Enhance Early Diagnosis Accuracy of Alzheimer's Disease by Elucidating Interactions Between Amyloid Cascade and Tau Propagation

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Abstract. Amyloid-beta (Aβ) deposition and tau neurofibrillary tangles (tau) are important hallmarks of Alzheimer's disease (AD). Although converging evidence shows that the interaction between Aβ and tau is the gateway to understanding the etiology of AD, these two AD hallmarks are often treated as independent variables in the current state-of-the-art early diagnostic model for AD, which might be partially responsible for the issue of lacking explainability. Inspired by recent progress in systems biology, we formulate the evolving biological process of Aβ cascade and tau propagation into a closed-loop feedback system where the system dynamics are constrained by region-to-region white matter fiber tracts in the brain. On top of this, we conceptualize that Aβ-tau interaction, following the principle of optimal control, underlines the pathophysiological mechanism of AD. In this context, we propose a deep reaction-diffusion model that leverages the capital of deep learning and insights into systems biology, which allows us to (1) enhance the prediction accuracy of developing AD and (2) uncover the latent control mechanism of Aβ-tau interactions. We have evaluated our novel explainable deep model on the neuroimaging data in Alzheimer's Disease Neuroimaging Initiative (ADNI), where we achieve not only a higher prediction accuracy for disease progression but also a better understanding of disease etiology than conventional ("black-box") deep models.

Keywords: Alzheimer's disease · Graph neural networks · Partial differential equations · Aβ-tau interaction · Systems biology

H. Greenspan et al. (Eds.): MICCAI 2023, LNCS 14222, pp. 66–76, 2023.
https://doi.org/10.1007/978-3-031-43898-1_7

1 Introduction

The human brain comprises millions of neurons that interconnect via intricate neural synapses, enabling efficient information exchange and transient, self-organized functional fluctuations. Regrettably, this rapid and efficient transport mechanism also facilitates the dissemination of toxic pathological proteins, including amyloid-beta (Aβ) plaques and neurofibrillary tangles (tau), which spread rapidly throughout the brain, exacerbating the progression of Alzheimer's disease (AD) [3]. Although tremendous efforts have been made to comprehend the principles and mechanisms that underlie complex brain cognition and behavior as a complex information-exchanging system [1], AD presents a distinct clinical course characterized cognitive decline as the earliest symptom, indicating an obstacle in the information-exchanging system in the brain. The studies so far indicate that the cause of such phenomenon is well-correlated with a progressive pattern of intracellular aggregates of tau (neurofibrillary tangles) [27]. However, other research suggests that amyloidosis precedes the spread of pathologic tau, ultimately leading to neurodegeneration and cognitive decline [21]. As such, the role of Aβ and tau in the pathogenesis of AD remains an open question, particularly with respect to the interaction between these two factors (Aβ-tau).

Aβ and tau represent pathological hallmarks of AD, which can be measured through PET (positron emission tomography) scan [6]. With the rapid advancement of neuroimaging technologies such as magnetic resonance imaging (MRI) and diffusion-weighted imaging (DWI), it has become feasible to investigate the wiring of neuronal fibers (aka. structural connectomes) of the human brain *in-vivo* [10,28]. As evidence suggests that AD is characterized by the propagation of tau aggregates triggered by the Aβ build-up [3,11], tremendous machine learning efforts have been made to predict the spreading of tau pathology in the progression of AD from longitudinal PET scans [26,30]. With the prevalence of public neuroimaging data cohorts such as ADNI [23], the research focus of computational neuroscience shifts to the realm of deep learning.

