# Alz-QNet: A Quantum Regression Network for Studying Alzheimer's Gene Interactions

1st Neerav Sreekumar
*Department of Chemical Engineering, Indian Institute of Technology, Tirupati, India*

2nd Debanjan Konar and 3rd Vaneet Aggarwal
*Purdue Quantum Science and Engineering Institute (PQSEI), and and School of Industrial Eng., Purdue University, West Lafayette, USA*

***Abstract*—Understanding the molecular level mechanisms underpinning Alzheimer's Disease (AD) by studying the crucial genes associated with the disease, however, remains a challenge. Our proposed Quantum regression Network (Alz-QNet) introduces a pioneering approach that merges Quantum Machine Learning (QML) techniques with insights from Gene Regulatory Networks (GRN) to unravel the gene interactions involved in AD pathology, particularly within the Entorhinal Cortex (EC) where early pathological changes occur. Using a quantum regression network framework, we explore the interactions between key genes such as Amyloid Beta Precursor Protein ($APP$), Sterol regulatory element binding transcription factor 14 ($FGF14$), Yin Yang 1 ($YY1$), and Phospholipase D Family Member 3 ($PLD3$) within the EC micro-environment of AD patients, studying on genetic samples from the $GSE138852$ database, all of which have are believed to have a crucial role in AD progression. Our investigation uncovers intricate gene-gene interactions, shedding light on the potential regulatory mechanisms that underlie the pathogenesis of AD, which help us to find potential gene inhibitors or regulators for theranostics.**

***Index Terms*—Quantum Machine Learning, Computational Biology, Alzheimer's Disease, Gene Regulatory Networks**

## I. Introduction

Alzheimer's disease (AD) presents a formidable challenge in healthcare, characterized by progressive cognitive decline and neurodegeneration [1]. The accumulation of peptides of Amyloid Beta ($A\beta$) from $APP$ is a crucial factor in AD pathology [2]. Despite extensive research efforts over decades, the intricate mechanisms underlying AD remain elusive, impeding the development of effective therapeutic interventions [3]. The amyloid cascade hypothesis, attributing neurotoxicity and neuronal loss to the accumulation of $A\beta$ peptides, has been a prominent theory but has encountered limitations in translating it into successful treatments [4]. Clinical trials targeting $A\beta$ accumulation have produced disappointing results, underscoring the multi-factorial nature of AD pathogenesis influenced by factors such as Reactive Oxygen Species (ROS) and ferroptosis [5]. Mounting evidence suggests that $A\beta$ deposition may be a downstream consequence rather than the primary driver of neurodegeneration, necessitating a reevaluation of therapeutic strategies and a deeper understanding of the molecular underpinnings of AD. Traditional hypotheses, including the amyloid cascade hypothesis, have failed to elucidate the complexity of the disease [6].

Quantum computing harnesses the principles of quantum mechanics to perform computations beyond the capabilities of classical computers. Unlike classical bits, which can only exist in a state of either 0 or 1, quantum bits or qubits can exist in superpositions of these states, enabling exponentially greater computational capacity and effective computations. This exponential scaling opens avenues for solving computationally intractable problems in genomics [7]. For instance, the human genome is given by 3 billion base pairs, which can be represented by $10^{10}$ classical bits, which are equivalent to 34 qubits ($2^n$ possible states for each). Building upon the foundations of QML seeks to leverage quantum algorithms and hardware to enhance traditional machine learning techniques [8]. QML offers the promise of accelerated learning and improved performance on large datasets by exploiting quantum parallelism and entanglement. Moreover, QML can potentially address challenges such as feature selection, dimensionality reduction, and pattern recognition, thereby extending the applicability of machine learning to complex scientific domains [7], [8]. However, the main problem lies in the computational expense and complexity of quantum circuits, considering the costs of gates like controlled rotation, which are extensively used in quantum machine learning (regression) circuits, which do not entirely make quantum computing an economically feasible option for data science in the short term. The traditional method of quantum GRN [9] has the slight disadvantage of being computationally very expensive to implement, as the quantum circuit with $n$ qubits requires $n(n-1)$ controlled rotation gates and $n$ rotation gates.

Recognizing these limitations, our Alz-QNet model harnesses the computational power of QML to explore high-dimensional genomic data to unveil intricate gene-gene interactions that contribute to the pathogenesis of AD [10]. In the midst of the intricate molecular mechanisms and unresolved queries in AD research, the integration of QML and GRN analysis holds promise for unraveling the complexities of AD pathogenesis.

