Dynamic Simulation of Parkinson's Disease and ALS Propagation in the Brain: A Reaction-Diffusion on Brain Networks Approach

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Abstract. Neurodegenerative diseases, such as Parkinson's Disease (PD) and Amyotrophic Lateral Sclerosis (ALS), progressively degrade neural systems, leading to considerable cognitive functional disorders. It is consequential to comprehend how these diseases spread within the brain to develop precise diagnosis and interventions. This study uses a reaction-diffusion model on a human brain network model to explore and replicate the actual dynamic progression of PD and ALS. By incorporating diffusion processes with empirical brain network data, we simulated the disease's progression through various regions. Our results show unique propagation patterns for PD and ALS and the effect of different network models on disease transmission. The structure of brain neural networks plays a vital function in neurodegeneration and offers insights that lead to early detection and focused treatments. This study presents a potential viewpoint on handling and interfering in neurodegenerative diseases by perceiving their dependency on brain neural connectivity.
Keywords: neurodegeneration, Parkinson’s disease, ALS, reaction-diffusion, brain network, connectome

1 Introduction

Neurodegenerative diseases like Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) pose substantial public health challenges due to their incapacitating effects and increasing prevalence in the elderly. Although there have been significant strides in comprehending these illnesses, the exact processes driving their progression in the brain are still not fully understood. This lack of knowledge obstructs the creation of efficacious treatments and delays early detection.

1.1 Motivation

The advancement and progressions of PD and ALS are marked by the complex interactions among genetic, molecular, and environmental aspects leading to the progressive loss of neurons and severe motoric dysfunction. This research utilizes reaction-diffusion models applied to brain networks, presenting a new methodology to simulate the propagation of pathological proteins like alpha-synuclein in PD and TDP-43 in ALS. These models, grounded in the connectivity and functionality of the brain, enable a detailed simulation of disease progression. PD and ALS are chosen in this simulation because these 2 diseases are not as widely discussed as Alzheimer's Disease so there might be a research gap for PD and ALS.

By providing a deeper insight and understanding of these diseases' dynamics, this method may reshape the advancement of therapies. It enables the identification of key routes and vulnerable network nodes that can be targeted with new treatments.

1.2 Problem Boundaries

In the pursuit of understanding neurodegenerative diseases for PD and ALS, our study adopts an innovative method by simulating their protein propagation in the brain connectome using a reaction-diffusion model on brain networks. Although this method has provided considerable understanding, it's important to acknowledge the limitations of our research:

a) Observation Limitation: The study primarily observes the spread of protein deposits, which are the main cause of Parkinson's disease and ALS. However, it does not explore the fundamental cause and reasons of initial damage and protein accumulation.
b) Cause and Effect: The study does not examine the effects of protein accumulation and brain damage on cognitive and motor abilities. This leaves a gap in understanding how these diseases impact patients' daily lives and functionalities.
c) Prevention and Cure: The study does not observe prevention or cure of diseases. This narrows the research's breadth, as it fails to offer perspectives on possible treatment methods or approaches to stop or mitigate the advancement of these neurological disorders.

1.3 Problem Formulation

The central question guiding this study is:

- How do the propagation patterns of Parkinson's disease and Amyotrophic Lateral Sclerosis (ALS) occur within the brain?

1.4 Purpose

The purpose of this study is to replicate the propagation patterns of Parkinson's disease and Amyotrophic Lateral Sclerosis (ALS) within the brain using mathematical modeling. By employing a reaction-diffusion model on brain networks, this research aims to simulate how these neurodegenerative diseases spread across different brain regions. The goal is to understand the underlying dynamics of disease progression, providing a detailed framework that reflects the complex interactions within neural circuits. This replication through mathematical modeling will help in identifying critical factors that influence disease spread and could pave the way for developing targeted therapeutic interventions.

2 Methods

2.1 Assumptions

The study is based on several key assumptions:

a) Irreversible Infection: Infected proteins cannot revert to their normal functional state.
b) Universal Susceptibility: All normal proteins in the brain can be infected by similar damaged proteins.
c) Diffusion Mechanism: The spread of damaged proteins follows a diffusion-like mechanism.
d) Homogeneity: The type of protein is considered homogeneous, without considering protein size.
e) Initial Conditions: The initial deposition point of proteins is determined from the literature, and the concentration of proteins at this point is initially set to be non-zero.
f) Propagation Order: The stage of disease progression assumes that the first appearance of proteins determines the order of propagation.