A plethora of deep learning models [14,15,24,25] have been proposed to predict clinical outcomes by combining network topology heuristics and pathology measurements, including Aβ and tau, at each brain region. In spite of various machine learning backbones such as graph neural network (GNN) networks [16], most of the methods are formulated as a graph embedding representation learning problem, that is, aggregating the node features with a graph neighborhood in a "blackbox" such that the diffused graph embedding vectors are aligned with the one-hot vectors of outcome variables (i.e., healthy or disease condition). Although the graph attention technique [20,29] allows us to quantify the contribution of each node/link in predicting outcome, its power is limited in dissecting the mechanistic role of Aβ-tau interactions, which drives the dynamic prion-like pattern of tau propagation throughout the brain network.

Fortunately, the partial differential equation (PDE)-based systems biology approach studies biological pathways and interactions between Aβ and tau from the mathematical perspective, allowing us to uncover the intrinsic mechanism that steers the spatiotemporal dynamics of tau propagation throughout the

brain. In this context, reaction-diffusion model (RDM) [17] has shown promising results by explicitly modeling the Aβ-tau interaction and the prion-like propagation of tau aggregates using PDEs [12,31]. Neuro-RDM [7], a recent study, has demonstrated the potential of using neural networks to predict the state of brain activities underlying the RDM mechanism. By treating the brain as a complex system, Neuro-RDM designs an equivalent deep model of RDM that addresses the issue of a-priori choice of basis function in the conventional PDE-based model and it unveils the brain dynamic. The model takes observation signals as input and characterizes the reaction of massive neuronal synapses at each brain region as the reaction process, while considering the diffusion process as the information exchange process between regions. Eventually, solving the PDE enables the inference of the evolutionary states of the brain.

Following this cue, we sought to integrate the principle of systems biology and the power of machine learning in a unified mathematical framework, with a focus on an RDM-based deep model for uncovering the novel biological mechanism. Specifically, we introduce a novel framework for producing fresh PDE-based solutions from an application-specific constrained functional, known as Aβ influence. We formulate the evolving biological process of Aβ cascade and tau propagation into a closed-loop feedback system where the system dynamics are constrained by region-to-region white matter fiber tracts in the brain. This approach enables accurate prediction of the progression of the underlying neurobiological process, namely tau propagation. Additionally, we develop an explainable deep learning model that is based on the newly formulated RDM. The neural network is trained to clarify the Aβ-tau interaction while adhering to the principles of mathematics. We demonstrate promising results in both predicting AD progression and diagnosing the disease on the ADNI dataset.

2 Method

Suppose we have a brain network $\mathcal{G} = (\Xi, W)$ with N brain regions $\Xi = \{\xi_i | i = 1, ...N\}$ and the structural connectcome $W = [w_{ij}] \in \mathcal{R}^{N \times N}$. Each brain region is associated with a feature vector $z_i \in \mathcal{R}^M$. The input of the model is the longitudinal data $Z(t) = [z_i(t)]_{t=1}^T$, and the output is the clinical outcome η_T. From the perspective of brain dynamics, we introduce an evolution state $v_i(t)$ for each brain region, which can be regarded as the intrinsic interaction trajectory of the features of each brain node. Herein, we investigate two prominent features on the basis of the brain region, namely tau-$x_i(t)$ and Aβ-$u_i(t)$, we then explore the interaction between tau propagation and amyloid cascade, which is believed to play a crucial role in the evolution dynamics $V(t) = [v_i(t)]_{i=1}^N$ of AD progression. In particular, we investigate how Aβ influences the spreading of tau in AD progression. Our study aims to shed light on the complex mechanisms underlying the progression of AD, a critical area of research in the field of neuroscience.

2.1 Reaction-Diffusion Model for Neuro-Dynamics

RDM, a mathematical model with the capability to capture various dynamic evolutionary phenomena, is often employed to describe the reaction-diffusion process [7,17] that governs the evolution of the dynamic state $v(t)$ of the brain.

$$\frac{dv}{dt} = Av(t) + R(x, v, t) \tag{1}$$

$A = -\nabla \cdot (\nabla)$ expresses the *Laplacian* operator, which is represented by the divergence $\nabla\cdot$ of gradient ∇. In this context, the first term of Eq. (1) denotes the *diffusion process* (i.e., the information exchange between nodes) constrained by the network topology A. $R(x, v, t)$ denotes the *reaction process* that encapsulates the nonlinear interaction between the observation x and the evolution state v. In the deep neural network chiché, the nonlinear interaction is often defined as $R_\Theta(t) = \sigma\left(\beta_1 V(t) + \beta_2 X(t) + \mu\right)$ with the learnable parameters $\Theta = \{\beta_1, \beta_2, \mu\}$.