## II. Quantum Regression Network Architecture

Our proposed Alz-QNet model studies the 8 genes specifically for Alzheimer's by significantly reducing the cost of the $C-R_Y$ gates by reducing their number by half through a bypass mechanism to study GRNs with less computational complexity. In our study, we utilized single-nucleus RNA sequencing (snRNA-seq) data from the entorhinal cortex of Alzheimer's disease (AD) patients to explore this neurodegenerative disorder's underlying genetic and molecular

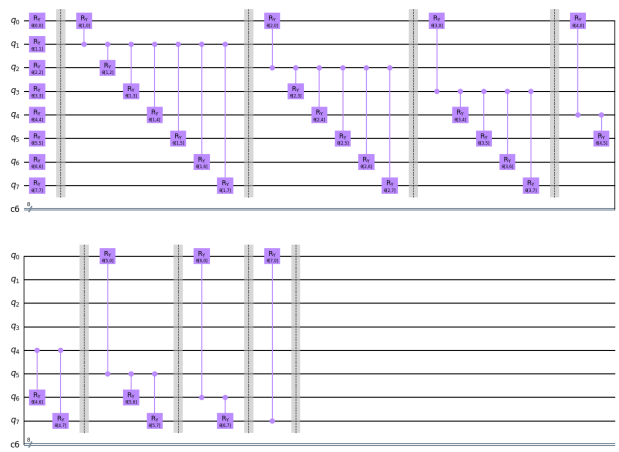


Fig. 1: A quantum regression network to study Alzheimer's gene interactions.

mechanisms-GSE138852 [11]. The entorhinal cortex is a critical region for memory and navigation, and it is one of the primary areas affected in AD, making it an ideal target for investigating early pathological changes. Inspired by the Quantum Gene Regulatory Networks (QGRN) [9], in our proposed Alz-QNet, as shown in Fig. 1, we leverage the computational speed-up quantum computing offers to draw gene regulatory relationships considering all the factors. In our proposed parameterized quantum circuit, each qubit represents a gene and initializes to phase 0. The proposed Alz-QNet is divided into two sections: the encoder and regulation layers. The encoder layer translates the $snRNA$-seq data into a superposition state, and the regulation layers entangle qubits to model gene-gene interactions in the quantum framework. Through these layers, we construct an 8∗8 matrix, with the unknown values of $\theta_{x,y}$ in the $c-R_Y$ gates used to entangle 2 qubits, where $x$ is the control qubit/gene and $y$ is the target qubit/gene. The optimized values of each $\theta$ in the matrix correspond to the strength of gene interaction, which helps us visually represent the same graphically. We use traditional Laplace smoothing and the gradient descent algorithm for the optimization procedure to minimize a loss function based on Kullback-Leibler (KL) divergence.

In the proposed Alz-QNet, $\theta_{k,k}$ as the parameter for the $R_Y$ gate on the $k$th qubit in the $L_{\text{enc}}$ layer, and $\theta_{k,p}$ for the c-$R_Y, n$ gate with the $k$th qubit as control and the $p$th qubit as target in the $L_k$ layer of an $n$-qubit system. For our case where $n = 8$, the layers are defined as follows:

$$L_{\text{enc}} = R_Y(\theta_{7,7}) \otimes R_Y(\theta_{6,6}) \otimes \cdots \otimes R_Y(\theta_{1,1}) \otimes R_Y(\theta_{0,0}), \quad (1)$$

and

$$\begin{aligned} L_k = \prod_{i=0, i\neq k}^{7} c - R_Y, n(\theta_{k,i}) = c - R_Y, n(\theta_{k,7}) \\ \otimes \cdots \otimes c - R_Y, n(\theta_{k,1}) \otimes c - R_Y, n(\theta_{k,0}) \end{aligned} \quad (2)$$

In our Alz-QNet circuit, we reduce the number of $c-R_Y$ gates to half compared to the traditional quantum gene regulatory network by only optimizing the upper triangular matrix of $\theta_{x,y}$ as we noted that the value of $\theta_{a,b} = \theta_{b,a}$, hence proving the fact that only a single controlled rotation gate between 2 qubits is sufficient to measure the interaction, provided we manually equate $\theta_{a,b} = \theta_{b,a}$ to construct the entire matrix:

$$\theta = \begin{pmatrix} \theta_{0,0} & \theta_{0,1} & \cdots & \theta_{0,7} \\ \theta_{1,0} & \theta_{1,1} & \cdots & \theta_{1,7} \\ \vdots & \vdots & \ddots & \vdots \\ \theta_{7,0} & \theta_{7,1} & \cdots & \theta_{7,7} \end{pmatrix},$$

## III. Simulation Results

A nodal graph is generated on Quantum simulations using Qiskit along with the observed vs. output frequency distributions graph and the observed vs. simulated frequency distributions graph, as shown in Fig. 2, which resembles the Gene Regulatory Networks (GRN) [12].

$$\begin{bmatrix} 1.058265 & 0.044794 & 0.050884 & 0.123109 & -0.054711 & 0.044286 & -0.000519 & 0.025685 \\ 0.044794 & 1.044976 & 0.174487 & -0.022467 & -0.025248 & 0.002224 & -0.047362 & -0.078536 \\ 0.050884 & 0.174487 & 0.773622 & -0.050870 & -0.105563 & -0.066458 & -0.153903 & 0.074156 \\ 0.123109 & -0.022467 & -0.050870 & 0.562070 & -0.058445 & -0.060104 & -0.168851 & -0.019798 \\ -0.054711 & -0.025248 & -0.105563 & -0.058445 & 0.540032 & -0.112907 & 0.034236 & -0.029027 \\ 0.044286 & 0.002224 & -0.066458 & -0.060104 & -0.112907 & 0.524879 & -0.033177 & -0.011903 \\ -0.000519 & -0.047362 & -0.153903 & -0.168851 & 0.034236 & -0.033177 & 0.485128 & -0.019015 \\ 0.025685 & -0.078536 & 0.074156 & -0.019798 & -0.029027 & -0.011903 & -0.019015 & 0.138786 \end{bmatrix} \quad (3)$$

The above matrix shows the values of $\theta_{x,y}$, where each row and column corresponds to a different gene. The upper triangular matrix in black is the optimized values of theta obtained, and the lower triangular matrix was constructed from the equated values from $\theta_{a,b} = \theta_{b,a}$.