By clearly defining these assumptions, we aim to provide a focused analysis of the disease propagation mechanisms, which can serve as a foundation for future research exploring broader aspects of PD and ALS.

2.2 Brain Network Model

In our simulation, we applied the concept of a graph. In this graph, the nodes represent different parts of the brain, while the edges depict the connections between these brain regions, with the weights corresponding to the edges. We also used 3 different types of connectivity matrix: master n, master w1, and master w2. The difference from all those three are master n is the raw data of brain, it contains the total of neuron fibres between the nodes in the brain. And then, master w1 is containing the total neuron fibres too but they are divided by the average length between nodes. Because of that, master w1 is representing the process of propagation. The last one is master w2, it contains the total neuron fibres divided by the squared averaged length between nodes. Master w2 representing the process of diffusion.

Below is the visualization of the connectivity matrix for master n, which also represents the edge weights, obtained from the graph based on the explanation above. The colors on the scale on the right side of the image represent the strength or intensity of the connections between nodes. The closer to red, the stronger the connection, and the closer to blue, the weaker the connection. This color scale helps identify the strength of the connections between nodes in the graph.

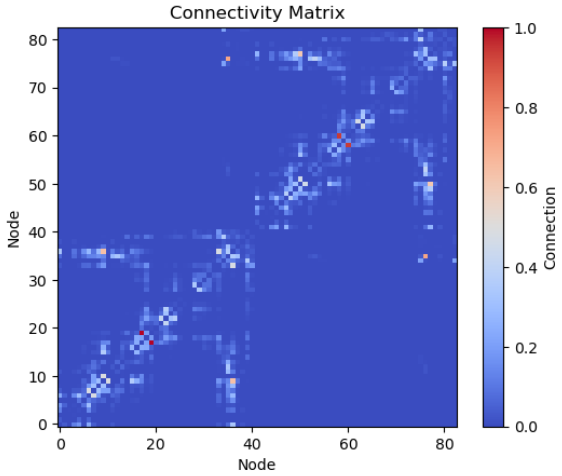


Figure 1. Connectivity Matrics master n

The figure above shows the range of value of connection for the connectivity matrix is 0-1. This happens because the matrix is already normalized. We can see that we are using 83 nodes in our brain model where for the right hemisphere and left hemisphere are equal in total of 42 each, and then we got 1 brainstem that located in the middle. The human brains are symmetrical, each brain parts are located equally in the left hemisphere and the right hemisphere. We can see the visualization below.

The figures below are the visualization of the brain graph with edge weights based on the aforementioned connectivity matrix. With the help of the coordinated node data, we can visualize this brain graph realistically. On the visualization, blue indicates a high level of connectivity between points, while red indicates a low level of connectivity.

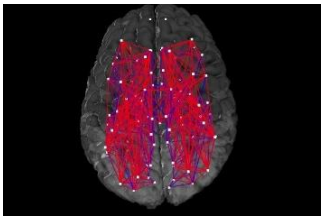


Figure 2. Horizonal

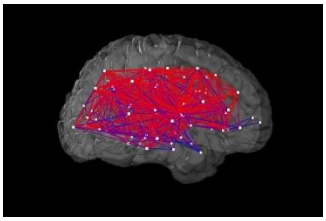


Figure 3. Sagital

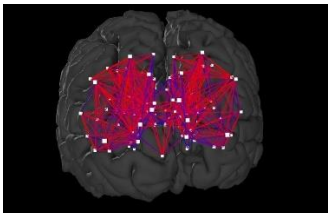


Figure 4. Coronal

Next, we divided the brain into seven main regions: frontal, parietal, occipital, temporal, basal ganglia, limbic, and brainstem. To simplify visualization, we assigned uniform weights to each edge.