2.2 Construction on the Interaction Between Tau and Amyloid

Conventionally the connection between tau and amyloid has been established by treating them as an embedding ($z_i\{x_i, u_i\} \in \mathcal{R}^M$) on the graph in a cutting-edge graph-based learning approach [14,24,25], such manner cannot capture the interaction between the features of embedding on the node. Herein, we propose a novel solution to model the interaction between tau x_i and amyloid u_i. Upon the RDM, we introduce an interaction term that describes how amyloid has influenced the spreading of tau during the evaluation of tau accumulation. Following this clue, we propose a new PDE as follows:

$$\frac{dv}{dt} = Av(t) + R(x, v, t) + Bu(t) \tag{2}$$

where the designed last term characterizes the interaction between the evolution state v and u with B denoting the interaction matrix. To reasonably and appropriately establish the interaction, we incorporate an interaction constraint that ensures a desirable evolution state. In the spirit of the linear quadratic regulator (LQR) in control theory [2], the interaction constraint is formulated by:

$$\mathcal{L} = \frac{1}{2} v^{\mathbf{T}} P v + \frac{1}{2} u^{\mathbf{T}} Q u \tag{3}$$

where the requirement that $\mathcal{L} \geq 0$ implies that both P and Q are positive definite. Minimizing the objective function Eq. (3) can yield the stable and high-performance design of the new PDE. To achieve this, we can minimize Eq. (3) through an optimal control constraint problem, as outlined in [4]. Such optimal control constraint is regarded as a closed-loop feedback system, u acts as the control term to yield the optimal feedback in control theory [4]. Moreover, to account for the known clinical outcome (i.e., ground truth η_T), we incorporate the clinical outcome as a terminal cost in the optimization process. In doing so,

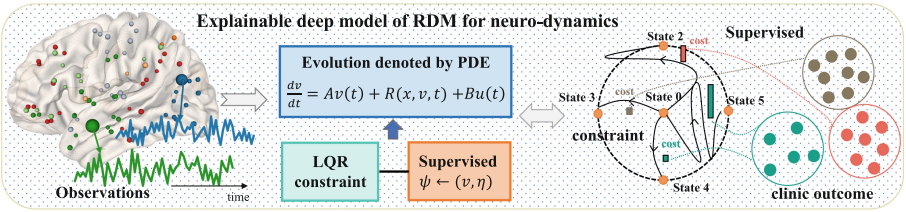

Fig. 1. The sketch of developing LQR-constrained RDM model in a supervised manner. (Color figure online)

we formulate the problem as a supervised evolution process, thereby enhancing the accuracy of the inference process in reflecting the actual disease progression.

$$\mathcal{J} = \psi(v_T, \eta_T) + \int_0^T \mathcal{L}(v(t), u(t), t)dt \tag{4}$$

where the terminal cost $\psi(v_T, \eta_T) = KL(v_T, \eta_T)$ is measured by Kullback-Leibler (KL) divergence [18] between predicted final status v_T and the ground truth η_T. The second term is the LQR constraint described in Eq. (3). To solve this optimization problem, we follow the approach outlined in [5], where we first construct a novel PDE (blue box in Fig. 1) to model the evolution of brain dynamics, introduce an interaction constraint on the basis of LQR (cyan box Fig. 1), followed by optimizing the equation with the aid of ground truth (orange box Fig. 1) to guide the learning. Figure 1 illustrates an overview of our framework.

