration of misfolded tau protein at time t and spatial position x within the brain.
- D*:* denotes the diffusion tensor.
- $f(c)$*:* Reaction term describing biochemical activities influencing tau protein dynamics.

The original system is modeled as a continuous-space reaction-diffusion equation, describing both the local accumulation of tau proteins (via $f(c)$) and their spread between regions (via $\nabla \cdot (D\nabla c)$). In order to apply the diffusion model to our brain network, we discretize Eq.1 on the weighted graph G. This leads to a discretized diffusion equation expressing for each node of the network i = 1,...,N the change in nodal concentration of misfolded protein c_i. The nodes of (G) represent distinct, non-overlapping brain regions, while the edges of (G) represent the axonal connections between these regions. Using the same method as [16,7]. In this context, we discretize Eq.1 on (G) and reformulate the PDE as an ODE system:

$$\frac{dc_i}{dt} = h_k^i(t, c) + f(c_i), \quad i = 1, \ldots, N \tag{2}$$

- c_i: Concentration of tau proteins in the i-th brain region.
- $h_k^i(t, c)$: Discretized diffusion term parameterized by κ, representing protein spread.
- $f(c_i)$: Reaction term modeling local biochemical processes.

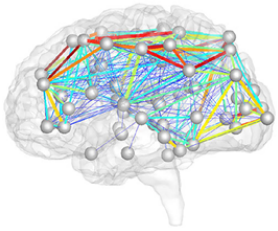


Fig. 1: Human brain connectome to illustrate the brain nodes approach

3 Methodology

As discussed in the previous section we reformulated the PDE as an ODE system 2 now we discuss the method we will use in predicting the unknown reaction in term $f(c_i)$ in Eq.2. Our approach consists of two main branches PINN and Symbolic Regression.

3.1 Physics-informed Neural Network (PINN)

PINNs are a specialized type of neural network designed to incorporate physical laws directly into their training process [17]. They achieve this by embedding governing differential equations into the neural network's architecture, allowing them to learn not just from data but also from established physical principles. The mechanism to predict the unknown term $f(c_i)$ consists of two steps predicting the concentration then use this prediction to predict $f(c_i)$. Now we explain in more detail how our PINN works.

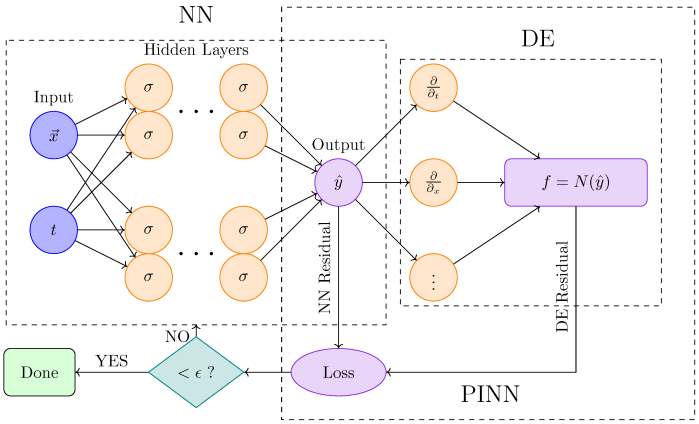


Fig. 2: PINN Mechanism

As mentioned above, we are using PINN to approximate the concentration and reaction term of our equation parameters, denoted as c_θ and f_ϕ; where θ and ϕ represent the weights and biases of the neural network. Let T_D denote the set of t on which the c data are (partially) available and T_R denote the set of t on which the residuals of the equation are computed (we assumed it to be 20 years). We used Adam optimization algorithm followed by L-BFGS to minimize the following loss function:

$$L(\Theta) = L_{\text{data}}(\theta) + L_{\text{res}}(\theta, \phi, \kappa) \tag{3}$$

with respect to $\Theta := \{\theta, \phi, \kappa\}$, where

$$L_{\text{data}}(\theta) = \frac{1}{|T_D|} \sum_{t \in T_D} \|c(t) - c_\theta(t)\|_2^2, \tag{4}$$

$$L_{\text{res}}(\theta, \phi, \kappa) = \frac{1}{|T_R|} \sum_{t \in T_R} \left\| \frac{dc_\theta}{dt}(t) - h_\kappa(c_\theta) - f_\phi(c_\theta) \right\|_2^2. \tag{5}$$