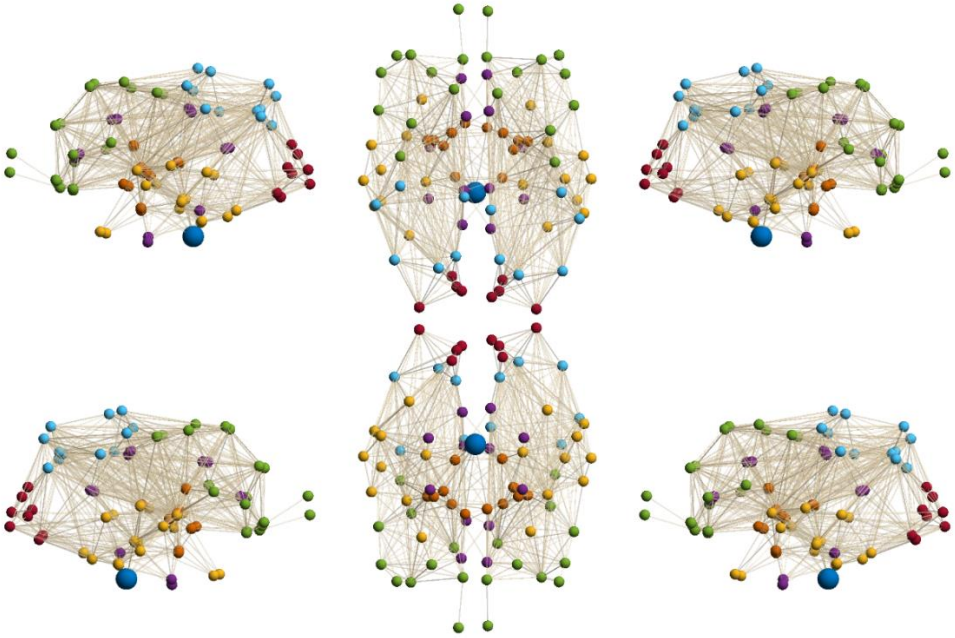


Figure 5. Non-weighted Brain Graph Models

Legend :

2.3 Reaction-Diffusion Model

To model the spread of Parkinson's disease and ALS, we consider the diffusion of disease-causing proteins. Suppose we have three points.

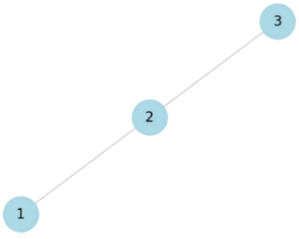


Figure 6. Example of a graph with 3 nodes

with the adjacency matrix as follows :

$$A = \begin{pmatrix} 0 & 1 & 0 \\ 1 & 0 & 1 \\ 0 & 1 & 0 \end{pmatrix}$$

The protein concentration at point i decreases by n times the concentration at point i where n is the degree of point i and also increases by the concentration at the points connected to point i. The equations for the change in protein concentration at these three points are as follows:

$$\frac{dC_1}{dt} = -C_1 + C_2$$
$$\frac{dC_2}{dt} = C_1 - 2C_2 + C_3$$
$$\frac{dC_3}{dt} = C_2 - C_3$$

In other words, the rate of change of protein concentration at each point is influenced by the concentration of the protein at that point and at the points directly connected to it. In general, the diffusion equation for the concentration at node *i* is as follows:

$$\frac{dC_i}{dt} = -\sum_{j=1}^{n}(A_{ij}C_i - A_{ij}C_j)$$

Description :

C_i = Concentration at node *i*

A = Adjacency matrix (nxn)

In representing the protein growth at each point, we utilized the Logistic Equation, formulated as follows.

$$\frac{dC_i}{dt} = -C_i(1 - C_i)$$

Description :

C_i = Concentration at node *i*

Thus, for the three points, the reaction-diffusion equations enhanced with the logistic equation are given as follows.

$$\frac{dC_1}{dt} = \alpha C_1(1 - C_1) - \rho(C_1 - C_2)$$
$$\frac{dC_2}{dt} = \alpha C_2(1 - C_2) - \rho(2C_2 - C_1 - C_3)$$
$$\frac{dC_3}{dt} = \alpha C_3(1 - C_3) - \rho(C_3 - C_2)$$

Consequently, the reaction-diffusion equation for the protein concentration at n points is derived as shown below.

$$\frac{dC_i}{dt} = \alpha C_i(1 - C_i) - \rho\sum_{j=1}^{n}(A_{ij}C_i - A_{ij}C_j)$$

Description :

C_i = Concentration at node *i*

A = Adjacency matrix (nxn)

α = Growth coefficient

ρ = Diffusion coefficient

n = Number of nodes

We might find a problem from the equation above because we need to run the simulation using 2 parameters α and ρ. That will take a lot of time, and a bunch of trials and errors. Because of that, we need to simplify this equation by dividing the equation with α.