2.3 Neural Network Landscape of RDM-Based Dynamic Model

In this section, we further design the explainable deep model based on the new PDE, and the designed deep model is trained to learn the mechanism of neuro-dynamics, i.e., tau propagation, which can predict disease progression and diagnosis accuracy.

The overall network architecture of our physics-informed model is shown in Fig. 2, in which the backbone is the reaction-diffusion model. Specifically, we first define the reaction process ($R(x, v)$ in Eq. (2)) by a deep neural network (DNN, green shadow), thereby yielding the reacted state $\tilde{v}_0$ by the initial state v_0 and the observed tau level x_0. A graph diffusion process is conducted by vanilla GNN (red shadow), and then we can obtain a desirable feature representation $\hat{v}_0$ by the tailored reaction-diffusion model. Inspired by the insights gained from the closed-loop feedback system, the LQR is implemented to accommodate problem constraints (cyan shadow) to produce the optimal interaction constraint $\hat{u}$ under a supervised manner (orange shadow). Upon the $\hat{v}_0$ and $\hat{u}$, the new PDE equation can be built according to Eq. (2), then we use the PDE solver with time-constant [13] (gray shadow) to recurrently seek the future evolutionary state trajectory v_1 to v_T. Eventually, the predicted $\hat{x}_T$ is derived by a mapping function formulated

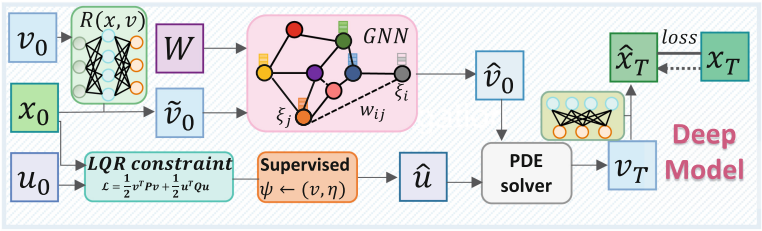

Fig. 2. The framework of our proposed deep RDM model. (Color figure online)

by a fully-connected layer on top of v_T. The driving force of our model is to minimize the mean square error (MSE) between the output $\hat{x}_T$ of our model and the observed goal x_T. The variation adaptive moment estimation (Adam) [9] (learning rate 0.001 and epoch 300) is used in gradient back-propagation.

3 Experiments

3.1 Data Description and Experimental Setting

We evaluate the performance of the proposed PDE-informed deep mode of neurodynamics on ADNI dataset [23]. We select 126 cohorts, in which the involved longitudinal observations of whole brain tau and $A\beta$ SUVR (standard update value ratio) levels through PET scans have two time-series data of each subject at least. For $A\beta$ data, we only retain the baseline as the interaction constraint reference. Each subject includes multiple diffusion-weighted imaging (DWI) scans, we merely extract the baseline to act as the structural connectome. We divided the involved cohorts into four groups based on the diagnostic labels of each scan, including the cognitive normal (CN) group, early-stage mild cognitive impairment (EMCI) group, late-stage mild cognitive impairment (LMCI) group and AD group. The precise description for the binary classification is the prediction of conversion of AD. Since the clinical symptom is not onset until converting from EMCI to LMCI, we consider CN+EMCI as 'non-convert' and LMCI+AD as 'converted' group. For each neuroimaging scan, we parcellate the whole brain into a cortical surface including 148 Destrieux regions [8] and 12 sub-cortical regions. The 148 cortical regions are separated into six lobes commonly identified in structural brain networks: frontal lobe, insula lobe, temporal lobe, occipital lobe, parietal lobe, and limbic lobe. Since the clinical diagnostic label is available at each visit time, we split long time series ($\geq$ 3-time points) into a collection of 2-time-point temporal segments to reach data augmentation. By doing so, we augment the sample pool to a magnitude of 1.6 times larger.