3.2 Symbolic Regression

Symbolic Regression [10] is a powerful technique aimed at discovering interpretable mathematical expressions that describe a dataset. Unlike traditional regression methods, which assume a specific functional form (e.g., linear, polynomial), Symbolic Regression searches for the best-fitting formula from a broad space of possible expressions.We used Python library PySR [5] which has a configurable Python interface built on the efficient *Julia backend SymbolicRegression.jl*. The underlying algorithm for PySR involves tree search and regularized evolution. In our case of study, we use PySR to distill knowledge from f_ϕ to obtain a symbolic expression f_{sym}.

Evaluation Metric Now we need to evaluate the correctness of the expression picked so we use *score* defined in [14]

$$score = -\Delta \log(\text{MAE})/\Delta C, \tag{6}$$

where MAE is the mean absolute error between the prediction and the data, C refers to the complexity of the expression, and Δ denotes local change [14]. Higher score means that with a slightly lower complexity, MAE of the symbolic regression model becomes much larger. A model with low loss and high score is preferred.

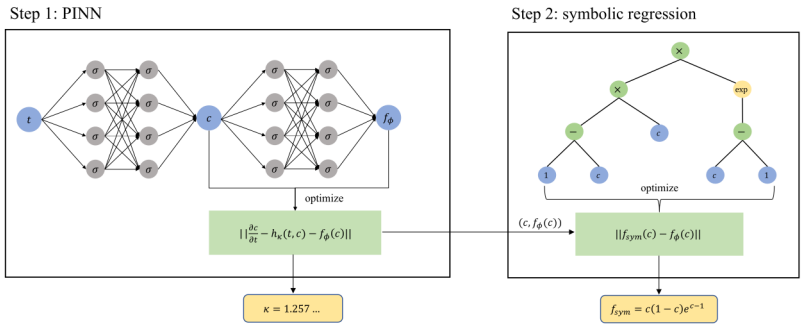


Fig. 3: Description of the whole process of PINN and Symbolic Regression

4 Results

In this section, we first present the outputs predicted by the Physics-Informed Neural Networks (PINNs) and the symbolic regression model for tau protein concentrations over time, compared with the synthetic data. This comparison highlights the predictive accuracy and interpretability of the discovered reaction-diffusion model. Following this, we simulate the reaction-diffusion process of misfolded tau proteins in the brain using COMSOL Multiphysics.

4.1 Data preparation

As discussed before we follow the same setup as in [2] and discretize Eq.1 on a graph G, which comes from [4] the Budapest Reference Connectome v3.0 and the Human Connectome Project [8]; see [2] for details on how to construct G. There are in total N = 83 nodes in the graph G, representing 83 considered cortical and subcortical brain regions. In this work, we adopt the graph G and discretization from [2] and Eq.1 is discretized as follows:

$$\frac{dc_i}{dt} = -\kappa \sum_{j=1}^{N} L_{ij} c_j + \alpha f(c_i),\ i = 1, \ldots, N, \tag{7}$$

- c_i: Concentration of tau proteins in the i-th brain region(node).
- k: Determines the transport rate of misfolded protein between regions.
- L_{ij}: Graph Laplacian, representing the connectivity of the graph.
- α: Denotes the reaction rate.
- $f(c_i)$: Denotes the reaction term in node i

We note that this corresponds to Eq.2 with $h_k^i(c) = -\kappa \sum_{j=1}^{N} L_{ij} c_j$. Unlike previous studies [2,20], which assume a single specific reaction model, $f(c) = c(1-c)$, herein we aim to identify the analytical form of the function f from tau concentration data of 76 subjects from synthetic data we made.