By simplifying the parameters ρ and α, we obtain the following nondimensional formulation.

$$\frac{dC_i}{d\tau} = -k \sum_{j=1}^{n} (A_{ij} C_i - A_{ij} C_j) + C_i(1 - C_i)$$

Description :

$k = \frac{\rho}{\alpha}$

2.4 Parameter

To observe the propagation of Parkinson's and ALS diseases spread, we need the values of the parameter k as explained earlier. Based on literature studies, the growth coefficient of the proteins that cause the Parkinson's and ALS diseases ranges from 0.01 to 0.1, while the diffusion coefficient ranges from 0.001 to 0.1. Consequently, a range of values for k is obtained, spanning from 0.01 to 10. Subsequently, discretization is performed with $\Delta = 0.01$ to observe the simulation of the spread of Parkinson's and ALS diseases for the aforementioned range of k. Thus, the simulation is conducted 1000 times.

2.5 Error Score

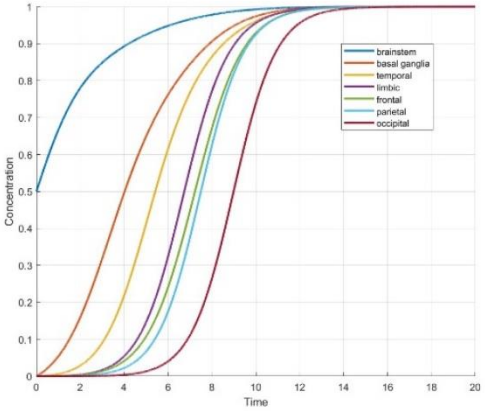
Error score (e) describes the magnitude of the error in the order of simulation results compared to the literature. This score provides a quantitative measure of how closely the simulated results align with the established rankings found in the literature. By using a ranking system, the simulation results are compared against the reference rankings from the literature. If the order of the simulation results deviates significantly from the literature order, the error score will increase accordingly. This means that a larger error score indicates a greater discrepancy between the simulation and the literature rankings, highlighting the extent to which the simulation results differ from the expected or known outcomes.

The error score is calculated by determining the sum of the absolute differences between the ranks of the simulation results and the ranks from the literature. This method ensures that each deviation, regardless of its direction, contributes positively to the overall error score. Consequently, a higher total of these absolute differences signifies a larger error score, reflecting a greater misalignment between the simulated and the reference rankings.

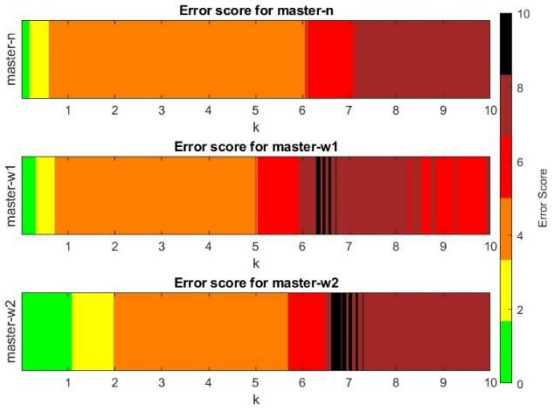
3 Results

In this chapter, we present the results of our simulations investigating the propagation of Parkinson's Disease and ALS in the brain. We analyze the concentration growth over time for the fastest nodes representing each brain region, determine the order in which these regions reach a critical concentration threshold, and compare these orders to literature to calculate error scores.

3.1 Parkinson's Disease Results



(a)



(b)

Figure 7. (a) Concentration growth over time for the fastest nodes representing each brain region for the Parkinson's simulation using the master-w2 adjacency matrix with ***k*=0.2**. The x-axis represents time, and the y-axis represents concentration. The legend indicates the different brain regions. (b) Error score visualizations for Parkinson's Disease simulations using different adjacency matrices. The x-axis represents the value of ***k***, and the color spectrum represents the error score. The color gradient indicates the level of deviation from the literature, with green representing an error score of 0 (indicating that the simulation order matches the literature exactly) and red representing higher deviations.