We (1) validate the performance of disease progression prediction (i.e., the future tau accumulation) of our proposed PDE-informed deep model, a PDE-based liquid time-constant network (LTC-Net) [13], a PDE-based neural network (Neuro-RDM) [7] and graph conventional network (GCN) [16] on ADNI dataset.

(2) predict the diagnosis accuracy of AD (i.e., the recognition of 'non-convert' vs. 'converted'), and further uncover the interaction between tau and $A\beta$. To assess fairness, we perform one solely utilizing tau as input, and the other incorporating both amyloid and tau as input. In the latter scenario, we conduct a concatenation operation for LTC-Net and Neuro-RDM, with tau and $A\beta$ serving as the graph embeddings based on GCN. To further verify the effectiveness of the proposed components of our deep model, we conduct an ablation study in terms of the presence/absence LQR constraint. Note, we report the testing results using 5-fold cross-validation, the evaluation metrics involve (1) the mean absolute error (MAE) for predicting the level of tau burden (2) the prediction accuracy for recognizing the clinical outcomes.

3.2 Ablation Study in Prediction Disease Progression

We design the ablation study in the scene of predicting the future tau burden x_T using the baseline tau level x_0, where we model the influence of amyloid build-up $(u_0...u_T)$ in the time course of tau propagation $\frac{dv}{dt}$. As shown in the first column of Fig. 3, the prediction error (MAE) by our method, denoted by "*OURS*" in blue, shows a reduction compared to our (down-graded) method without LQR constraint, denoted by "*OURS (w/o LQR)*", and our full method but without the supervised LQR constraint, denoted by "*OURS (w LQR)*", where '*' indicates the performance improvement is statistically significant ($p < 0.0001$). We also display the prediction MAE results by *LTC-Net* in green, *Neuro-RDM* in red, and *GCN* in purple, using 'tau' only and 'tau+$A\beta$' as the input, respectively.

It is clear that (1) the prediction error by the counterpart methods is much less reliable than our PDE-informed method since the machine learning model does not fully capture neurobiological mechanism, and (2) adding additional information ($A\beta$) does not contribute to the prediction, partially due to the lack of modeling $A\beta$-tau interaction, implying that the $A\beta$ interacts with the propagation of tau to a certain extent.

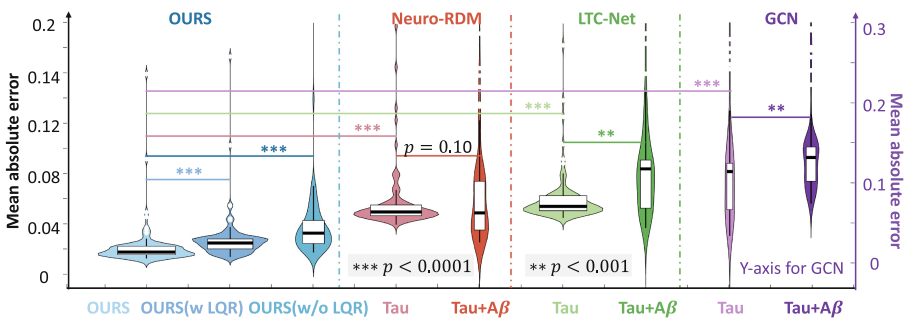

Fig. 3. The performance in predicting disease progression on four methods, including *OURS*, *Neuro-RDM*, *LTC-Net* and *GCN*. (Color figure online)