Synthetic Data We will construct synthetic data to argue the performance of our model and this data simulates the real data which can be obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database but this is outside this paper's focus. As discussed in section 2 we will use KPP equation where we found empirically that requirements from the Fisher equation [18] and the KPP equation [21] on the reaction term were necessary to provide better and more realistic results. As a generalized form of the Fisher equation, the KPP equation requires that the reaction term f has the following properties:

$$f(0) = f(1) = 0,\ f(c) > 0, \tag{8a}$$

$$f'(c) < f'(0),\ \forall c \in [0, 1], \tag{8b}$$

Additional types of KPP equations, including the Newell Whitehead-Segel equation and the Zeldovich-Frank-Kamenetskii equation, are summarized in Table 1

Group	Equation	General form	Reference	Our case
1	Fisher	$kc(1-c)$	[18]	$c(1-c)$
2	Newell-Whitehead-Segel	$kc(1-c^q)$	[1,11]	$\frac{3\sqrt{3}}{8}c(1-c^2)$
3	Newell-Whitehead-Segel	$kc(1-c^3)$	[1,11]	$\frac{2^{2/3}}{3}c(1-c^3)$
4	Zeldovich-Frank-Kamenetskii	$kc(1-c)e^{\beta(c-1)}$	[22]	$\frac{\sqrt{5}+2}{4}c(1-c)e^{c-1-\frac{\sqrt{5}-3}{2}}$

Table 1: **Reaction term f in KPP equations.** We stratify the subjects into 4 groups with the assumption that subjects in each group share the same reaction term $f(c)$. Diverse reaction terms are associated with distinct KPP equations, which are in turn indicative of particular biological characteristics. We normalize f to make its maximum value $\frac{1}{4}$ in all groups.

In this study, we conducted a simulation of tau concentration for a sample of 76 subjects(patients) with varying initial conditions, parameters, and reaction terms, employing Equation 7. The subjects were stratified into four groups of equal size, with differing reaction terms across groups, as detailed in Table 1. The parameters k, α_i, and α_{ij} were assumed to follow probability distributions of BoundNormal(1,0.52), N(0.6,0.12), and N(α_i,0.22), respectively, where α_{ij} denotes the j-th subject in the i-th group. The initial tau concentration for the i-th node, denoted by $c_i(0)$, was sampled from a normal distribution with equivalent mean and variance as the real data.The tau concentrations $c(tk)$ are sampled at tk = k for k = 0,1,2....,20 years as shown in Fig. 4.

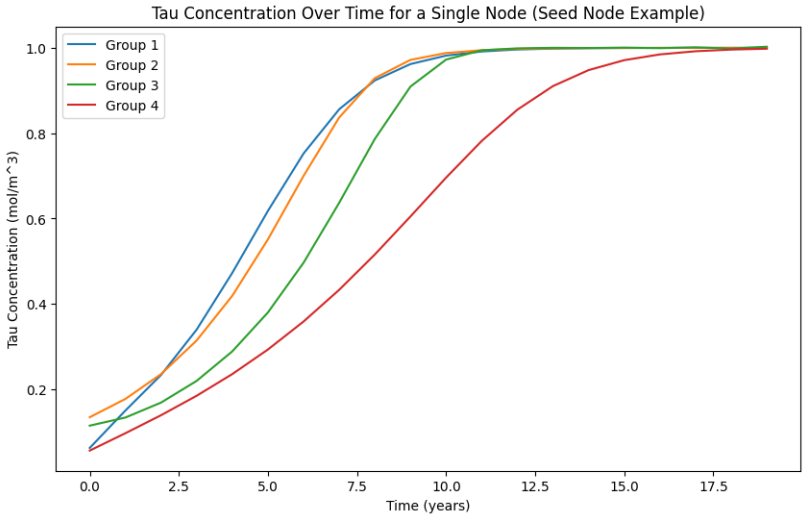


Fig. 4: Tau Progression in Four Alzheimer's Groups

4.2 PINN training

Overview The training of the Physics-Informed Neural Network (PINN) aims to approximate the tau protein concentration over time and discover the reaction term governing its dynamics by embedding physical laws into the loss function. This eliminates the need for explicit numerical methods, making PINNs suitable for high-dimensional or complex systems.