The concentration growth graphs in Figure 7(a) illustrate the progression of Parkinson's Disease over time for the fastest nodes representing each brain region. All simulations for Parkinson's Disease maintain a consistent initial condition where node 83 (brainstem) starts with a concentration value of 0.5, while all other nodes begin at 0. The specific example shown here uses the master-w2 adjacency matrix with ***k*=0.2**. On the x-axis, time is represented, and on the y-axis, concentration. Each line in the graph corresponds to a different brain region, demonstrating how concentration changes over time. The legend indicates the various brain regions, and the exact nodes representing each brain region in this example are brainstem (node 83), basal ganglia (node 76), temporal (node 81), limbic (node 56), frontal (node 51), parietal (node 57), and occipital (node 65).

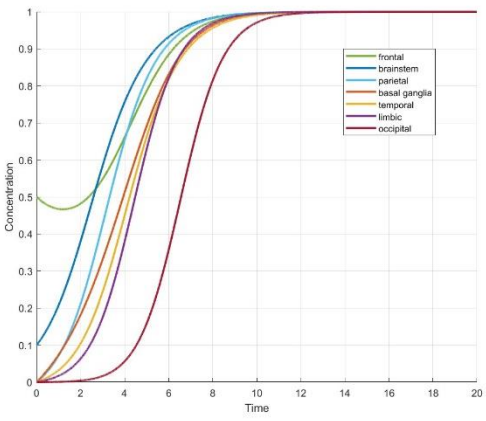
This figure is an example from thousands of simulations conducted. We determine the staging in our simulation by identifying which node in each brain region reaches a concentration of 0.5 first. Observations from this figure indicate that the brainstem reaches the 0.5 concentration threshold first, followed sequentially by the basal ganglia, temporal, limbic, frontal, parietal, and occipital regions. This order reflects the typical progression of Parkinson's Disease, starting from the brainstem and spreading to other regions at varying rates.

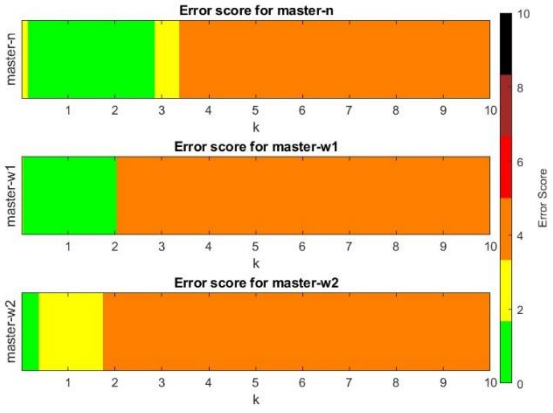
To ascertain the order in which brain regions reach the 0.5 concentration threshold, we analyzed the concentration growth across all 83 nodes post-iteration. Each brain region was ranked based on the earliest node to reach a 0.5 concentration. This analysis was repeated 3000 times, accounting for three different adjacency matrices and 1000 different values of ***k***. Figure 7(a) exemplifies the outcome for one such simulation.

After obtaining the orders for all matrix and ***k*** variations, we compared these results with the literature to identify the variations that best match documented progression patterns of Parkinson's Disease. Comparing the simulation stages with the literature is essential for validation, aligning our simulation outputs with the known spread of alpha-synuclein in the brain. The error score visualizations in Figure 7(b) illustrate this comparison. The x-axis represents the value of ***k***, while the color spectrum represents the error score. The color gradient indicates the level of deviation from the literature, with green representing an error score of 0 (indicating an exact match with the literature) and red indicating higher deviations. The three subplots correspond to the adjacency matrices: master-n (top), master-w1 (middle), and master-w2 (bottom).

The error score analysis in Figure 7(b) demonstrates that the master-w2 adjacency matrix with ***k*** values between 0.01 and 1.10 shows the least deviation from the literature, indicating the highest accuracy in simulating Parkinson's Disease progression. This finding highlights the suitability of the master-w2 matrix with these ***k*** values for accurately modelling the disease's spread.

3.2 ALS Results





(a) (b)

Figure 8. (a) Concentration growth over time for the fastest nodes representing each brain region for the ALS simulation using the master-w1 adjacency matrix with ***k*=0.2**. The x-axis represents time, and the y-axis represents concentration. The legend indicates the different brain regions. (b) Error score visualizations for ALS simulations using different adjacency matrices. The x-axis represents the value of ***k***, and the color spectrum represents the error score. The color gradient indicates the level of deviation from the literature, with green representing an error score of 0 (indicating that the simulation order matches the literature exactly) and red representing higher deviations.