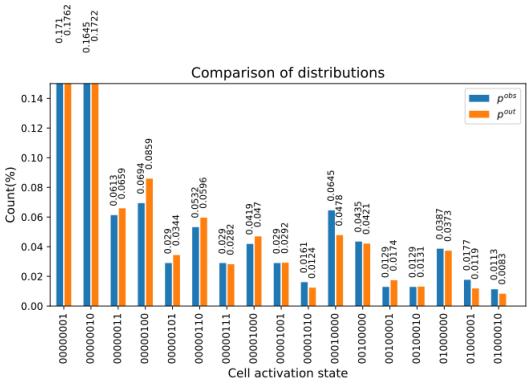
Apart from the gene interactions that affect prominent genes like $APP$ and $AKT3$, which have direct correlations, our findings extend and support the detailed epigenetic and transcriptomic insights [1], particularly through the interactions involving $YY1$ and $PLD3$.

### A. YY1 and PLD3 Interaction

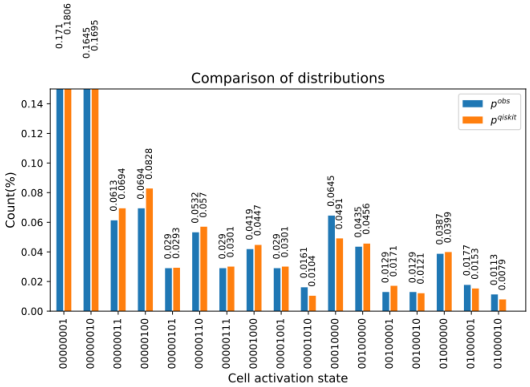
$YY1$ (Yin Yang 1) is a transcription factor with dual gene activation and repression roles. It influences gene expression epigenetically by recruiting proteins that modify chromatin structure. Our results show a negative interaction between $YY1$ and $PLD3$ (-0.112907), suggesting $YY1$'s repressive role on $PLD3$. This aligns with the known function of $YY1$ in gene repression and epigenetic regulation.

### B. Role of PLD3 in Alzheimer's Disease

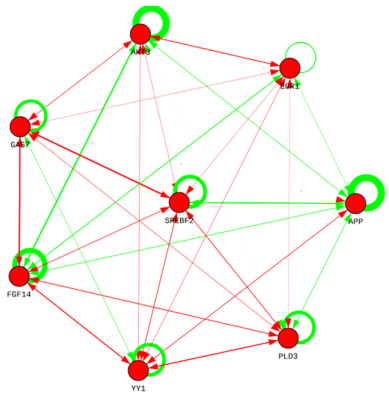
$PLD3$ (Phospholipase D Family Member 3) is involved in the processing of APP and the regulation of amyloid-beta levels, which are critical in Alzheimer's disease (AD) pathology. Our study reveals complex interactions between $PLD3$ and other genes, such as $APP$ and $SREBF2$. These interactions suggest that the regulatory network of $PLD3$ is influenced by both transcriptional and epigenetic mechanisms, supporting the emphasis of the neurobiology literature on the importance of epigenetic modifications in brain development and disease.




(a)




(b)




(c)

Fig. 2: (a) The observed vs output frequency distributions graph, (b) The observed vs simulated frequency distributions graph, and (c) The final nodal graph, where each node corresponds to the specific gene and the edges determine the gene regulatory interactions. Green edges represent upregulation, and red edges represent downregulation. The weight of the edges determines the strength of the interaction between genes.

## IV. Conclusion

Integrating transcriptomic and epigenetic data, our Alz-QNet offers insights into how regulatory mechanisms at the genetic and epigenetic levels contribute to AD. This supports the study conducted by Grubman*et al.* [1] with an emphasis on considering transcriptional and epigenetic factors in understanding brain function and disease, highlighting the importance of integrating multiple layers of biological data to understand the molecular underpinnings of diseases like Alzheimer's. This interdisciplinary methodology offers valuable insight into the molecular foundations of AD and underscores the promising role of QML research in elucidating complex biological phenomena.

## V. Data Availability

The Alzheimer's Dataset used for our model can be found at: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE138852

## VI. Code Availability & Description

The code required using IBM Qiskit, PyTorch, NumPy, and MatPlotLib for the graph. The code of the final .csv file used as the dataset for the experiment can be found at https://github.com/NeeravSreekumar/AD_Quantum.

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