Training Process The training process employs two optimization techniques as mentioned in Fig 5:

- Adam Optimizer: A stochastic optimization algorithm for initial coarse training.
- L-BFGS Optimizer: A quasi-Newton method for fine-tuning the solution, ensuring rapid convergence.

Steps:

1. Initialization: The neural network is initialized with a suitable architecture to approximate the solution of the PDE.
2. Adam Phase:
   - *Epochs*: 20,000
   - *Purpose*: Rapidly minimize the loss to provide a good starting point.
3. L-BFGS Phase:
   - *Epochs*: 20,000
   - *Purpose*: Refine the solution, ensuring adherence to both data and the PDE constraints.

4.3 Output results

In the last stage of our analysis, after we have identified the unknown parameters κ and α and the unknown function f_{sym} as in table 2, we substitute them back into the ODE 7 and solve the equation up to $t = 20$ with the built-in Python method `scipy.integrate.odeint` to examine the predictability of our models.The projections of the tau concentration over 20 years after the first PET scan for 1 node is illustrated in Fig. 6a.

κ	α	f_{sym}
0.92	0.43	$8.908 \cdot c^3 - 23.446 \cdot c^2 + 15.667 \cdot c + 0.792$

Table 2: Table of parameters κ, α, and the symbolic reaction model f_{sym}.

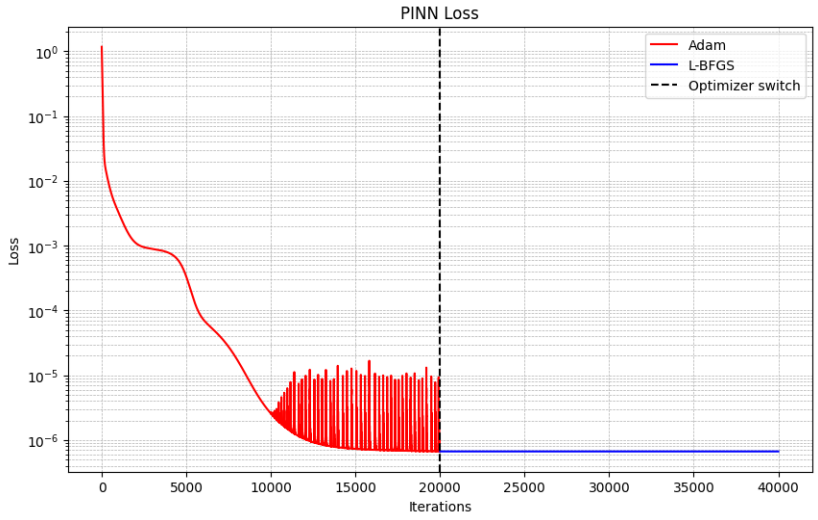


Fig. 5: PINN training process

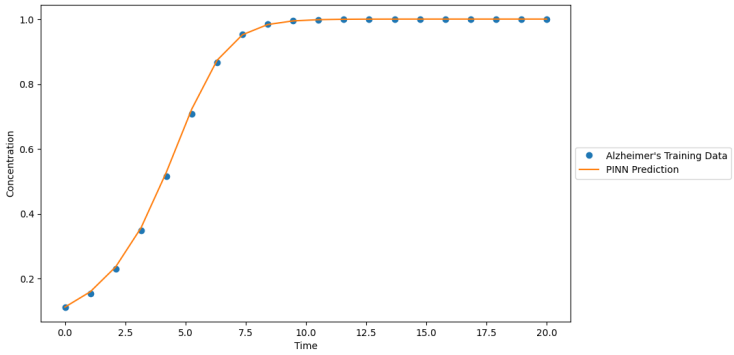
4.4 COMSOL Multiphysics Simulation

To enhance the interpretation of our results, we utilized COMSOL Multiphysics to simulate and visualize the diffusion-reaction dynamics of tau protein across a 2D isotropic domain. This domain represents the spatial area containing all nodes from our discretized brain model, providing a comprehensive view of the diffusion and reaction processes across the brain. To illustrate the idea of our application we used a reaction term inferred in [23] where they predicted the reaction term using real data collected from The Alzheimer's Disease Neuroimaging Initiative (ADNI) using the same mechanism.