The concentration growth graphs in Figure 8(a) illustrate the progression of ALS over time for the fastest nodes representing each brain region. Unlike the Parkinson's Disease simulations, ALS simulations have different initial conditions. For ALS, nodes 10 and 51 (frontal) start with concentration values of 0.5, while node 83 (brainstem) starts with a concentration of 0.1. All other nodes begin with a concentration of 0. This setup reflects literature findings that ALS typically first manifests in the frontal region and then progresses to the brainstem. Unlike Parkinson's simulations, which only initialize the first stage in the brainstem, ALS simulations include initial values for both the frontal and brainstem stages to ensure that the simulation ranks align with literature observations. If we only initiated the frontal region, the simulation results would not match the literature.

In this example, we use the master-w1 adjacency matrix with ***k*=0.2**. The x-axis represents time, and the y-axis represents concentration. Each line in the graph corresponds to a different brain region, showing how concentration changes over time. The legend indicates the various brain regions, and the exact nodes representing each brain region in this example are brainstem (node 83), basal ganglia (node 78), temporal (node 75), limbic (node 55), frontal (node 10), parietal (node 11), and occipital (node 63).

This figure is an example from thousands of simulations conducted. To determine the staging in our simulation, we identify which node in each brain region first reaches a concentration of 0.5. Observations from this figure illustrate the sequence in which different brain regions reach the 0.5 concentration threshold, providing insights into the progression of ALS in the brain.

To determine the order in which brain regions reach the 0.5 concentration threshold, we analyzed the concentration growth across all 83 nodes after the iterations. Each brain region was ranked based on the earliest node to reach a 0.5 concentration. This process was repeated 3000 times, using three different adjacency matrices and 1000 different values of ***k***. Figure 8(a) exemplifies the result for one such simulation.

Due to the limited literature on ALS progression, our comparison only considers the progression across four brain regions: frontal, brainstem, parietal, and basal ganglia. The literature often mentions stages occurring in smaller regions within these larger brain regions and stages involving the spinal cord, which our model does not represent. As our method uses representative nodes, we do not account for these repetitions and lack a spinal cord node. Consequently, we focused on the primary regions mentioned. The error score visualizations in Figure 8(b) illustrate this comparison. The x-axis represents the value of ***k***, and the color spectrum represents the error score. The color gradient indicates the level of deviation from the literature, with green representing an error score of 0 (indicating that the simulation order matches the literature exactly) and red representing higher deviations. The three subplots correspond to the adjacency matrices: master-n (top), master-w1 (middle), and master-w2 (bottom).

The error score analysis in Figure 8(b) demonstrates that the master-n adjacency matrix with ***k*** values between 0.15 and 2.80 shows the least deviation from the literature, indicating the highest accuracy in simulating ALS progression. This finding highlights the suitability of the master-n matrix with these ***k*** values for accurately modelling the disease's spread.

4 Conclusion

In conclusion, this study has shown that our mathematical reaction-diffusion model is robust and effective for accurately replicating the spread of both ALS and Parkinson's disease. The model's success in capturing the dynamics of these neurodegenerative diseases suggests it could be a valuable tool for understanding how these diseases progress. For Parkinson's disease, we found that the master-w2 provided the most reliable simulation results. This is because it closely matches the observed data, which has the widest range of ***k*** compared to master-n and master-w1 and has the least deviation from the literature, which validates the model's accuracy. In contrast, for ALS, the master-n emerged as the most effective which has the widest range of ***k*** compared to master-w1 and master-w2 and has the least

deviation from the literature, showing a strong correlation with actual disease spread patterns and proving to be highly suitable for modeling ALS progression. These findings not only deepen our understanding of how ALS and Parkinson's spread but also pave the way for future research to refine and optimize mathematical models for other neurodegenerative diseases. Our results could help develop targeted therapeutic strategies and improve predictive capabilities in clinical settings.

For the future researcher, we suggest doing the simulation with different values of α and ρ, so that the equation will no longer be dimensionless and hopefully the accuracy of the simulation will be increased. We can also reduce some of the assumptions for better reflect to actual cases and consider adding other variables, like medications that can slow the progression of the disease.

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