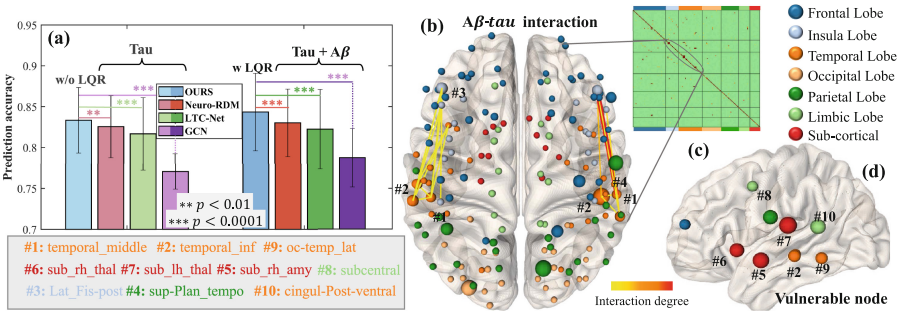

Fig. 4. (a) The prognosis accuracies on forecasting AD risk. (b) The visualization of local (diagonal line in Θ) and remote (off-diagonal line) interaction of $A\beta$-tau interactions. The node size and link bandwidth are in proportion to the strength of local and remote interactions, respectively. (c) Interaction matrix B. (d) The top-ranked critical brain regions that are vulnerable to the intervention of amyloid build-up. (Color figure online)

3.3 Prognosis Accuracies on Forecasting AD Risk

First, suppose we have the baseline amyloid and tau scans, we evaluate the prediction accuracy in forecasting the risk of developing AD by *LTC-Net* (in green), *Neuro-RDM* (in red), *GCN* (in purple), and *OURS* (in blue) in Fig. 4(a). At the significance level of 0.001, our method outperforms all other counterpart methods in terms of prediction accuracy (indicated by '*'). *Second*, we sought to uncover the $A\beta$-tau interaction through the explainable deep model, by answering the following scientific questions.

(1) *In what mechanism that local or remote $A\beta$-tau interaction promotes the spreading of tau aggregates?* Our explainable deep model aims to uncover the answer from the interaction matrix B in Eq. (2), which is the primary motivation behind our research. We visualize the interaction matrix B and the corresponding brain mapping (node size and link bandwidth are in proportion to the strength of local and remote interaction, respectively) in Fig. 4(b). Our analysis reveals that $A\beta$ plaques primarily contribute to the local cascade of tau aggregates (Fig. 4(c)). However, we observe a few significant remote interactions in the middle-temporal lobe, where the high activity of tau pathology has been frequently reported [19, 30]. (2) *Which nodes are most vulnerable in the progression of AD?* We retrain our method using AD subjects only. Then, following the notion (*Gramian* matrix $\mathcal{K} = \sum_{t=0}^{T} (A)^t BB^{\mathbf{T}} (A^{\mathbf{T}})^t$) of control theory [22], we calculate the node-wise $Trace(\mathcal{K}_{\xi_i})$ that projects the amount of effort (amyloid build-up in the scenario of AD progression) needed to reach the terminal state v_T (i.e., developing AD). Note, a small degree of $Trace(\cdot)$ indicates that the underlying node is vulnerable to the intervention of amyloid plaques. In this context, we display the top 10 most vulnerable brain regions in Fig. 4(d). It is apparent that most brain regions are located in temporal and limbic lobes, and sub-cortical areas, which is in line with the current clinical findings [19].

4 Conclusion

In this endeavor, we have embarked on an explainable machine learning initiative to unearth the intrinsic mechanism of Aβ-tau interaction from the unprecedented amount of spatiotemporal data. Since RDM has been well studied in the neuroscience field, we formulate optimal constraint in vanilla RDM and dissect it into the deep model. We have applied our RDM-based deep model to investigate the prion-like propagation mechanism of tau aggregates as well as the downstream association with clinical manifestations in AD, our tailored deep model not only achieves significant improvement in the prediction accuracy of developing AD, but also sheds the new light to discover the latent pathophysiological mechanism of disease progression using a data-driven approach.

Acknowledgment. This work was supported by Foundation of Hope, NIH R01AG068399, NIH R03AG073927. Won Hwa Kim was partially supported by IITP-2019-0-01906 (AI Graduate Program at POSTECH) funded by the Korean government (MSIT).

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