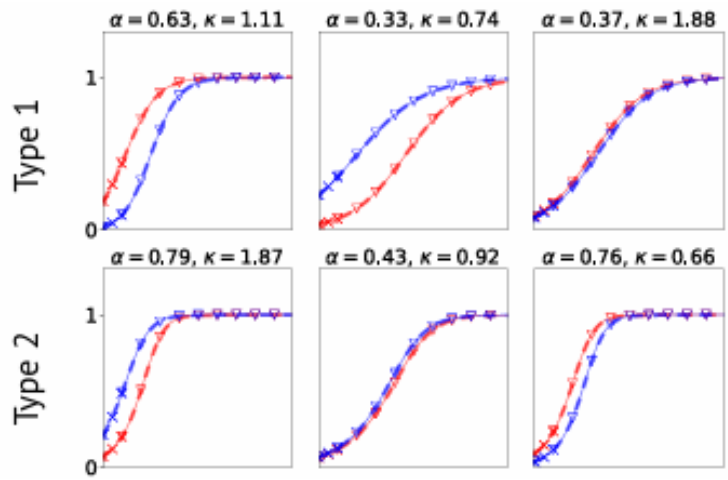
$$f(c) = 0.23c^3 - 1.34c^2 + 1.11c \tag{8}$$

Then it was incorporated into the diffusion-reaction PDE 1 applied across this 2D space. This simulation allowed us to examine the spatial and temporal progression of tau protein across the interconnected nodes, reflecting the global effects of the reaction term on diffusion. These simulations validate our approach by demonstrating its capability to model the diffusion-reaction dynamics across a realistic spatial domain, bridging the gap between theoretical predictions and biologically meaningful visualizations.

2D Model Setup and Physics Setup For simplicity and computational efficiency, we assumed a rectangular geometry to represent a section of the brain that contains the nodes where we study the diffusion-reaction process. We selected the *Transport of Diluted Species* module to model the diffusion-reaction process. The model was then defined with appropriate boundary conditions to



(a) PINN Output results



(b) Output from other reference for validation [23]

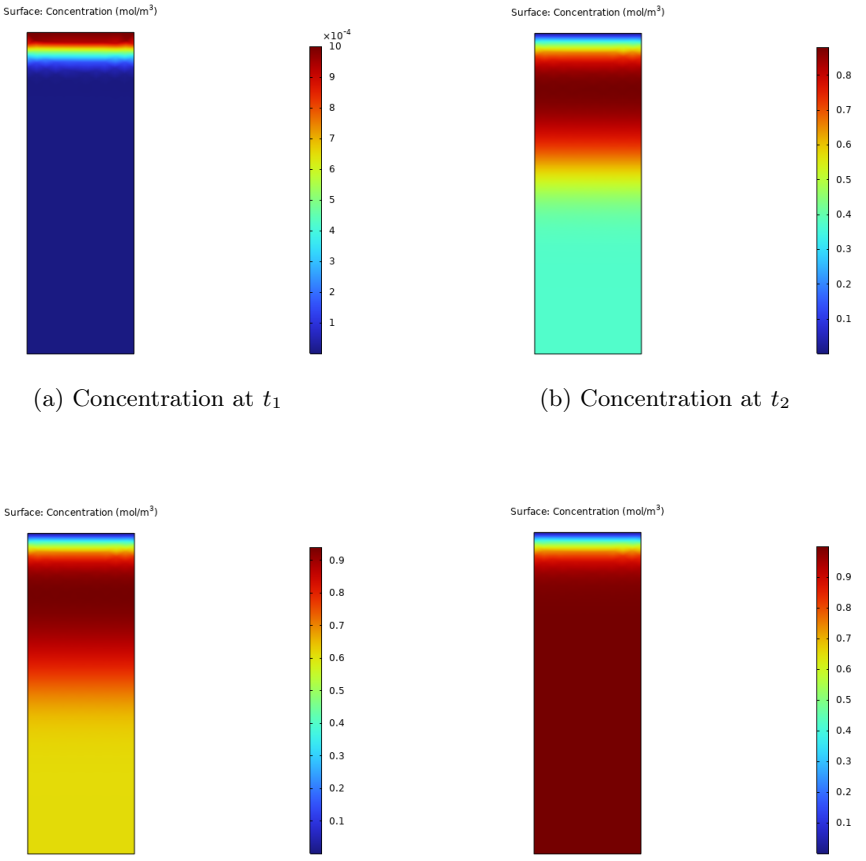
reflect the physiological environment. At the top boundary of the rectangular domain, a Dirichlet boundary condition was applied, representing a fixed concentration of tau protein Which is considered as the source of the initial concentration c_i. This was mathematically expressed as:

$$C = C_d \quad \text{on } \Gamma_{\text{Dirichlet}} \tag{9}$$

where C is the tau protein concentration, C_d is the constant concentration at the source, and $\Gamma_{\text{Dirichlet}}$ refers to the top boundary where this condition is applied. On the remaining edges of the rectangular domain, Neumann boundary conditions were used, which set the diffusive flux to zero, ensuring no transfer of tau protein across these boundaries. This is expressed as:

$$\frac{\partial C}{\partial n} = 0 \quad \text{on } \Gamma_{\text{Neumann}} \tag{10}$$

where $\frac{\partial C}{\partial n}$ represents the concentration gradient normal to the boundary, and Γ_{Neumann} denotes the boundaries where this condition holds. To isolate the diffusion effects, convection was excluded from the model, allowing the simulation to focus only on tau protein diffusion-reaction. After setting up the geometry, material properties, and boundary conditions, a mesh was generated to discretize the domain followed by the configuration of a time-dependent study. The model was then solved, and the results were visualized through surface plot. This visualizations provided insights into tau protein concentration and diffusion patterns within the brain tissue. And here are the results of this simulation .



(a) Concentration at t_1

(b) Concentration at t_2

(c) Concentration at t_3

(d) Concentration at t_4

Fig. 7: The Diffusion Process at different time stamps where $t_1 < t_2 < t_3 < t_4$

5 Discussion

We have encountered significant challenges in this study, especially the difficulty in finding source code for our project or real-world data needed for accurate modeling. To address this, we created synthetic data to simulate how tau protein spreads over time and across different brain regions. Using the reaction-diffusion equation mentioned in Equation (1), we simplified the model by reducing the PDE to an ODE, where the brain was divided into distinct regions, as shown in Equation (7). This approach, which utilizes PDEs, is a method not commonly explored in Alzheimer's disease modeling. It allowed us to group subjects into different groups, each with unique reaction patterns, as shown in Table 1, making the synthetic data closely resemble real-world conditions. Here you can find the code used in this study: Github repo, which handles the computational complexity and effectively simulates the brain network dynamics.

To analyze this data, we built a computational system that uses Physics-Informed Neural Networks (PINNs) and symbolic regression. The PINNs were designed to predict tau protein concentrations over time and find the reaction patterns, ensuring the results were accurate and followed the physical rules defined by the equations. Even though we used synthetic data, our method showed excellent accuracy in predicting tau dynamics and identifying meaningful reaction patterns, proving that our approach works effectively.

6 Future Work

We aim to enhance the tau dynamics model by integrating PET and MRI imaging data to improve the analysis of tau concentration across different brain regions. This integration will provide a more comprehensive understanding of tau's spatial and temporal distribution, offering deeper insights into the patient's disease stage. To facilitate this integration, we plan to develop a web-based platform designed for both researchers and clinicians. The platform will allow users to visualize tau concentration trends, monitor disease progression over time, and evaluate the impact of different treatments. This approach aims to support early diagnosis, personalized treatment, and continuous monitoring, ultimately leading to more effective Alzheimer's disease management.

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